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Reacciones de ciclación de compuestos quirales poliinsaturados fluorados catalizadas por metales de transición

Tesis Doctoral

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Dra. Mercedes Medio-Simón, Catedrática de Química Orgánica de la Universidad de Valencia y,

Dr. Santos Fustero Lardiés, Catedrático y Profesor Honorario de Química Orgánica de la Universidad de Valencia.

CERTIFICAN:

Que la presente Tesis Doctoral, titulada "**Reacciones de ciclación de compuestos quirales poliinsaturados fluorados catalizadas por metales de transición**", ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universidad de Valencia por **Alberto Llobat Nicolás,** y autorizan su presentación para que se cumplan los trámites reglamentarios para la obtención del título de Doctor en Química.

Valencia, Enero de 2022

Fdo.: Mercedes Medio-Simón

Fdo.: Santos Fustero Lardiés

A continuación, se enumeran las publicaciones científicas correspondientes a la presente Memoria de tesis escrita por compendio de publicaciones, con su factor de impacto (IF) incluido al final de cada una:

1. **Llobat, A.**; Román, R.; Mateu, N.; Sedgwick, D. M.; Barrio, P.; Medio-Simón, M.; Fustero, S. The Fluoro-Pauson−Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C−F Stereogenic Center. *Org. Lett.* **2019**, *21*, 7294-7297 (IF 6.005).

2. **Llobat, A.**; Sedgwick, D.M.; Cabré, A.; Román, R.; Mateu, M.; Escorihuela, J.; Medio-Simón, M.; Soloshonok, V.; Han, J.; Riera, A.; Fustero, F. Asymmetric Synthesis of Fluorinated Monoterpenic Alkaloid Derivatives from Chiral Fluoroalkyl Aldimines via the Pauson-Khand reaction. *Adv. Synth. Cat.* **2020**, *362*, 1378-1384 (IF 5.837).

3. **Llobat, A.**; Escorihuela, J.; Sedgwick, D.M.; Rodenes, M.; Román, R.; Soloshonok, V.; Han, J.; Medio-Simón, M.; Fustero, S. The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/ Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles. *Eur. J. Org. Chem.* **2020**, *27*, 4193-4207 (IF 3.021).

4. **Llobat, A.**; Escorihuela, J.; Fustero, S.; Medio-Simón, M. On the Diastereoselectivity of the Addition of Propargylic Magnesium Reagents to Fluorinated Aromatic Sulfinyl Imines. *Org. Lett.* **2021**, *23*, 3691-3695 (IF 6.005).

La publicación científica que figura como Scientific Article 5 en la Memoria actualmente se encuentra en revisión para ser publicada lo más pronto posible. Para concluir, la siguiente publicación también fue de utilidad para redactar el Background perteneciente a la reacción de Pauson-Khand:

- Escorihuela, J.; Sedgwick, D.M.; **Llobat, A.**; Medio-Simón, M.; Barrio, P.; Fustero, S. Pauson-Khand Reaction of Fluorinated Compounds. *Beilstein J. Org. Chem.* **2020**, *16*, 1662-1682 (IF 2.883).

El trabajo correspondiente a la presente Memoria ha sido financiado con fondos del proyecto CTQ2017-84249-P. Agradezco al Ministerio de Economía, Industria y Competitividad por financiar y por lo tanto hacer posible la investigación científica llevada a cabo.

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Tampoco me olvido de ti, Cristina Negro. A ti tengo mucho que agradecerte y no sabría ni por donde comenzar. Contigo siempre me ha costado expresar lo que se me pasa por la cabeza. Te deseo lo mejor en lo referente a tu formación académica y laboral, estoy seguro de que te irá de maravilla. De momento espero estar presente el día de tu defensa para brindarte apoyo y calmar un poco esos nervios que te entran cuando tienes que ponerte frente al público.

Para terminar, me gustaría señalar que yo no estaría donde estoy a día de hoy si no fuera por la educación y los valores recibidos por parte de mis padres. Vosotros me habéis impulsado y motivado desde el principio. Aún recuerdo cuando empecé mi aventura universitaria y veía lejos y casi imposible lo de convertirme en doctor en Química. Mentiría

si dijera que ha sido un camino fácil, pero haber llegado al final de este camino es una de las cosas más satisfactorias que he hecho en mi vida.

Pero sobre todo este trabajo está dedicado a mis padres. Sin vosotros esto no hubiera sido posible, Julio y Rosa.

Tabla de contenido

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Preface

The Thesis report next presented has been written by compendium of publications according to the regulations established by the University of Valencia (UV) and with the following structure format:

1. **Summary**
2. **Contextual General Overview and Objectives**
3. **Background**
4. **Results and Discussion**
5. **Scientific Publications**
6. **Conclusions**
7. **References**

First, a brief summary, both in English and Spanish, of the work carried out has been provided.

In second place, a contextual framework of the synthesized compounds is described in this Thesis report. With the contextual overview established, the proposed objectives are introduced. This section shall be divided into two parts. The first one is focused on the synthesis of the starting substrates and the second one focusing on cyclisation reactions involving transition metals as catalysts.

Once the objectives and the contextual overview have been described, the previous background on the topics covered in this Thesis report is introduced. These topics will be the synthesis of the starting materials and the cycloadditions involving different transition metals and reaction conditions.

Then, a brief discussion of the results obtained in the laboratory is introduced. Once again this section will be divided in two blocks, one of them will be based on the formation of the starting materials and the other one focusing on the cycloaddition reactions in order to obtain the final products.

The scientific articles are introduced without further modifications in order to respect to the maximum the format of each one of them. The numbering of the tables, diagrams, figures and compounds is independent in each article, as well as the bibliographic references.

Finally, a section with the conclusions drawn and a list of general bibliographic references referring to the entire text of this Thesis report are included.

Supplementary information of each article retains its original format with the following exceptions: 1) Change of the numbering of its pages by the numbering of this Thesis report 2) The pages corresponding to the NMR spectra, which are on the attached CD, have not been included in this report.

The summary of results and discussion contained in each chapter is written both in English and Spanish and the numbering of the compounds is consecutive for the successive sections.

Abbreviations List

Å	Armstrong
Alk	Alkyl
Ar	Aromatic
BARF	[Tetra-(3,5-(CF3)2C6H3)] sodium borate
Bn	Benzyl group
Bpin	Boron pinacolate
Bs	broad singlet
Bus	*tert*-Butylsulfonyl group
CEYM	Cross enyne metathesis
CM	Cross metathesis
CO	Carbon monoxide
COD	1,5-Cyclooctadiene
D	Doblet
DA	Diels-Alder
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereoisomeric excess
DEA	Diethanolamine
DFT	Density functional theory
DMAD	Dimethyl acetylendicarboxylate
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
ee	Enantiomeric excess

Abbreviations List

er	Enantiomeric ratio
Equiv	Equivalent
ESI	Electrospray Ionization
G1	First generation Grubbs catalyst
G2	Second generation Grubbs catalyst
HF.DMPU	Hydrogen fluoride-*N,N'*-Dimethylpropyleneurea reagent
HG1	First generation Hoveyda-Grubbs catalyst
HG2	Second generation Hoveyda-Grubbs catalyst
HOESY	2D Heteronuclear Overhauser Effect Spectroscopy
HMDSLi	Litihum bis(trimethylsilyl)amide
HRMS	High Resolution Mass Spectroscopy
IRC	Intrinsic Reaction Coordinate
K	Kelvin
LA	Lewis acid
LB	Lewis base
Ln	Ligand
M	Multiplet
m	meta
m-CPBA	3-Chloroperbenzoic acid
MEG	Mono-ethylene glicol
MeO-BIPOP	(2*R*,2'*R*,3*R*,3'*R*)-3,3'-Di-*tert*-butyl-4,4'-dimethoxy-2,2',3,3'-tetrahydro-2,2'-bibenzo[*d*][1,3]oxaphosphole
MHz	Megaherzt
NBO	Natural bond orbital
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOESY	2D Nuclear Overhauser Effect Spectroscopy
O	ortho

OD	Octadiene
p	para
PKR	Pauson-Khand Reaction
QTOF	Quadrupole time of flight
RCEYM	Ring Closing Enyne Metathesis
RCM	Ring Closing Metathesis
Rt	Room temperature
(*R*)-BINAP	(*R*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
(*S*)-BINAP	(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
T	Triplet
TCE	Tetracyanoethylene
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
Tol	Tolyl group
TS	Transition state
Ts	Tosyl group
UV	Ultraviolet

Summary

The purpose of the presented Thesis is to report the synthesis of different types of new cyclic compounds through cycloadditions reactions catalyzed by transition metal complexes using as substrates chiral 4-aza-1,7-enynes and *N*-bridged-1,7,13-triynes, more of them containing fluorine atoms or aryl or alkyl fluorinated groups. For the preparation of these compounds, homopropargyl amides were used as starting building blocks. The presence of chirality and the nitrogen and fluorine atoms in the structure is noteworthy because they are elements omnipresent in the structure of many bioactive compounds. The chiral homopropargyl amides used as basic building blocks were also products obtained by synthetic procedures developed in the present work and consisting in the diastereoselective propargylation reactions of Ellman´s imines.

The Thesis is structured in two parts, the first one devoted to the synthesis of the homopropargyl amides and their derivatization to the chiral 4-aza-1,7-enynes and *N*-bridged-1,7,13-triynes used as substrates for the different cycloaddition reactions and the second part devoted in the study of the RCEYM, Pauson-Khand and [2+2+2]-cycloadditions leading to monocyclic, bicyclic and tricyclic compounds.

Resumen

En el presente trabajo de Tesis se ha llevado a cabo la síntesis de compuestos quirales cíclicos de estructura compleja mediante reacciones de cicloadición catalizadas por metales de transición empleando como sustratos de partida 4-aza-1,7-eninos y 5,10-diaza-1,7,13-triinos quirales que, en la mayor parte de los casos, contienen átomos de flúor o agrupaciones fluoradas. La preparación de estos compuestos se basa en la utilización de homopropargilamidas como sustrato común en la estructura de todos ellos. Los elementos de quiralidad y la presencia de átomos de nitrógeno y agrupaciones fluoradas en los sustratos de partida son importantes en cuanto a que están presentes en muchos compuestos bioactivos. Las amidas homopropargílicas quirales son el elemento básico para la construcción de los sustratos sometidos posteriormente a diferentes reacciones de ciclación para obtener distintos derivados, y además son, a su vez, compuestos de síntesis que se obtienen mediante reacciones de propargilación diastereoselectiva de iminas de Ellman.

El trabajo de la Tesis se estructura en dos partes: En la primera se describen los procedimientos de síntesis de las amidas homopropargílicas y su transformación en los eninos y triinos; en la segunda parte se comentan las reacciones de cicloadición que se han llevado a cabo en este estudio y, más concretamente, reacciones de metátesis de eninos por cierre de anillo (RCEYM), reacciones de Pauson-Khand y reacciones de cicloadición [2+2+2] que dan acceso respectivamente a derivados monocíclicos, bicíclicos y tricíclicos.

Contextual General Overview

The construction of complex cyclic structures is an objective of main interest both in classic and modern organic synthesis. Cycloaddition[1] and ring closing metathesis (RCM) reactions[2] represent powerful tools for this purpose. On the other hand, the incorporation of fluorine in bioactive molecules has been demonstrated over the last decades as an effective strategy to improve their initial properties.[3] The main objectives of this PhD thesis are related with all the above cited topics and consist of the preparation of complex chiral fluorinated cyclic structures applying current synthetic methodology based in transition metal catalyzed reactions such as Pauson-Khand reactions, [2+2+1]-cycloadditions, [2+2+2]-cycloadditions or enyne ring-closing metathesis reactions.

Cycloaddition reactions represent straightforward routes for constructing an array of complex cyclic skeletons, many of which are found in natural products, biologically active substances, and functionalized materials.[4] A paradigmatic example is the Diels-Alder reaction reported in 1928 and widely applied due to its versatility and stereochemistry control in both inter- and intramolecular versions. After this pioneering [4+2]-cycloaddition, the ene reaction, the 1,3-dipolar cycloaddition reactions and the [2+2]-cycloadditions were progressively incorporated to the toolbox of the organic synthesis. Noteworthy, the contribution by Woodward and Hoffmann[5] in the sixties offering rational insight of the rules that govern the cycloaddition reactions had a marked incidence in this development. During the last century, a variety of new cycloadditions variants such as [2+2+1], [2+2+2]

[1] Carruthers, W. (**1990**). *Cycloaddition Reactions in Organic Synthesis*. Pergamon Press.

[2] Grubbs, R. H. (**2003**). *Handbook of Metathesis Vol. 1 y 2*. Wiley-VCH.

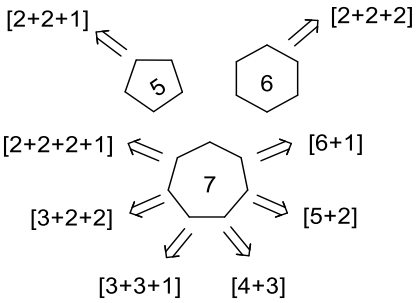
[3] Uneyama, K. (**2006**)**.** *Organofluorine Chemistry*. Blackwell Publishing Ltd. Oxford. b) Chambers, R. D. *Fluorine in Organic Chemistry*. Blackwell Publishing Ltd. Oxford. **2004**. c) Hiyama, H. (**2000**). *Organofluorine Compounds: Chemistry and Applications Springer*. Berlín.

[4] Kobayashi, S.; Jorgensen, K. A. (**2001**). *Cycloaddition Reactions in Organic Synthesis*. Wiley-VCH.

[5] Woodward, R. B. Hoffmamm, R. (**1970**). *The Conservation of the Orbital Symmetry*. Verlag chemie.

and the high order cycloadditions [6+1], [5+2], [4+3], [4+2+1], [3+3+1], [3+2+2] and [2+2+2+1] all of them conducting to diverse cyclic systems were progressively incorporated to the realm of organic synthesis.[6]

The drawbacks associated to the harsh conditions required for conventional cycloadditions reactions together to the lack of chemo- and regioselectivity forced the development of new methods and strategies. In this context, the concomitant development of the transition-metal catalysis offered new opportunities to the cycloaddition reactions, a topic that although started decades ago is still an active field of research in the present century. Different metals such as Rh, Ni, Pd, Ru, Co, Mo, and Fe complexes among others have been usually reported as catalysts for higher order cycloadditions (Scheme 1).[7]



Scheme 1. Main transition metal-catalyzed cycloadditions.

Among the transition-metal catalyzed cycloadditions the [2+2+1]-reaction developed initially by Pauson and Khand (PKR)[8] has been widely explored because allows the preparation of the core of cyclopentenone ring, which is present in many chemical

[6] Trost, B. M.; Zuo, Z.; Schutlz, J. E. *Chem. Eur. J*. **2020**, *26*, 15354 – 15377.

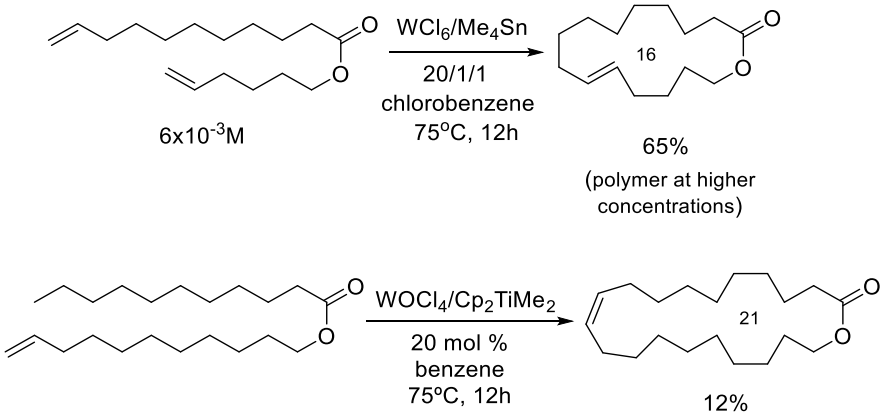
[7] Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49-92.

[8] a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans*. I. **1973**, *9*. 997-981. b) Chung, Y. K.; *Coord. Chem. Rev*. **1999**, *188*, 297-314. c) Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1800-1810.

structures of biological and synthetic importance. Enynes and carbon monoxide are the starting materials used in this transformation that is usually promoted by cobalt complexes although catalysis by rhodium and other complexes have also been reported.

The versatility of the cycloaddition reactions is largely related to the ability to vary the unsaturated components used as staring materials. So, the transition metal-catalyzed cyclotrimerization of alkynes through [2+2+2]-cycloadditions[9] is applied to synthesize highly substituted benzenes. Inter- and intramolecular variants of the reaction have been developed with the consequent wide array of cyclic structures generated in each case.

On the other hand, metathesis reactions constitute another robust topic in organic synthesis. In particular, the ring closing metathesis (RCM), as describes its name, is the modality that allow the construction of cyclic structures. Villemin[10] and Tsuji[11] independently discovered in 1980 that diolefins could be cyclized to form macrocyclic systems (Scheme 2).



Scheme 2. First metathesis reactions with molybdenum complexes.

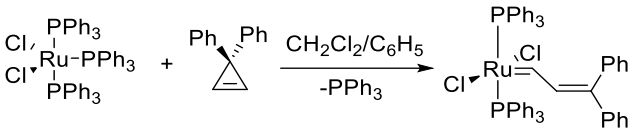
[9] a) Tanaka, K. (**2019)**. *Rhodium Catalysis in Organic Synthesis: Methods and Reactions.* Wiley-CVH. b) Tanaka, K.; Shibata, Y. (Tanaka, K. (Ed.)). (**2013)**. *[2+2+2] and Related Cycloadditions Mediated by Other Transition Metals* John Wiley & Sons. Inc. c) Tanaka, K. *Chem. Asian J*. **2009**, *4*, 508 – 518

[10] Villemin, D. *Tetrahedron Lett*. **1980**, *21*, 1715-1718.

[11] Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett*. **1980**, *21*, 2955-2958.

Besides dienes, diynes or enynes can be also employed as starting materials. Development of the metathesis reactions was parallel to that of the catalysts, in particular those that can tolerate the presence of functional groups in olefin molecules. Initially, it was a molybdenum catalyst that provided functional group tolerance, allowing to study metathesis reactions, which play a role in the organic synthesis of highly functionalized compounds.

Thereafter, several generations of ruthenium complexes mainly developed by Grubbs since the discovery of the first metathesis-active ruthenium alkylidene complex in 1992, which were even more functional group tolerant than earlier metal complexes and that could be used with standard organic methods instead of the techniques required with molybdenum systems. These, rapidly accelerated the applications of metathesis reactions in organic synthesis (Scheme 3).



Scheme 3. First well-defined metathesis-active ruthenium alkylidene complex.

Objectives

In this section, the general objectives are presented along with a brief indication of the novelty represented by each of the presented contributions.

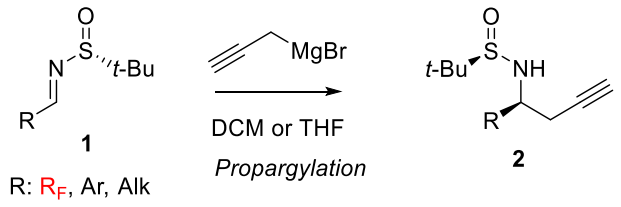
The general objectives of the present Thesis are the preparation of chiral mono-, bi- and tricyclic fluorinated structures by means of metathesis and cycloadditions reactions using as starting materials polyunsaturated compounds such as enynes and triynes. The designed synthesis for these substrates are based in the use of chiral fluorinated homopropargyl amines that are accessible *via* the diastereoselective addition of Grignard reagents to Ellman´s imines.

The proposed objectives are presented in the report divided in headings, one devoted to the synthesis of the starting materials and the other related to the cyclization reactions. These objectives are summarized below in schematic form.

Synthesis of the starting materials

a) Synthesis of homopropargyl amides

The original contribution developed in this work relays in the study of the behavior of aliphatic and aromatic fluorinated Ellman's imines in propargylation reactions using propargylic Grignard reagents. Analysis of solvent effects with fluorinated and non-fluorinated Ellman's imines were also carried out (Scheme 4).

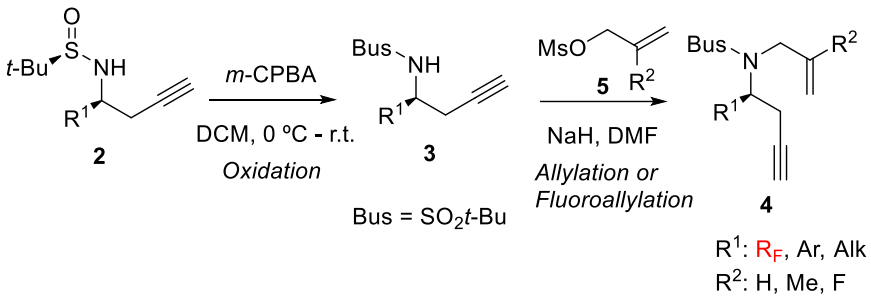


Scheme 4. Diastereoselective propargylation of chiral sulfinyl imines.

b) Synthesis of enynes and triynes

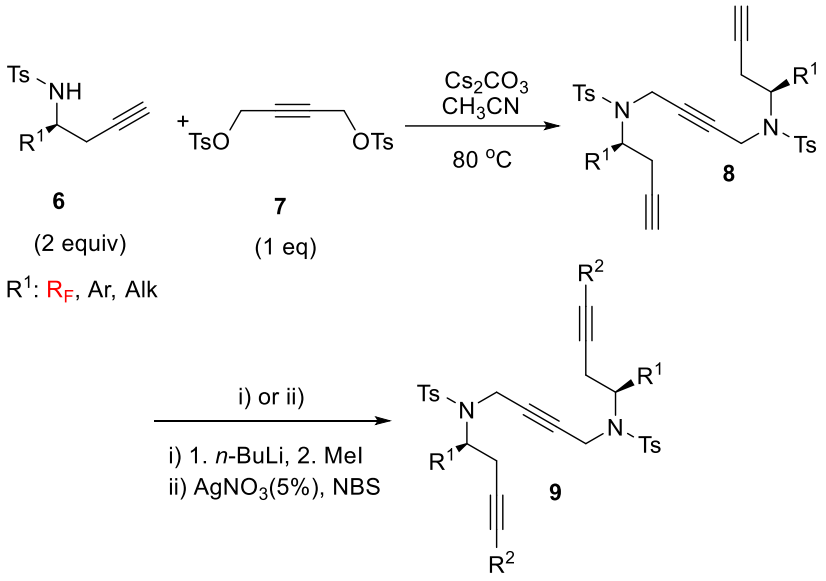
This objective was focused into the preparation of chiral *N*-bridged-*1*,7-enynes **4** (Scheme 5) and *N*-bridged-1,7,13-triynes **8** and **9** (Scheme 6), whose synthesis is unprecedented in the literature.

Chiral 1,7-enynes **4** were obtained by *N*-allylation or *N*-fluoroallylation of the corresponding homopropargyl sulfonamides **3** with different substituted allyl reagents **5**. Substrates **3** were obtained by oxidation of the homopropargyl sulfinamides **2**. Derivatization of sulfinamides **2** in sulfonamides **3** was required due to the former are poor substrates in the allylation reactions.



Scheme 5. Synthesis of chiral 1,7-enynes **4** from homopropargyl amides **2.**

On the other hand, the new chiral *N*-bridged-1,7,13-triynes **8** were prepared by reacting homopropargyl tosylamides **6** with 2-butyn-1,4-ditosylate **7**. Triynes **9** (substituted at the terminal alkyne) were obtained from the unsubstituted triynes **8** by reaction of the corresponding dianion with the appropriate electrophile (MeI or NBS) (Scheme 6).

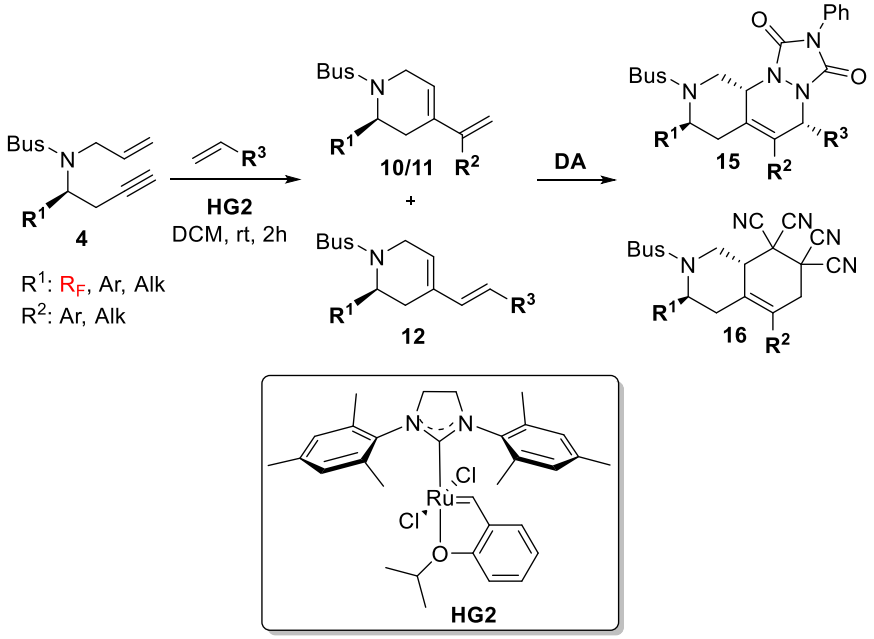


Scheme 6. Synthesis of chiral 1,7,13-triynes **8** and **9** from *N*-tosyl amides **6**.

Cyclization reactions

a) *Synthesis of monocyclic compounds via metathesis reactions (Tandem RCEYM/CM) and further derivatization to bicyclic derivatives.*

The main objective in this section was the development of a simple route to obtain useful scaffolds such are piperidine-based 1,3-dienes **10-12** *via* tandem RCEYM / CM reactions. Primary monocyclic products **10-12** were further transformed into chiral bicyclic compounds through Diels- Alder reactions (DA) with ethylenic dienophiles (PTAD and TCE) (Scheme 7).



Scheme 7. RCEYM/CM synthesis of chiral 1,7-enynes **4** and different substituted alkenes followed by DA of **10-12** with different dienophiles.

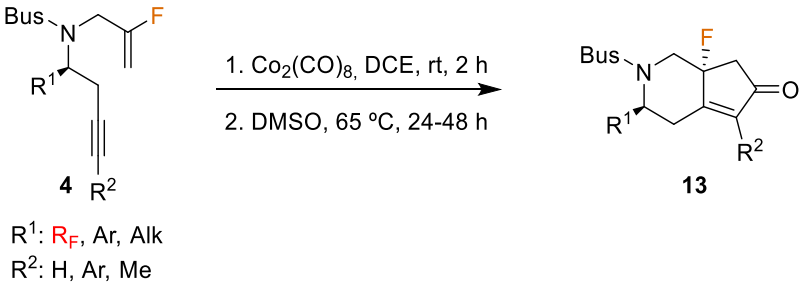
b) Synthesis of bicyclic and tricyclic compounds via cycloaddition reactions: Transition-metal catalyzed [2+2+1] and [2+2+2]-cycloaddition reactions.

b.1. *Nitrogenated bicyclic compounds through [2+2+1] Pauson-Khand reactions (PKR) with chiral 2-fluoro-1,7-enynes.*

The objective in this section was the development of a new route to access fluorinated analogs of monoterpene alkaloids such as *Tecomanine*, a bioactive compound with hypoglycemic activity.[12] The key step of the sequence is a Pauson-Khand reaction involving fluoro-1,7-enynes **4** containing a vinyl fluoride moiety in the olefin coupling partner, a

[12] Constantino, L.; Raimondi, L.; Pirisino, R.; Brunetti, T.; Pessotto, P.; Giannessi, F.; Lins, A.P.; Barlocco, D.; Antolini, L.; El-Abady, S. A. *Il Farmaco.* **2003**, 781-785.

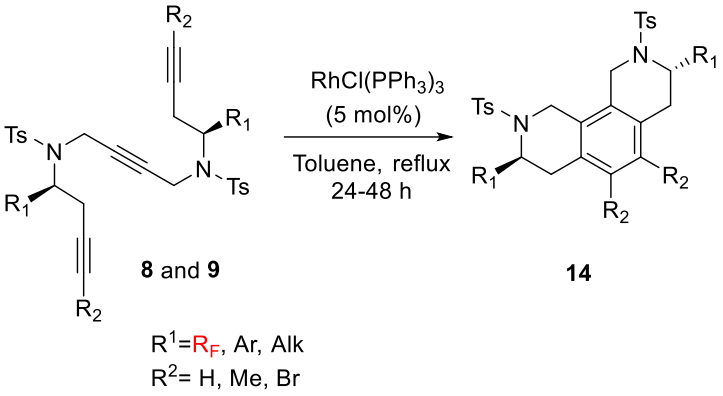
structural feature unprecedented in the field of the Pauson-Khand reactions (Scheme 8). Moreover, conditions to perform stoichiometric and catalytic versions of the PKR have been developed.



Scheme 8. PKR of chiral fluoro-1,7-enynes **4**.

b.2. *Nitrogenated tricyclic compounds through* [2+2+2]-cycloaddition reactions of chiral *N*-bridged-1,7,13-enynes.

The final chapter of the Thesis was addressed to the synthesis of the tricyclic compounds **14** having central chirality via [2+2+2]-cycloadditions and involving triynes **8** an **9** as starting materials. The most innovative aspect of the proposed transformation relies in the use of chiral triynes as substrates, which through of [2+2+2]-cycloadditions provide tricyclic compounds having central chirality (Scheme 9). The preparation of this kind of compounds via [2+2+2]-cycloadditions usually requires the use of sp^2 hybridized substrates, which have in these reactions decreased reactivity compared with the sp hybridized ones.



Scheme 9. Cycloaddition reaction of chiral 1,7,13-triynes **8** and **9**.

Background

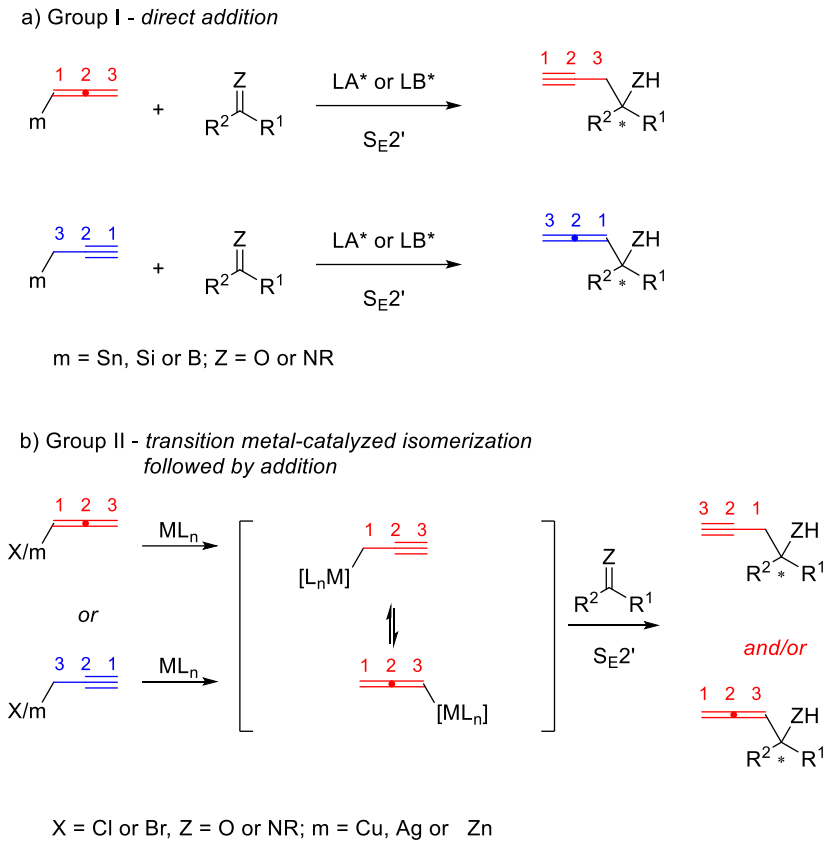
1. Synthesis of the starting materials

1.1. Synthesis of chiral homopropargyl amines

Homopropargyl amines are important building blocks for organic synthesis, particularly because they are starting materials for the rapid construction of heterocycle motifs with high bond-forming efficiency and atom economy *via* a transition-metal-catalyzed cyclization process, which is initiated by intramolecular alkyne hydroamination.[13]

The stereoselective propargylation of imines with propargyl or allenylmetal reagents is one of the most frequently employed procedure for the preparation of chiral homopropargyl amines. One important problem in this transformation is the control of the regioselectivity since homoallenyl amines are usually competing regioisomers. Thus, the propargylation reaction is, in general, a complex reaction that requires both regio- and stereocontrol. Regioselectivity depends on two basic mechanisms: a) direct addition of the organometallic reagent and b) an oxidative addition or transmetalation to form a new organometallic species capable of isomerization followed by addition (Scheme 10).

[13] Tashrifi, Z.; Khanaposhtani, M. M.; Biglar, M.; Larijani, B.; Mahdavi, M. *Asian J. Org. Chem.* **2020**, *9*, 969-991

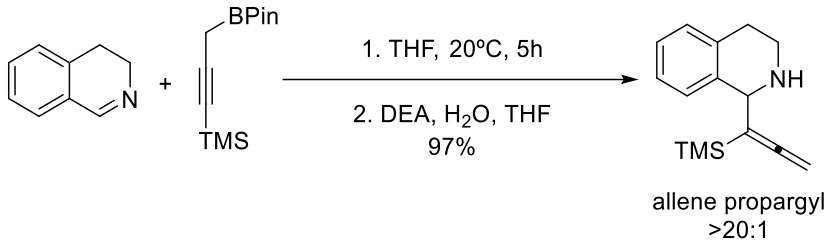


Scheme 10. Regioselectivity in different mechanisms of addition.

Boron-reagents

The reactions of imines with allenylboronates are usually not productive apart from the reactions of imines derived from cyclic imines, salicylaldehydes or α-hydroxy aldehydes.

The uncatalyzed reaction of pinacol propargylboronate with dihydroisoquinoline reported by Fandrick *et al.* proceeded at room temperature achieving the allenic product in 97% yield (Scheme 11).[14]

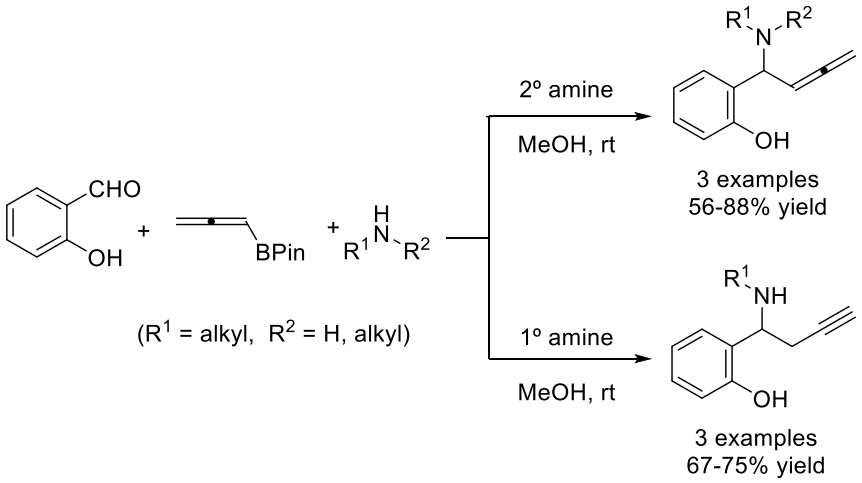


Scheme 11. The uncatalyzed reaction of pinacol propargylboronate with dihydroisoquinoline.

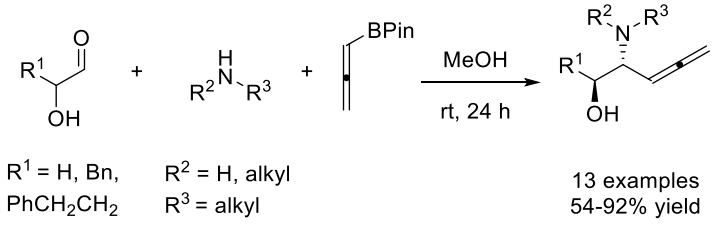
Borono-Mannich reactions involving salicylaldehyde,[15] a primary or secondary amine and pinacol allenylboronate provided regioselectively racemic homopropargylic or α-allenyl amines (Scheme 12) respectively, while the reaction of α-hydroxy aldehydes (as their cyclic acetal dimers), primary or secondary amines and pinacol allenylboronate provided regioselectively *anti* α-allenyl amines (Scheme 13).

[14] Fandrick, D. R.; Roschangar, F.; Kim, C.; Hahm, B. J.; Cha, M. H.; Kim, H. Y.; Yoo, G.; Kim, T.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Haddad, N.; Shen, S.; Grinberg, N.; Lee, H.; Yee, N.; Senanayake, C. H. *Org. Process Res. Dev*. **2012**, *16*, 1131-1140.

[15] Thaima, T.; Pyne, S. G. *Org. Lett*. **2015**, *17*, 778-781.



Scheme 12. Borono-Mannich reaction of salicylaldehyde, primary or secondary amines and pinacol allenylboronate.



Scheme 13. Borono-Mannich reaction of hydroxyl aldehydes with primary or secondary amines and pinacol allenylboronate.

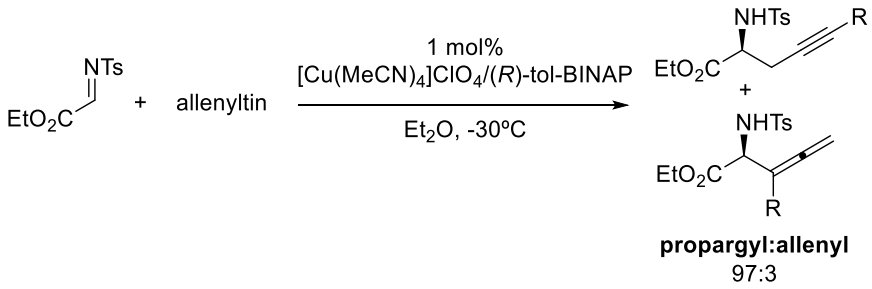
Metal-catalyzed propargylation reactions

In this variant, propargyltin or propargylboron reagents can serve as precursors of the organometallic reagent, which is generated *in situ* by metal exchange.

Copper-catalyzed

The enantioselective addition of allenylcopper species to imines provides a straightforward protocol to access chiral homopropargyl amines. Preformed propargyltin or propargylboron reagents can serve as precursors of the required allenylcopper reagents being activated aldimines the most frequent substrates.

Following this strategy, Akiyama *et al.*[16] reported in 2002 the enantioselective addition of allenyltin reagents to α-iminoesters using $[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP as catalyst leading to the propargyl-substituted α-amino esters in a S_E2' reaction (Scheme 14).



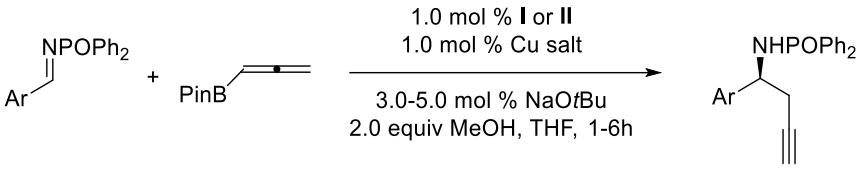
Scheme 14. Enantioselective addition of allenyltin reagents to α-iminoesters.

Later Hoveyda and coworkers[17] described the enantioselective addition of allenylboron reagents to different substituted *N*-phosphinoyl imines in the presence of a chiral *N*-heterocyclic carbene (NHC) complex of copper to give the corresponding homopropargyl amine derivatives with good yields and *er*.

[16] Kagoshima, H.; Uzawa, T.; Akiyama, T. *Chem. Lett*. **2002**, 298-299.

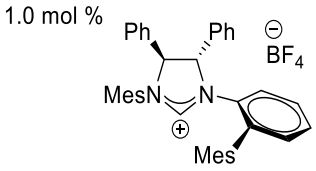
[17] Vieira, E. M.; Haeffner, F.; Snapper, M. L.; Hoveyda, A. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 6618-6621.

Table 1. Addition of allenylboron reagents using different catalysts and *N*-phosphinoyl imines.



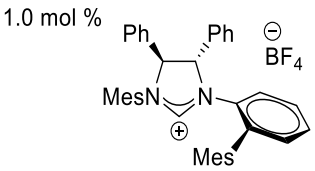
Entry	Substrate (Ar)	Catalyst	With CuCl		With $CuCl_2.H_2O$	
			Yield [%]	*er*	Yield [%]	*er*
1	(2-naphthyl)	**II**	97	98:2	95	94:6
2	(*o*-FC_6H_4)	**II**	96	97.5:2.5	96	95:5
3	(*o*-MeC_6H_4)	**I**	93	97.5:2.5	92	94:6
4	(*o*-$MeOC_6H_4$)	**I**	97	97:3	98	94:6
5	(*m*-BrC_6H_4)	**I**	97	96:4	93	93:7
6	(*p*-ClC_6H_4)	**I**	92	97:3	88	96:4
7	(*p*-$MeOC_6H_4$)	**I**	98	97:3	92	96:4

I



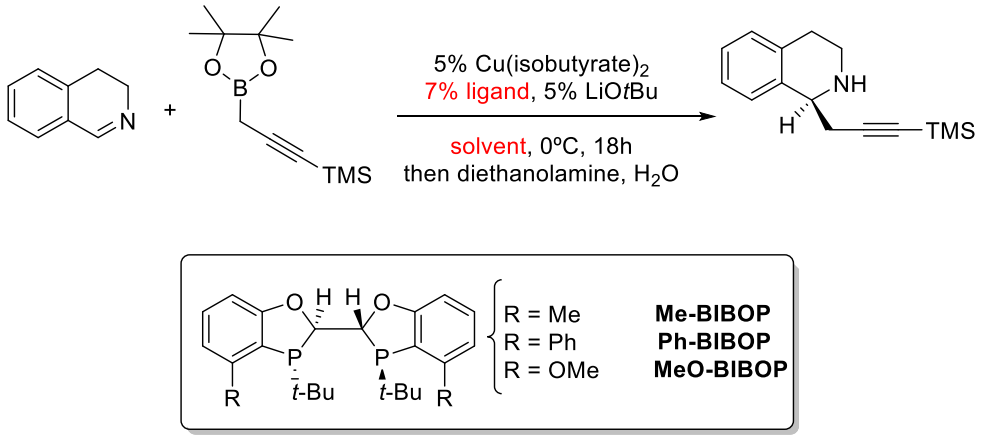
1.0 mol % CuCl

II



1.0 mol % $CuCl_2.H_2O$

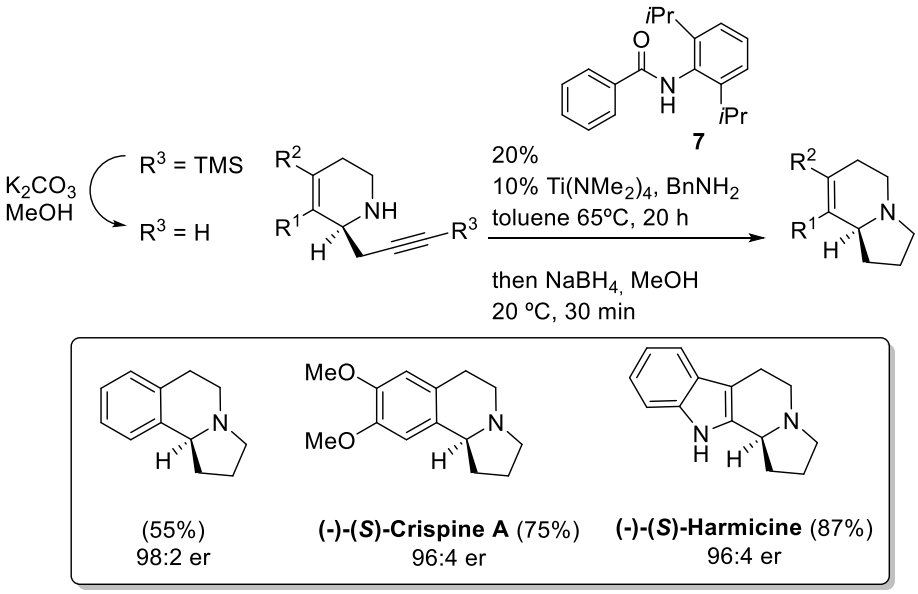
The boron−copper exchange strategy has been also applied to copper-catalyzed asymmetric propargylation reactions of cyclic aldimines with propargylboron reagents (Scheme 15).[18] Among the screened chiral phosphine ligands, MeO-BIBOP afforded the best enantioselectivity.



Scheme 15. Asymmetric propargylation of cyclic aldimines using boron-copper exchange strategy.

The obtained chiral homopropargyl amines were subsequently submitted to a titanium catalyzed hydroamination and reduction to generate the chiral indolizidines (−)-*crispine A* and (−)-*harmicine* (Scheme 16).

[18] Fandrick, D. R.; Hart, C. A.; Okafor,I. S. ; Mercadante, M. A.; Sanyal, S.; Masters, J. T.; Sarvestani, M.; Fandrick, K. R.; Stockdill, J. L. ; Grinberg, N.; Gonnella, N.; Lee, H.; Senanayake, C. H. *Org. Lett.* **2016**, *18*, 6192-6195.

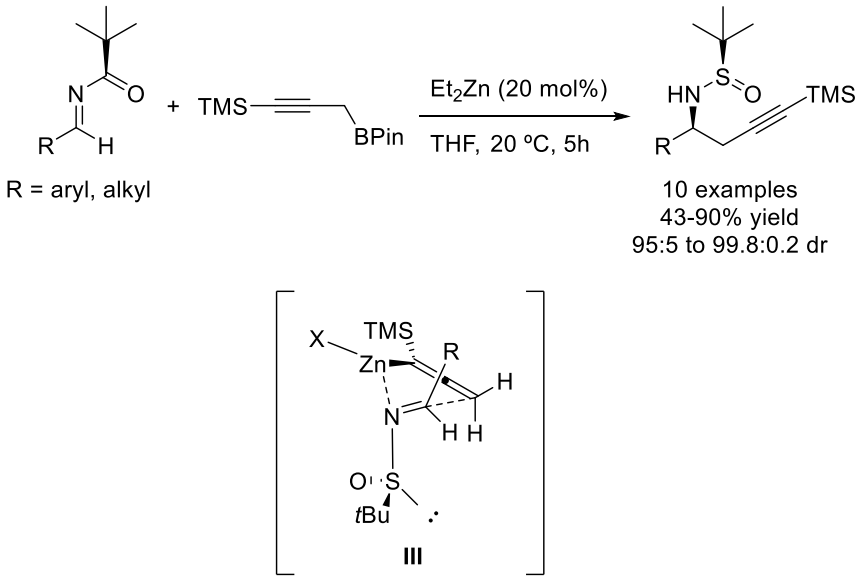


Scheme 16. Titanium catalyzed hydroamination and reduction of chiral cyclic homopropargyl amines.

Zinc-catalyzed

Following a boron−zinc exchange strategy Fandrick[19] described the reaction of (*R*)-*N*-*tert*-butylsulfinyl imines derived from aromatic and aliphatic aldehydes and pinacol propargylboronate in THF at room temperature. Propargyl derivatives were generally obtained in good yields and high diastereoselectivities (Scheme 17). The chelated 6-membered transition state structure **III** was proposed to explain the stereochemical outcome of these reactions.

[19] Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett*. **2010**, *12*, 748-751.

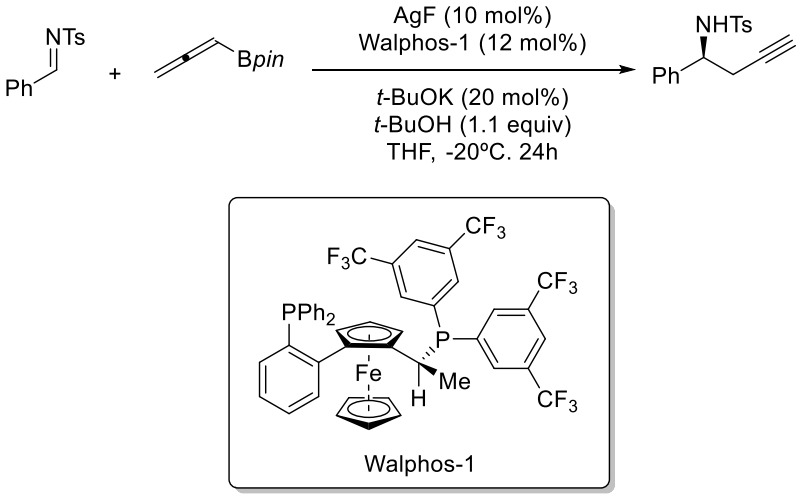


Scheme 17. Zinc-catalyzed reactions of (*R*)-*N*-*tert*-butylsulfinyl imines and pinacol propargylboronate.

Silver-catalyzed propargylation

The silver-catalyzed enantioselective propargylation reactions of *N*-tosyl imines using pinacol allenylboronate, (*R,R*)- Walphos-1 (12 mol%), AgF (10 mol %), *t*BuOK (20 mol%) and *t*BuOH (1.1 equiv) in THF at -20 ºC has been developed by Jarvo *et al* (Scheme 18).[20]

[20] Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci*. **2011**, *2*, 807-810.



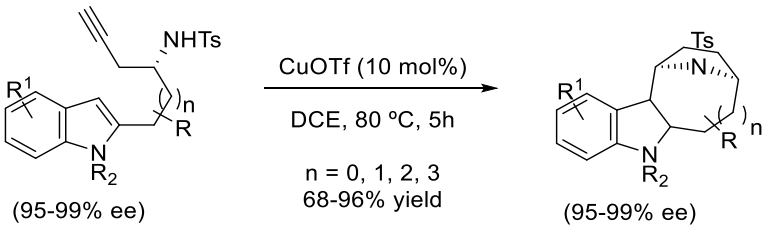
Scheme 18. Silver-catalyzed enantioselective propargylation described by Jarvo's group.

Magnesium reagents

Ellman´s chemistry based on the use of chiral auxiliaries such as *tert*-butylsulfinylimines has been applied to the synthesis of homopropargyl amides. Thus, the addition of magnesium propargyl bromide to the Ellman´s imines provides access to chiral homopropargyl amides with high diastereoselectivities.[21] Homopropargyl amides, obtained following the above approach, have been applied in diverse context as basic building blocks to construct complex nitrogen containing skeletons (Scheme 19).[22]

[21] a) Cui, L.; Li, C.; Zhang, L. *Angew. Chem. Int. Ed*. **2010**, *49*, 9178-9181; b) Shu, C.; Liu, M-Q.; Wang, S-S.; Li, L.; Ye. L-W. *J. Org*. *Chem*. **2013**, *78*, 3292-3299.

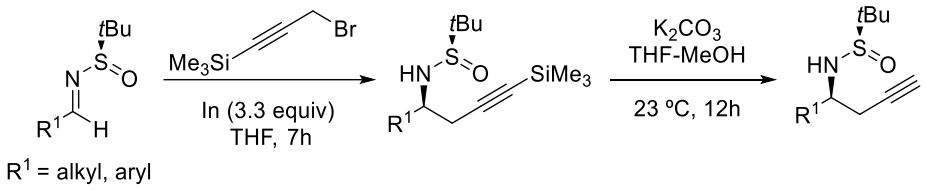
[22] Liu, K.; Zhu, C.; Min, J.; Peng, S.; Xu, G.; Sun, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 12962-12967.



Scheme 19. Illustrative application of chiral homopropargyl amides used as building blocks.

Indium reagents

The Ellman´s chemistry strategy has also been extended to indium-based reagents prepared from the corresponding propargylic bromides applying Barbier-conditions (Scheme 20).[23]

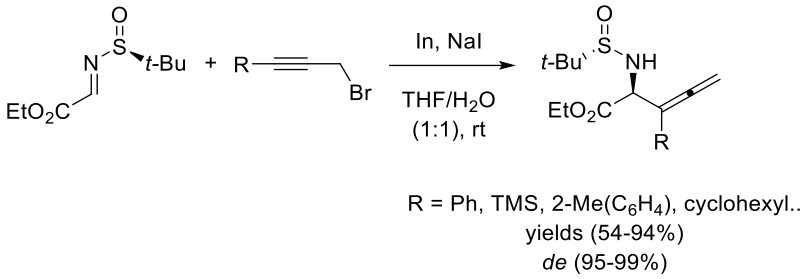


Scheme 20. Addition of propargyl bromide promoted by indium with different Ellman's imines.

An indium-mediated allenylation of different *N*-tert-butanesulfinyl imino esters has also been reported by Xu and Jin. In this approach, use of iodide additives is important to obtain higher yields. It is likely that the iodide anion in aqueous solution will displace bromide to produce a propargylic iodide *in situ*, thus facilitating the formation of reactive

[23] a) García-Muñoz, M. J.; Foubelo, F.; Yus, M. *J. Org. Chem*. **2016**, *81*, 10214-10226; b) García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem*. **2013**, 1287-1295.

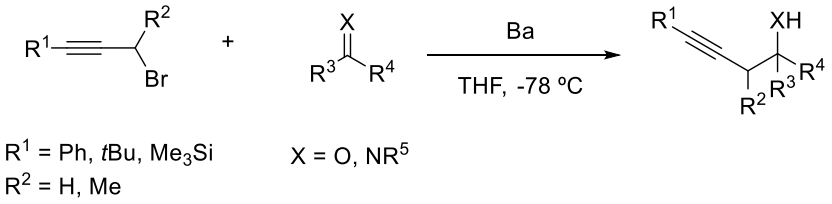
propargylindium. Once the reactive species is formed, diastereoselective allenylation takes place in general with both high diastereolectivity and chemical yields (Scheme 21). [24]



Scheme 21. Indium-mediated diastereoselective allenylation of *N*-tert-butanesulfinyl imino esters.

Barium reagents

Barbier-type conditions also work for the regioselective propargylation of imines with (3-bromobut-1-ynyl)trimethylsilane using reactive barium generated from barium iodide and lithium biphenylide as a low-valent metal in THF (Scheme 22).[25]



Scheme 22. Barbier-type reaction of propargylic bromides with carbonyl compounds and imines promoted by active barium.

[24] Jin, S.; Xu, M. *Adv. Synth. Catal.* **2010**, *352*, 3136-3140.

[25] Yanagisawa, A.; Suzuki, T.; Koide, T.; Okitsu, S.; Arai, T. *Chem. Asian J*. **2008**, *3*, 1793-1800.

2. Synthesis of chiral N-bridged-1,7-enynes and N-bridged-1,7,13-triynes

2.1. Synthesis of chiral N-bridged-1,7-enynes

Chiral *N*-tethered-1,7-enynes are useful starting materials for the synthesis of monoterpenic alkaloids possessing a piperidine heterocycle fused with a five-membered carbocyclic ring, which are of utmost interest because they present important biological activities (Figure 1).

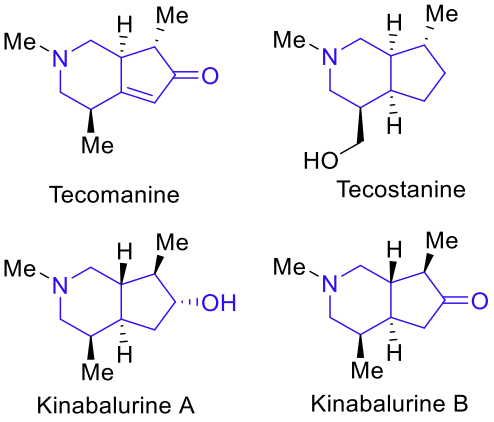
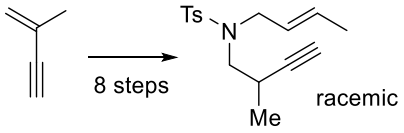


Figure 1. Natural monoterpenic alkaloid t*ecomanine* and derivatives.

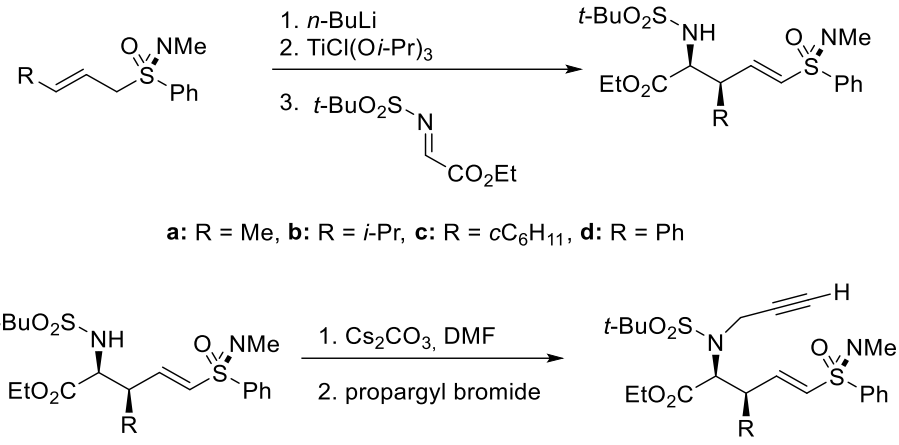
In this regard, several syntheses of enantioenriched aza-1,7-enynes have been reported in the literature although the described synthetic sequences required various steps. Thus, Schore *et al.* described in 2003 the preparation of a racemic enyne in eight steps as part of the synthesis of the bicyclic alkaloid *tecomanine* (Scheme 23).[26]



Scheme 23. Synthesis of racemic *tecomanine* precursor.

[26] Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron*, **2003**, *59*, 5377-5381.

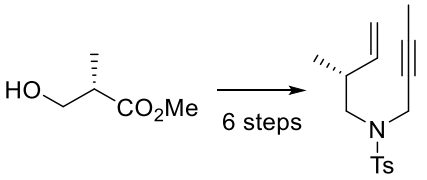
In the same year, Gais *et al.* synthesized enantioenriched 5-aza-1,7-enynes by a highly selective allylation of *N*-*tert*-butylsulfonyl imino esters with bis(allylsulfoximine)titanium complexes leading to allylic sulfoximines, that were subsequently derived by *N*-propargylation (Scheme 24).[27]



a: R = Me, **b:** R = *i*-Pr, **c:** R = *c*C_6H_{11}, **d:** R = Ph

Scheme 24. Amino alkylation of allylic sulfoximines.

Later, Evans synthesized in six steps a new chiral 1,7-enyne as precursor of bicyclic scaffolds using as starting material a chiral-pool derived alcohol (Scheme 25).[28]

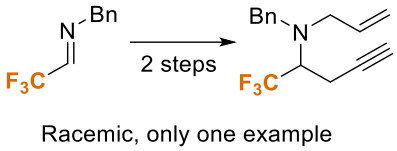


Scheme 25. Preparation of enantioenriched 1,7-enyne using chiral-pool derived alcohol.

[27] Günter, M.; Gais, H.-J. *J. Org. Chem*. **2003**, *68*, 8037-8041.

[28] Kavanagh, Y.; O'Brien, M.; Evans, P. *Tetrahedron*. **2009**, *65*, 8259-8268.

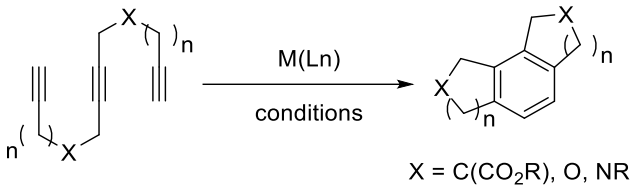
Regarding the preparation of fluorine containing 1,7-enynes only one precedent was reported by Bonnet-Delpont in which an enyne was prepared in two steps albeit in racemic form (Scheme 26).



Scheme 26. Synthesis of racemic fluorinated 1,7-enynes from fluorinated benzyl imines.

2.2. Synthesis of chiral N-bridged-1,7,13-triynes

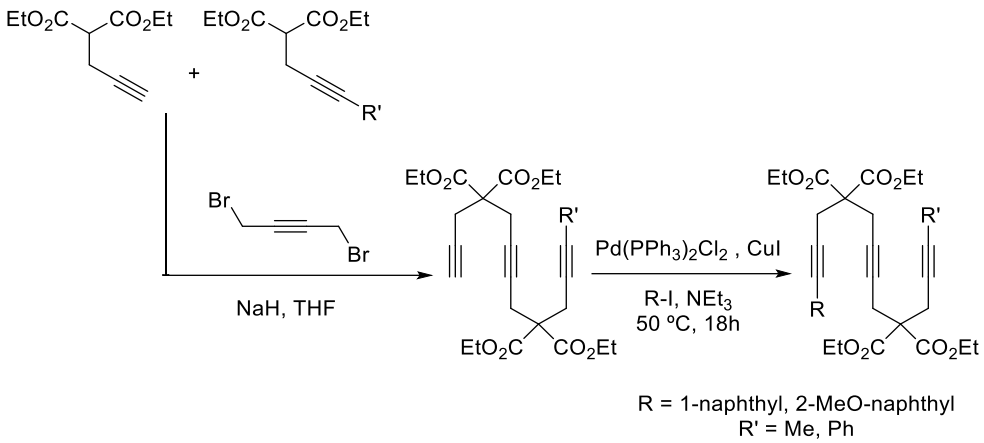
Triynes are very interesting compounds because they can be transformed with relative easiness in complex carbo- and heterocyclic compounds via intramolecular metal catalyzed [2+2+2]-cycloadditions using them as starting materials (Scheme 27).



Scheme 27. Preparation of tricyclic compounds from different triynes via [2+2+2]-cycloaddition.

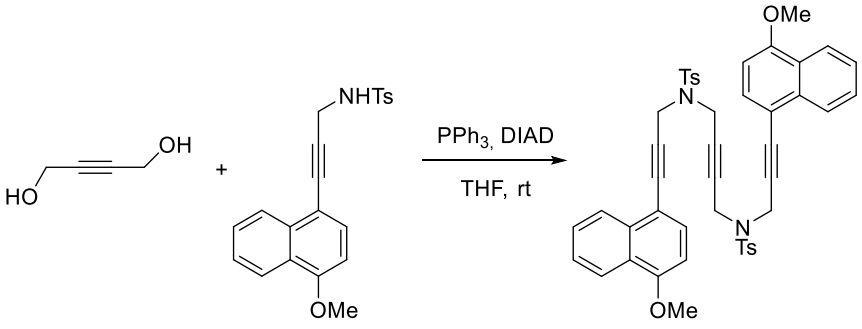
The synthetic route used to obtain triynes is generally based on a strategy where propargylic scaffolds are linked to a dibromoalkyne through a S_N2 reaction. Once triynes are obtained, they can be functionalized in the terminal alkynes position through Sonogashira coupling or alkylation. Hapke and coworkers developed a synthetic route that afforded different achiral malonate derivative triynes in a few steps (Scheme 28).[29]

[29] Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem.* **2015**, 9781-9793.



Scheme 28. Synthesis of malonate derivative triynes.

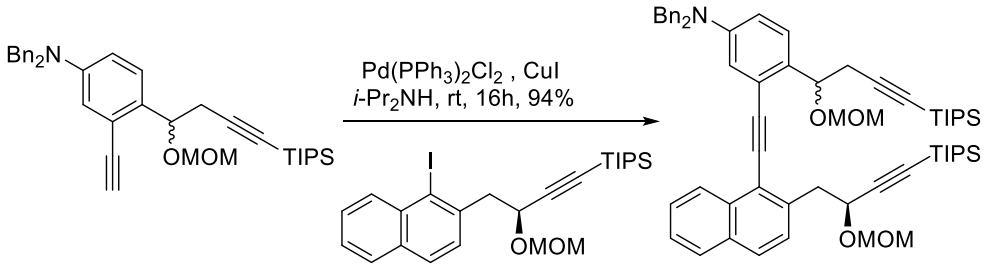
Shibata *et al.* also developed the synthesis of achiral *N*-bridged-triynes using highly hindered aromatic groups to generate atropoisomeric chirality in the following cycloaddition step performing a Mitsunobu reaction between the starting diol and different *N*-tosylamides (Scheme 29). [30]



Scheme 29. Achiral triynes obtained by Shibata.

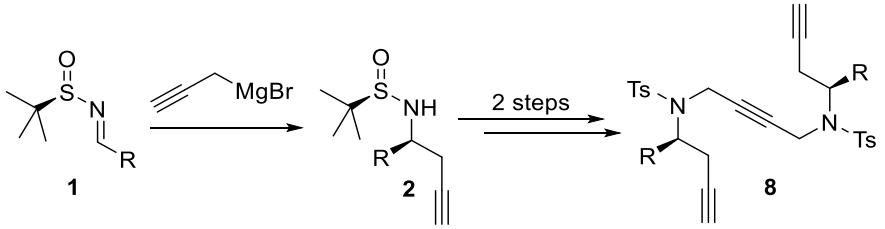
[30] Shibata, T.; Tsuchikama, K.; Otsuka, M. *Tetrahedron: Asymmetry.* **2006**, 614-619.

Despite the synthesis of triynes has been widely studied, it must be emphasized that only a few examples where the triyne synthesized is optically pure have been reported. Thus, in 2018, Karras *et al.* obtained an asymmetric chiral triyne from chiral pool substrates through a Sonogashira coupling (Scheme 30).[31]



Scheme 30. Synthesis of an asymmetric chiral triyne via Sonogashira coupling described by Karras and coworkers.

The strategy proposed by our group was to take advantage of the diastereoselective propargylation of fluorinated and non-fluorinated imines which represents a powerful tool for the generation of chiral centers. Once the homopropargyl amides are synthesized, *N*-bridged-1,7,13-triynes were prepared in two steps (Scheme 31).



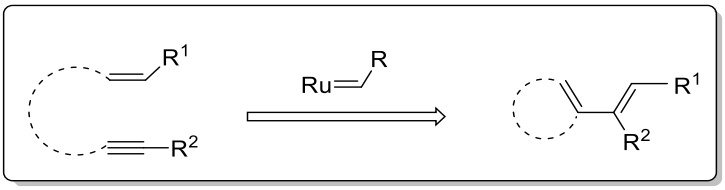
Scheme 31. Synthetic strategy proposed for the formation of chiral *N*-bridged-1,7,13-triynes.

[31] Karras, M.; Holec, J.; Bednárová, L.; Radek, P.; Schmidt, B.; Stará, I. G.; Stary, I. *J. Org Chem.* **2018**, 5523-5538.

3. RCEYM and EYCM reactions

The metathesis reaction has become an essential tool in organic synthesis. Enyne metathesis is a useful variant where the double and triple bonds are cleaved and multiple bonds are simultaneously formed. The reaction is catalyzed by transition metal-carbene complexes and it is more often conducted in the intramolecular version. In this case, it is referred as ring-closing enyne metathesis (RCEYM).

RCEYM reactions have widely been applied to the synthesis of medium and large-sized rings containing 1,3-dienes, which are interesting building blocks amenable to further synthetic transformations (Scheme 32).[32]

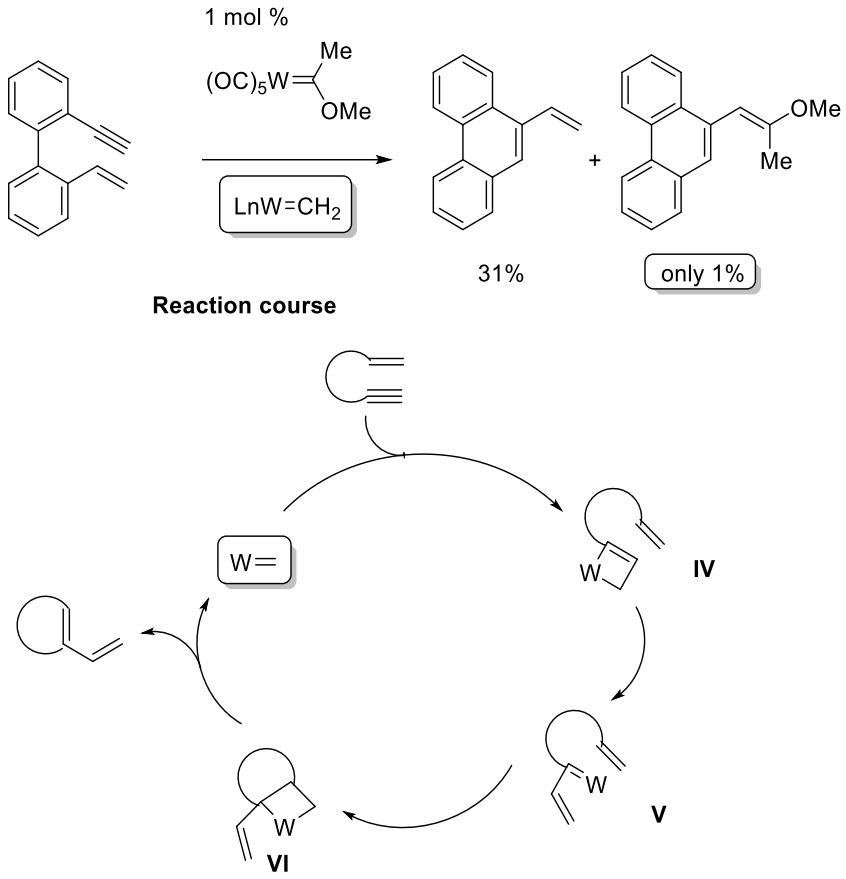


Scheme 32. General example for enyne metathesis.

Enyne metathesis was first discovered by Katz[33] in 1985 using the Fischer tungsten-carbene complex**.** This complex exchanges its substituents with the substituents of the alkene moiety of the enyne, generating a methylene tungsten-carbene complex which is the catalytic species in the successive cycles. The reaction of enyne afforded the cyclic compound in 31 % yield, which was formed via formal [2+2]-cycloaddition of carbene complex and the alkyne moiety (Scheme 33).

[32] a) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, j. G. *Angew. Chem.* **2005**, *117*, 7608-7613; *Angew. Chem. Int. Ed*. **2005**, *44*, 7442-7447; b) Wu, C.-J.; Madhushaw, R. J.; Liu, R.-S. *J. Org. Chem*. **2003**, *68*, 7889-7892; c) Tonogaki, K.; Mori, M. *Tetrahedron Lett*. **2002**, *43*, 2235-2238; d) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc*. **1997**, *119*, 12388-12389.

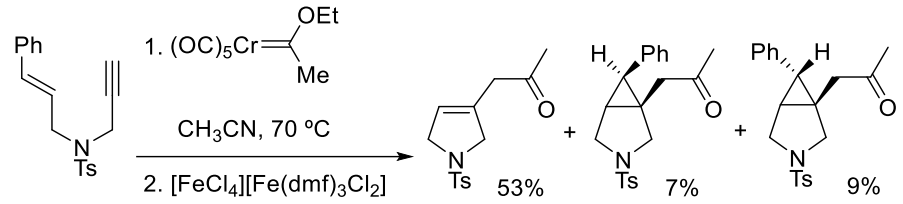
[33] Katz, T. J.; Sivavec, T. M, *J. Am. Chem. Soc*. **1985**, *107*, 737-738.



Scheme 33. Tungsten-catalyzed enyne metathesis.

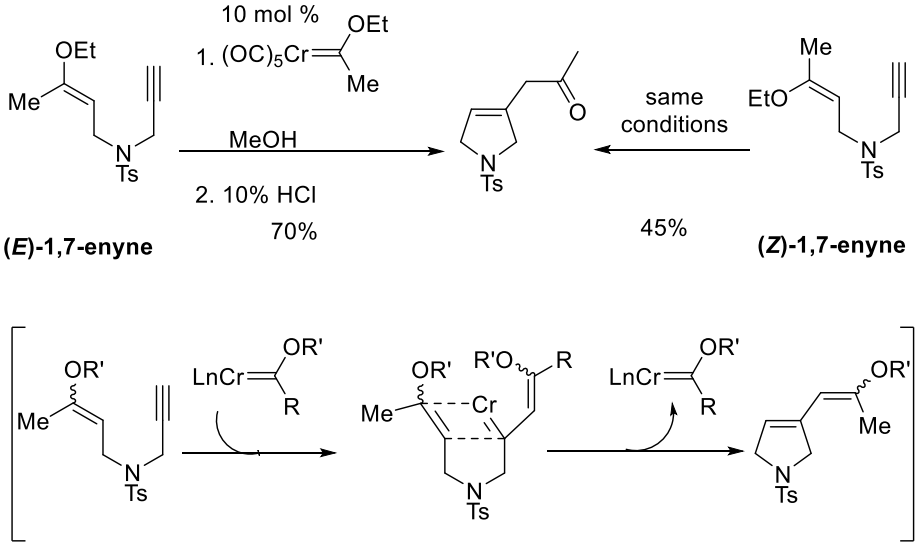
Later, Mori reported a chromium-mediated catalyzed enyne metathesis.[34] When the enyne was treated with a Fischer chromium-carbene complex followed by hydrolysis, the metathesis product was obtained in 53% yield along with carbene insertion products (7% and 9% respectively) (Scheme 34).

[34] a) Mori, M.; Watanuki, S. *J. Chem. Soc. Chem. Comm*. **1992**, 1082-1084. b) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129-4130.



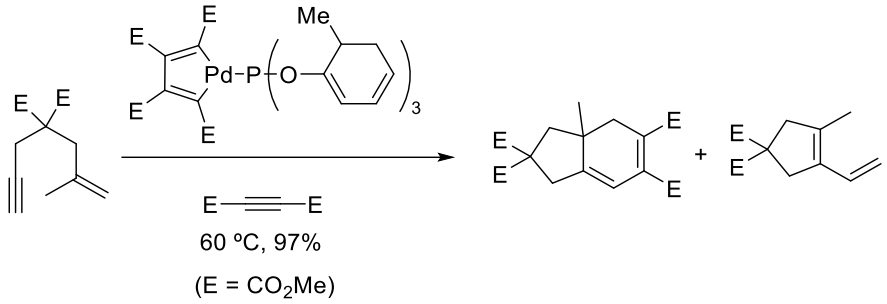
Scheme 34. Chromium-catalyzed metathesis

This reaction was further developed as a chromium-catalyzed enyne metathesis, when the enyne has the same substituent on the alkene moiety as that Fischer chromium-carbene complex. Treatment of (*E*)- and (*Z*)-1,7-enyne with 10 mol % of chromium-carbene complex followed by hydrolysis afforded the same compound (Scheme 35).



Scheme 35. Proposed mechanism for chromium-catalyzed metathesis.

In 1988, Trost reported the palladium-catalyzed enyne metathesis reaction with a 1,6-enyne leading to the diene product that reacts *in situ* with DMAD to give a secondary bicyclic product (Scheme 36).[35]



Scheme 36. Palladium-catalyzed metathesis.

Thereafter, Grubbs developed the catalytic reaction using the ruthenium-carbene complexes **G1a** and **G1b** (Figure 2).[36]

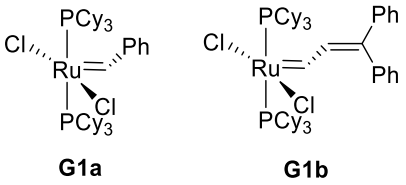
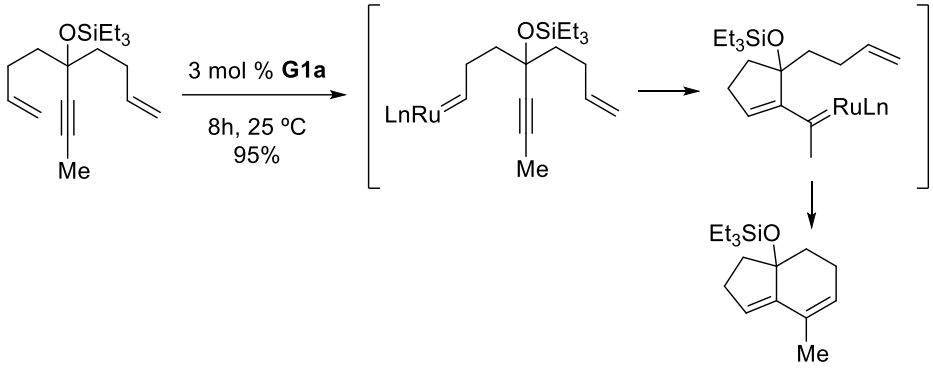


Figure 2. Ruthenium-carbene complexes developed by Grubbs.

[35] a) Trost, B. M.; Yanoury, G. J. *J. Am. Chem. Soc.* **1988,** *110*, 1636-1638. b) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824-832.

[36] a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2039-2041. b) Grubbs, R. H.; Chang, S.; *Tetrahedron* **1998**, *54*, 4413-4450. c) Kim, S. H; Bowden, N. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. d) Kim, S. H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem*. **1996**, *61*, 1073-1081.

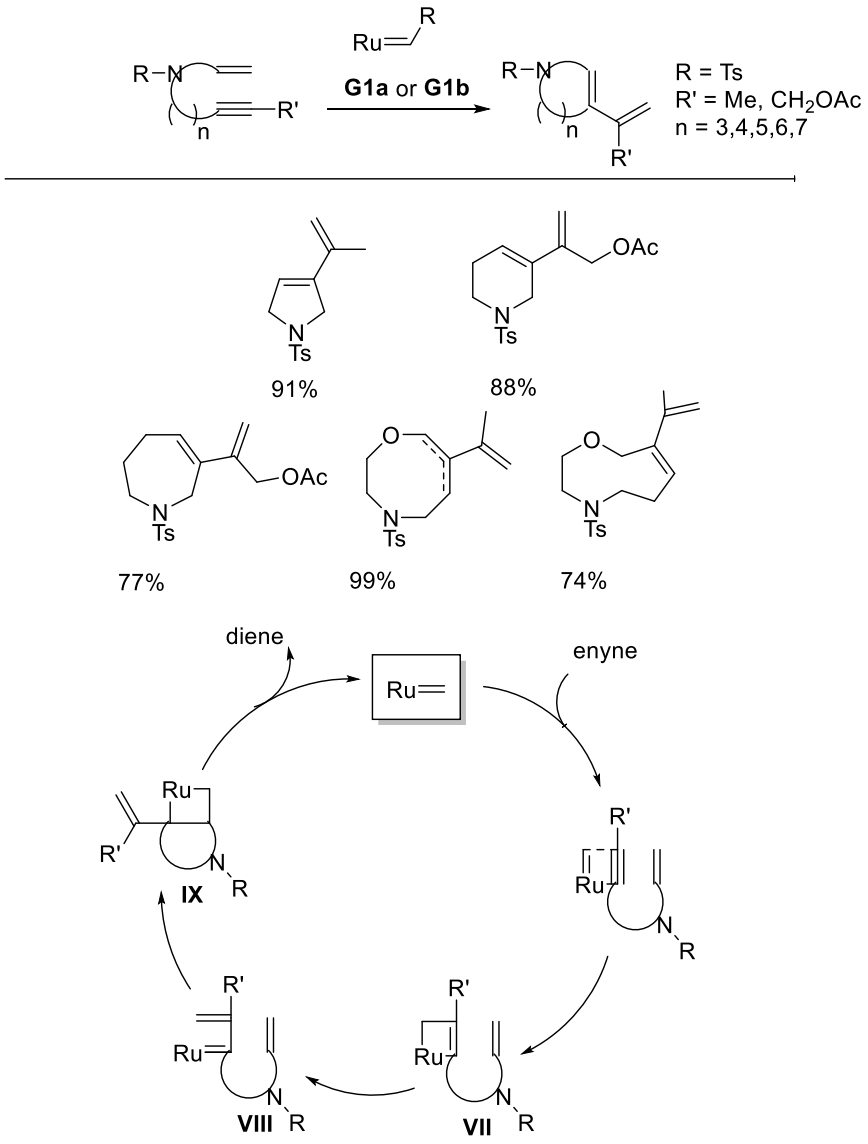
These complexes were used in the dienyne metathesis giving bicyclic compounds via a tandem cyclization (Scheme 37).[37]



Scheme 37. Ruthenium-catalyzed dienyne metathesis.

Later, Mori *et al.* applied complexes **G1a** and **G1b** to different enynes. Thus, 5-to 9-membered carbo- and heterocyclic compounds were synthesized from the corresponding enynes in high yields (Scheme 38).

[37] a) Kinoshita, A.; Mori, M. *Synlett*. **1994**, 1020-1022. b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron.* **1999**, *55*, 8155-8167. c) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett*. **2000**, *2*, 543-545. e) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis.* **2001**, 654-664.

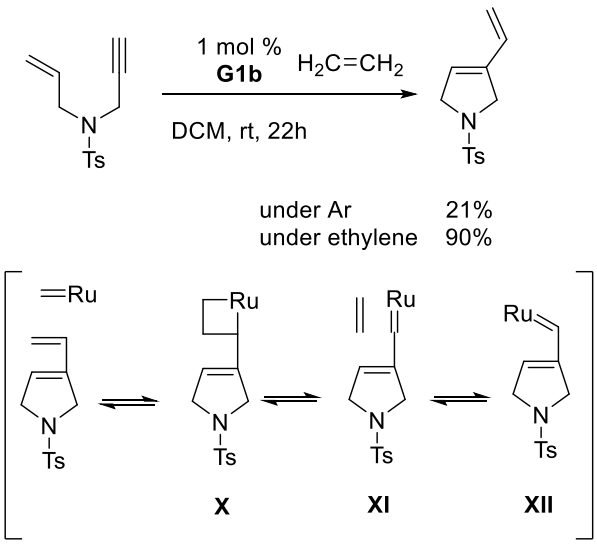


Scheme 38. Ruthenium-catalyzed enyne metathesis.

The reaction proceeds by [2+2]-cycloaddition of carbene complex and the alkyne moiety of the enyne to form **VII**, followed by a ring opening of this complex to give **VIII**, which reacts later with the alkene moiety intramolecularly to afford **IX**. Ring opening of this complex gives the final product, and a methylidene carbene complex was reproduced. Even if the

reaction starts from [2+2]-cycloaddition of carbene complex and the alkene, a similar reaction pathway should be followed.

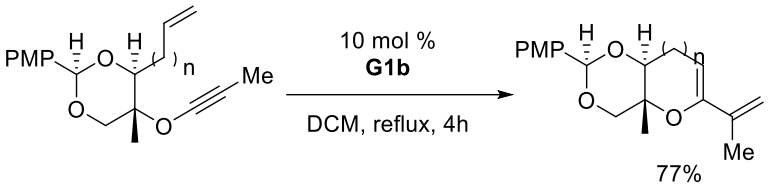
In this reaction, although enynes having a disubstituted alkyne affords cyclized compounds in high yields, enynes having a terminal alkyne did not give good results. The problems encountered with these kind of substrates were identified as a result of the reaction of the terminal alkene moiety of the diene with the carbene complex that afforded ruthenium carbene complex **X** coordinated by the alkene. When the reaction was carried out under ethylene gas the desired compound was obtained in high yield, because methylidene-carbene complex would be regenerated from complex **XI** under ethylene gas.[38] The presence of ethylene gas helps to maintain the concentration of active catalytic species, methylidene-ruthenium complex, higher than in absence of the gas by inhibiting the reaction of the active species with the diene product (Scheme 39) .



Scheme 39. Terminal alkyne-ene metathesis.

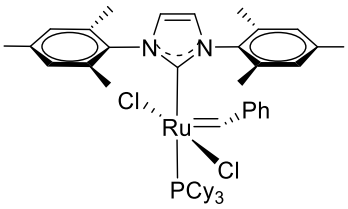
[38] Mori, M; Sakakibara, N.; Kinoshita, A. *J. Org. Chem*. **1998**, *63*, 6082-6083.

Ring-closing metathesis of enynes (RCEYM) was used for the synthesis of various useful compounds. Clark and coworkers reported the synthesis of alkenyl-substituted cyclic enol ether from alkynyl ether using complex **G1b** as catalyst (Scheme 40).[39]



Scheme 40. RCEYM using ruthenium-carbene complex **G1b** as catalyst.

The development by Herrmann, Nolan, and Grubbs at the end of the past century of the called second-generation ruthenium-carbene complexes, which have greater reactivities than those of the first-generation ruthenium-carbene complexes, offered new opportunities to the RCEYM reaction (Scheme 41). [40]



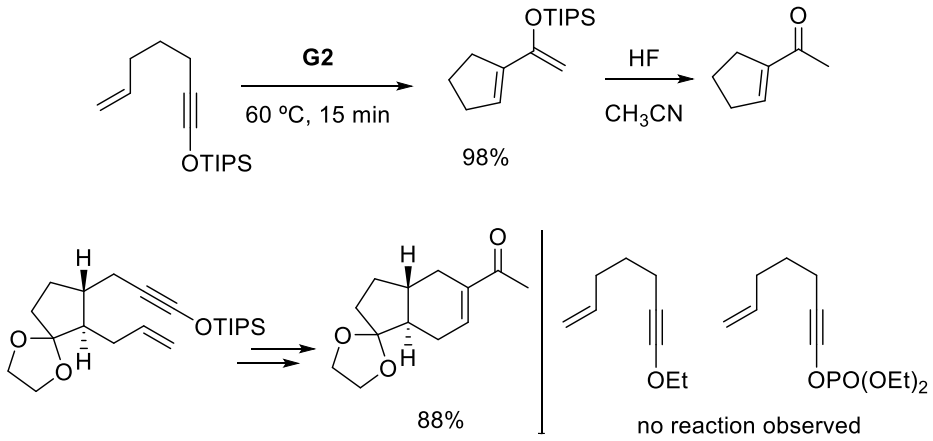
G2

Scheme 41. Second-generation ruthenium-carbene complex.

[39] Clark, J. S.; Trevitt, P.; Botali, D.; Stammen, B. *Chem. Comm*. **1998**, 2629-2633.

[40] a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1998**, *37,* 2490-2493. b) Huang, J., Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 2674-2678. c) Scholl, M.; Trnka, T.M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron. Lett*. **1999**, *40*, 2247-2250.

Using second-generation ruthenium-carbene complex **G2**, Kozmin *et al.* reported siloxyalkyne-alkene metathesis.[41] The reaction proceeded smoothly in the presence of **G2**, and the desired product was obtained in high yield. Deprotection of the silyl group of the metathesis product afforded the methyl ketone product. In a similar manner, ketone product was obtained from cyclic acetal substrate in 88% yield. Interestingly, in the case of ethoxy alkyne or alkynyl phosphate, no detectable amount of the corresponding metathesis product was formed (Scheme 42).

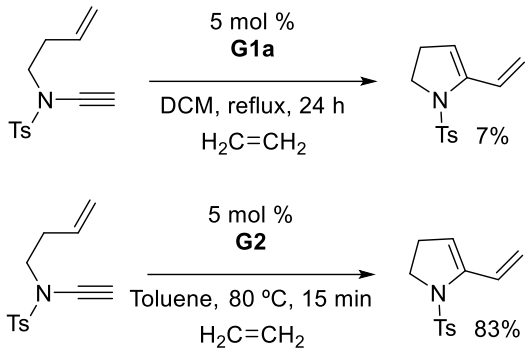


Scheme 42. RCEYM using ruthenium-carbene complex **G2** as catalyst.

Small ring nitrogen heterocycles such pyrrolines and tetrahydropyridines have been successfully prepared from the appropriate amines via RCEYM reactions. The synthesis of these molecules received continuous attention, because nitrogen heterocycles represent the core of many natural products. For example, metathesis reaction of ene-ynamide substrate using catalyst **G2** under ethylene gas afforded a pyrrolidine derivative having a dienamide moiety.[42] Use of first-generation ruthenium-carbene complex **G1a** afforded a small amount of this compound (Scheme 43).

[41] Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4274-4277.

[42] Saito, N.; Sato, Y.; Mori, M. *Org. Lett*. **2002**, *4*, 803-805.

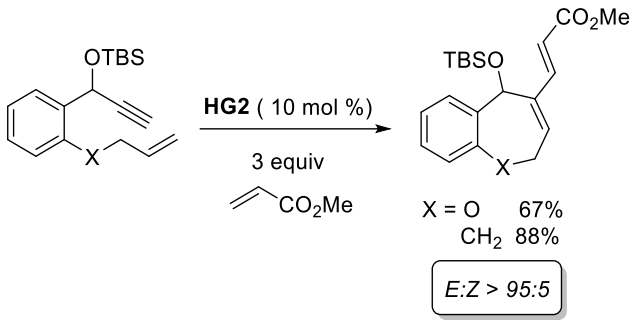


Scheme 43. Ring-closing metathesis of ene-ynamide.

Furthermore, the possibility of performing an *exo* cross enyne metathesis reaction between the triple bond of the enyne and a monoalkene would widen the structural diversity of the final products (Scheme 44).[43] For this reason, as well as their wide functional group tolerance, they have become a fundamental part of the modern synthetic chemist's toolkit.[44]

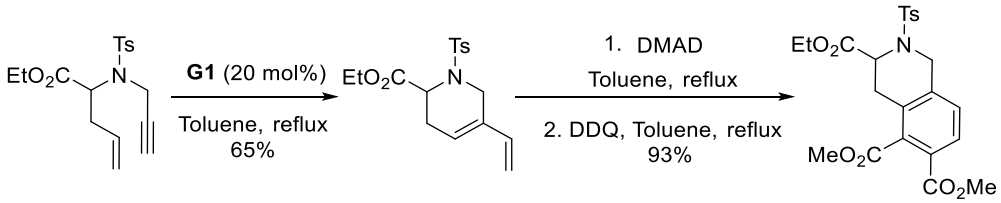
[43] a) Prada Gori, D. N.; Permingeat Squizatto, C.; Cornier, P. G.; Delpiccolo, C. M. L. *J. Org. Chem*. **2018**, *83*, 12798-12805; b) Arimitsu, S.; Hammond, G. B. *Beilstein J. Org. Chem*. **2010**, *6*, doi:10.3762/bjoc.6.48; c) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 2805-2808; d) Royer, F.; Vilain, C.; Elkaïm, L.; Grimaud, L. *Org. Lett*. **2003**, *5*, 2007-2009.

[44] a) Becker, M. R.; Watson, R. B.; Schindler, C. S. *Chem. Soc. Rev*. **2018**, *47*, 7867-7881; b) Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev*. **2015**, *115*, 871-930; c) Diver, S. T.; Griffiths, J. R.; in *Olefin Metathesis: Theory And Practice*, (Ed.: K. Grela), John Willey & Sons, Inc., Hoboken, NJ, **2014**, pp; 153-185; d) Vougioukalakis, G. C.; Grubbs, R.H. *Chem. Rev*. **2010**, *110*, 1746-1787; e) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199-2238; f) Diver, S. T.; Giessert, A. J.; *Chem. Rev*. **2004**, *104*, 1317-1382.



Scheme 44. *Exo* cross enyne metathesis between enyne and a monoalkene.

These ruthenium-catalyzed transformations have also been applied to various cascade reaction during the past decade,[45] often leading to the introduction of high molecular complexity in a single step, for example through coupling with Diels–Alder (DA) (Scheme 45) or other cyclization reactions to form polycyclic systems,[46] as well as in the synthesis of alkaloids and other natural products.



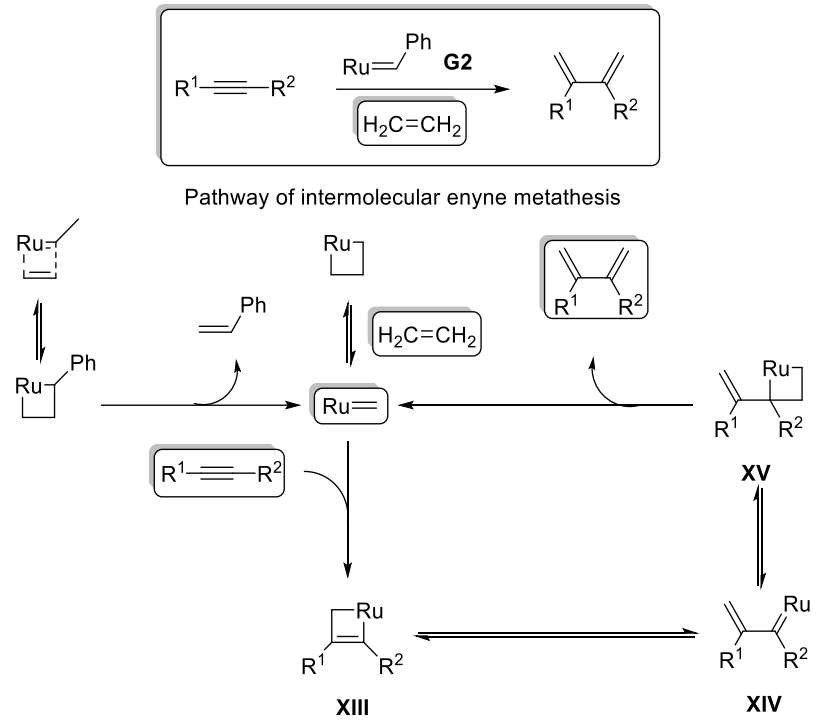
Scheme 45. Cascade reaction (RCEYM and DA) of 1,6-enyne.

[45] a) Letort, A.; Long, D. L.; Prunet, J. *J. Org. Chem*. **2016**, *81*, 1231-1233; b) Ma, C.; Letort, A.; Aouzal, R.; Wilkes, A.; Maiti, G.; Farrugia, L. J.; Ricard, J.; Prunet, J. *Chem. Eur. J*. **2016**, *22*, 6891-6899; c) Miró, J.; Sánchez-Roselló, M.; Sanz, A.; Rabasa, F.; del Pozo, C.; Fustero, S. *Beilstein J. Org. Chem*. **2015**, *11*, 1486–1493; d) Mukherjee, S.; Lee, D. *Org. Lett*. **2009**, *11*, 2916-2919.

[46] a) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev*. **2009**, *38*, 2065-2092; b) K. C. Shital, B. Titas, N. Kaushik, *Chem. Lett*. **2006**, *35*, 376-77; c) Y.-K. Yang, J.-H. Choi, J. Tae, *J. Org. Chem*. **2005**, *70*, 6995-6998; d) B. G. Kim, M. L. Snapper, *J. Am. Chem. Soc*. **2006**, *128*, 52-53; e) M. Eckert, F. Monnier, G. T. Shchetnikov, I. D. Titanyuk, S. N. Osipov, L. Toupet, S. Dérien, P. H. Dixneuf, *Org. Lett.* **2005**, *7*, 3741-3743.

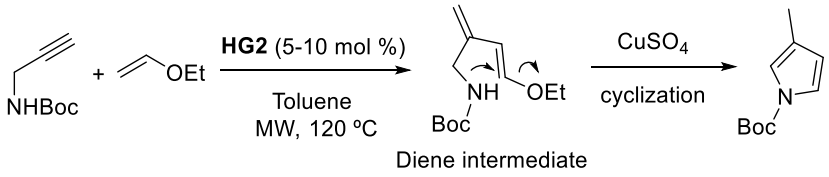
It is noteworthy that although the intramolecular variant of the reaction highly predominates in the reports, the intermolecular version of the alkyne/alkene metathesis (enyne cross metathesis, EYCM) is a unique and interesting reaction if it can be performed, but it is very difficult because it involves olefin metathesis, enyne metathesis, and diyne metathesis. It is likely that various olefins, dienes, and polymers would be formed by intermolecular enyne metathesis. Nevertheless, the use of methylidene-carbene complex **G2** in the presence of ethylene gas allowed circumvent these drawbacks, and a method for 1,3-diene synthesis from alkyne was developed using cross enyne metathesis. [47] The reaction course is shown in Scheme 46. Methylidene-carbene complex **G2** reacts with alkyne to give ruthenacyclobutene **XIII**. Ring opening of **XIII** affords ruthenium-carbene complex **XIV**, which reacts with ethylene and not with the alkyne, because ethylene is a very reactive species and this reaction is carried out under ethylene gas. Ring opening of complex **XV** affords 1,3-diene product. The reaction procedure is very simple. That is, a DCM solution of alkyne is stirred in the presence of ruthenium-carbene complex **G2** at room temperature under an atmosphere of ethylene gas for 48 h to give 1,3-diene in 71% yield (Scheme 46).

[47] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc*. **1997**, *119*, 12388-12389.



Scheme 46. Plan for 1,3-diene synthesis using intermolecular enyne metathesis.

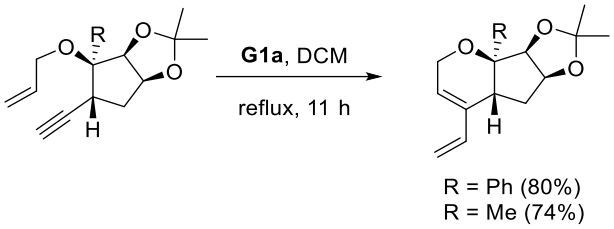
EYCM reactions, which represent the intermolecular variant of the reaction, have been comparatively less employed in the synthesis of small ring nitrogen heterocycles. One example of synthesis of pyrrole derivatives was reported by Castagnolo *et al.* by reacting propargylamines with ethyl vinyl ether (Scheme 47). [48]



Scheme 47. Synthesis of pyrrole derivatives *via* EYCM reaction.

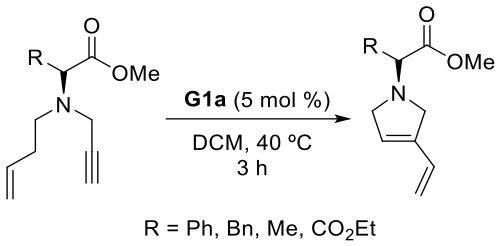
[48] Chachignon, H.; Scalacci, N.; Petricci, E.; Castagholo, D. *J. Org. Chem*. **2015**, *80*, 5287-5295.

As regards the preparation of chiral substrates *via* RCEYM reactions, it is a topic that has been progressively addressed. Examples of RCEYM reactions have been reported with different chiral enynes whose can be prepared following different approaches. One of these approaches is based in the chiral pool synthesis. In this way, Sayyad *et al.* carried out a RCEYM with different sugar derivatives to obtain chiral cyclic compounds using, in this case, complex **G1a** as catalyst (Scheme 48).[49]



Scheme 48. RCEYM of chiral sugar derivatives.

Also based in the chiral pool synthesis, Alper and coworkers synthetized chiral enynes derived of chiral amino acids. RCEYM reaction provided pyrrolidine derivatives with high yield. The reaction occurs smoothly under catalysis of complex **G1a** (first generation) and without the presence of ethylene gas (Scheme 49).[50]

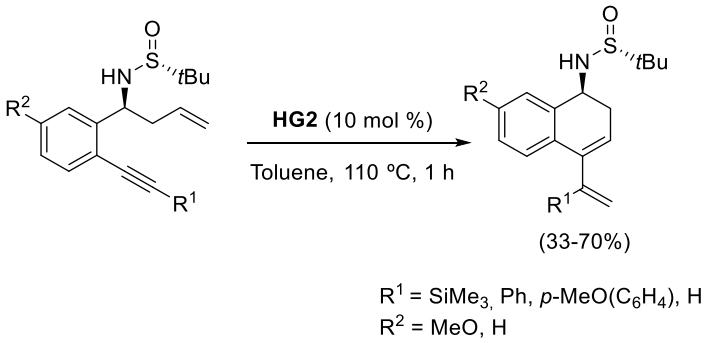


Scheme 49. RCEYM of chiral enynes derived from aminoacids.

[49] Sayyad, A. A.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2017**, 5055-5065.

[50] Yang, Q.; Alper, H.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 769-771.

A different strategy for access to the chiral enynes relies in the asymmetric allylation or propargylation of imines. The groups of Fustero and Yus independently applied this approach to the synthesis of a homoallyl amine by diastereoselective allylation of Ellman's imines. Once the enynes were prepared, RCEYM was carried out using **HG2** as catalyst (Scheme 50).[51]



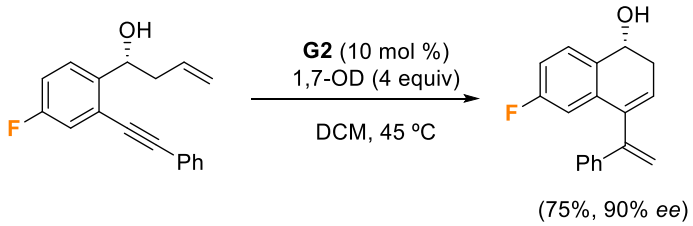
Scheme 50. RCEYM of chiral sulfonamides bearing Ellman's auxiliary.

It should be noted that despite the extensive development of the RCEYM reaction, there are only a few examples in which a halogen or halogen-containing groups are present in the enyne structure either the alkene part, the alkyne part or the linker part.

Asymmetric RCEYM of fluorinated enynes has been developed by Fustero's group, which carried out RCEYM with chiral fluorinated enynes obtaining both high diastereoselectivities and chemical yields (Scheme 51).[52]

[51] García-Muñoz, M. J.; Sirvent, A.; Foubelo, F.; Yus. M. *An. Acad. Bras. Cienc.* **2018**, 1059-1072.

[52] Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506-2514.



Scheme 51. RCEYM of chiral fluorinated enynes.

4. *Intramolecular Pauson-Khand reactions of fluorine containing compounds*

Despite the increasing demand of fluorinated compounds and the impressive development of the PKR, until now the combination of these two fields has been understudied. The Pauson–Khand reaction (PKR) formally consists of a [2+2+1]-cycloaddition between an alkyne, an olefin and carbon monoxide, resulting in the regioselective formation of a cyclopentenone derivative (Scheme 52).[53,54,55,56,57] This cobalt-mediated reaction was initially discovered by Pauson and Khand in the early of the 70s[58,59,60] and it has become a powerful tool widely used in the synthesis of polycyclic complex molecules. The intermolecular variant shows a wide alkyne scope, but in terms of the olefin counterpart is limited to the use of ethylene or strained alkenes, such as norbornene and norbornadiene.

[53]Ricker, J. D.; Geary, L. M. *Top. Catal.* **2017**, *60*, 609-619.

[54] The Pauson Khand Reaction. Scope, Variations and Applications; Ríos Torres, R., Ed; Wiley: Chichester, UK, **2012**.

[55] Lee, H.; Kwong, F. *Eur. J. Org. Chem.* **2010**, 789-811.

[56] Park, J. H.; Chang, K.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461-2480.

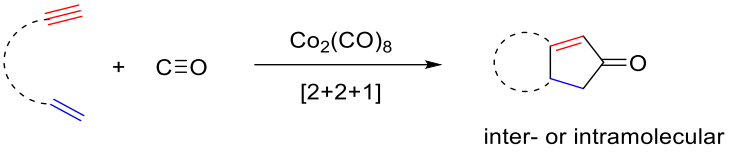
[57] Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32-42.

[58] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E., *J. Chem. Soc. D.* **1971**, 36a-36a.

[59] Khand, IU.; Knox, GR.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. Perkin Trans.* **1973**, *1*, 975-977.

[60] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans.* **1973**, *1*, 977-981.

The high prevalence of five-membered ring systems in natural products, pharmaceuticals and other added-value compounds accounts for the great applicability that this reaction has found. [61,62,63,64,65,66,67]



Scheme 52. Schematic representation of the PKR.

A fluorine atom or fluorine-containing group can influence the reaction outcome. Fluorine can be installed at either unsaturated counterpart, bound to either the olefin and/or the alkyne (*vide infra*) (Scheme 53) and in the intramolecular version, the fluorine atom or fluorinated group can also form a part of the linker. The reaction yields are dependent on the degree of substitution, bulkiness, and electronic effects of the substituents of both the alkyne and alkene moieties. In general, electron-deficient alkynes are poor substrates for the PKR as they are deactivated in the cobalt-complexation step, and the highest yields are usually obtained with terminal alkynes. The scenario is similar in the case of fluorinated substrates, with the intramolecular version being much more developed than the intermolecular one.

[61] García-Lacuna, J.; Domínguez, G.; Blanco-Urgoiti, J.; Pérez-Castells, J. *Org. Biomol. Chem.* **2019**, *17*, 9489-9501.

[62] Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 8431-8435.

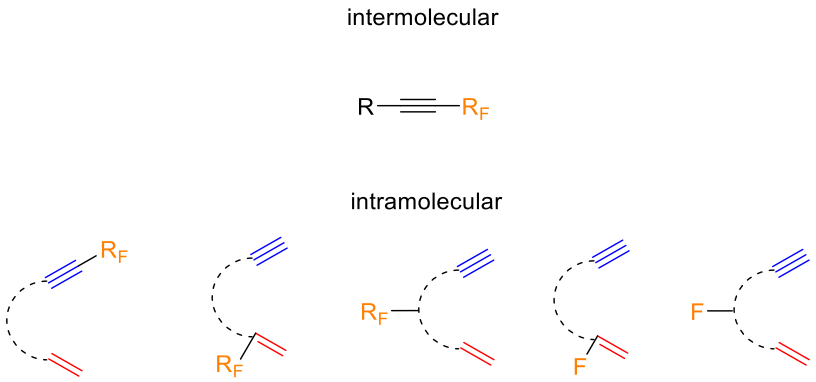
[63] Zhao, N.; Xie, S.; Tian, P.; Tong, R.; Ning, C.; Xu, J. *Org. Chem. Front.* **2019**, *6*, 2014-2022.

[64] Hu, N.; Dong, C.; Zhang, C.; Liang, G. *Angew. Chem. Int. Ed.* **2019**, *58*, 6659-6662.

[65] Kaneko, H.; Takahashi, S.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2019**, *84*, 5645-5654.

[66] Cabré, A.; Khaizourane, H.; Garcon, M.; Verdaguer, X.; Riera, A. *Org. Lett.* **2018**, *20*, 3953-3957.

[67] Huang, Z.; Huang, J.; Qu, Y.; Zhang, W.; Gong, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2018**, *57*, 8744-8748.



Scheme 53. Substrates included in this section.

The mechanism of reaction was proposed by Magnus over 30 years ago and is still valid nowadays,[68] although only the first intermediate (**XVI**) has been isolated and characterized.[69] Firstly, two coordination vacancies are freed after the extrusion of two carbon monoxide ligands from the starting cobalt species, allowing the alkyne group to bind to the cobalt metal centers. The subsequent coordination of the olefin counterpart requires the extrusion of a third carbon monoxide ligand, leading to pentacarbonyl complex **XVII**. This highly endotermic process is the rate-limiting step and long reaction times are generally associated to this. However, the reaction can be accelerated in conditions that facilitate the dissociation of CO ligands such as heating, microwave irradiation,[70,71] visible light, or ultrasonication.[72] Alternatively, mild oxidizing additives such as amine oxides,

[68] Magnus, P.; Principe, L. M. *Tetrahedron* **1985**, *26*, 4851-4854.

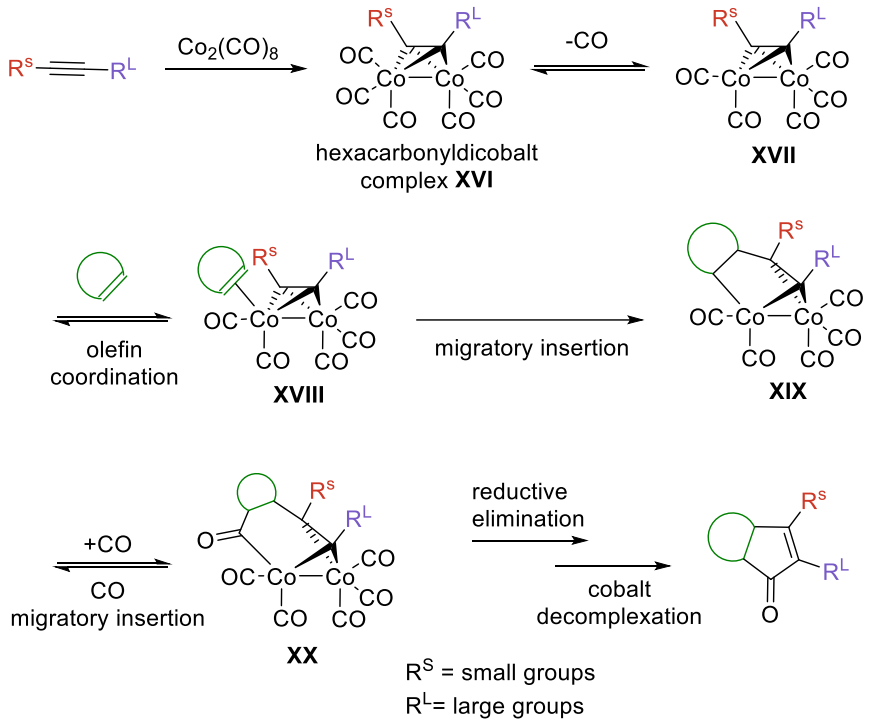
[69] An alkene–pentacarbonyldicobalt–alkyne complex of type III has also been isolated; however, it was shown not to evolve toward the final cyclopentenone product and, hence, it cannot be considered an intermediate in the PKR: Banide, E. V.; Müller-Bunz, H.; Manning, A. R.; Evans, P.; McGlinchey, M. J. *Angew. Chem. Int. Ed*. 2007, 46, 2907-2910.

[70] Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett*. **2002**, *43*, 7859-7862.

[71] Rodríguez, A. M.; Prieto; P. *Tetrahedron* **2016**, *72*, 7443-7448.

[72] Son, S. U.; Lee, S. I.; Chung, Y. K.; Kim,S.-W.; Hyeon, T. *Org. Lett*. **2002**, *4*, 277-279.

aminophosphines, phosphine oxides, and sulfoxides may be used as promoters to facilitate the dissociation step, by oxidatively removing one of the CO ligands in form of CO_2.[73] The most common oxidants are *N*-morpholine *N*-oxide (NMO), trimethylamine *N*-oxide (TMANO), and dimethyl sulfoxide (DMSO). Once a new coordination vacancy has been opened on one of the cobalt centers, coordination of the olefin sets the stage for the subsequent C–C bond forming steps. The olefin is inserted into the less hindered Co–C bond, determining both the regio- and stereochemical outcome of the overall process. A carbon monoxide ligand then undergoes migratory insertion into one of the Co–C bonds in cobaltacycle **XX**, followed by reductive elimination to release the final product (Scheme 54).



Scheme 54. Commonly accepted mechanism for the PKR.

[73] Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S.; Yoo, S.-E. *Synlett.* **1991**, 204-206.

Many deviations from the classic reaction conditions have been described, including the use of metals other than cobalt (such as rhodium, iridium, titanium, ruthenium, nickel, and palladium), or the use of CO surrogates such as aldehydes, alcohols and formates. Recently, its utility in flow chemistry has also been described.[74]

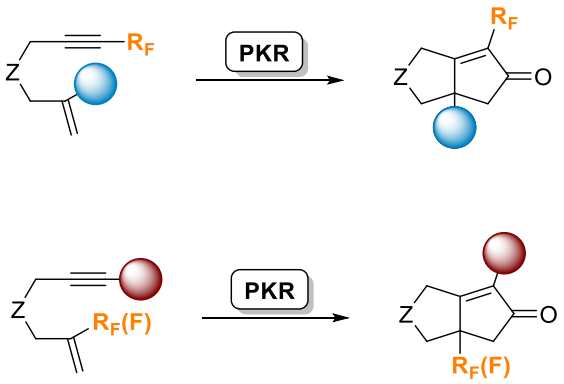
The utility of the Pauson-Khand reaction in the preparation of polycyclic compounds bearing both nitrogenated and cyclopentenone rings, two ubiquitous domains in drugs and natural products, has been reported in various contributions using 1,n-enynes, particularly 4-aza-1,7-enynes as starting materials.[75,76,77] However, the synthesis of fluorinated 1,n-enynes as well as the corresponding Pauson-Khand adducts has, until recently, scarcely been described in the literature. The intramolecular version of this reaction has recently gained recognition since it facilitates the synthesis of cyclopentenone-fused ring systems, which tend to be difficult to construct. The Pauson-Khand reaction has also been used as a key step in the synthesis of a number of biologically-relevant compounds, including fluorine-containing piperidine-fused cycles. Of course, where the fluorinated group is positioned in the final compound depends on whether it is attached to the alkene or alkyne counterpart of the substrate (Scheme 55).

[74] Lam, F. L.; Lee, H. W.; Wang, J.; Kwong F. Y. In Recent Advancement of Catalytic Pauson-Khand-type Reactions. The Pauson Khand Reaction. Scope, Variations and Applications; Ríos Torres, R., Ed; Wiley: Chichester, UK, 2012, pp181-210.

[75] Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377-5381.

[76] Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett*. **2006**, *8*, 83-86.

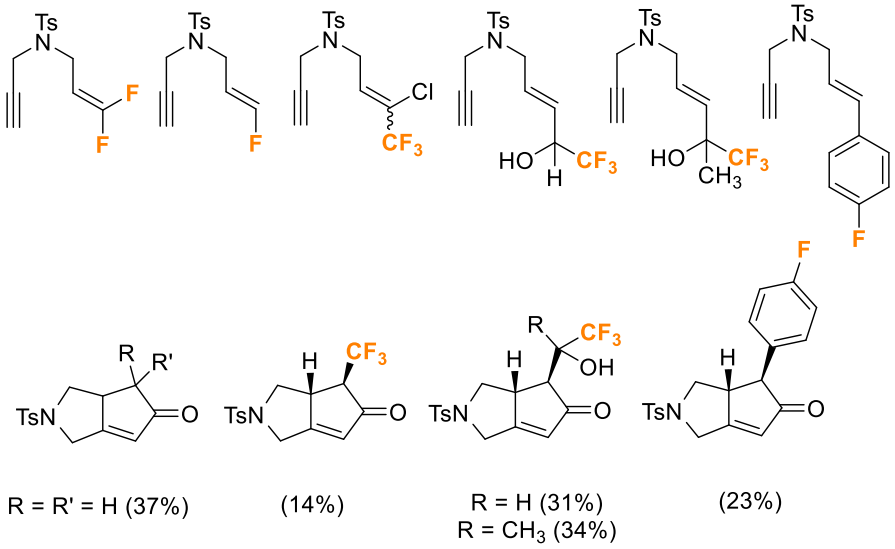
[77] Miller, K. A.; Shanahan, C. S.; Martin, S. F. *Tetrahedron* **2008**, *64*, 6884-6900.



Scheme 55. Variability at the acetylenic and olefinic counterpart.

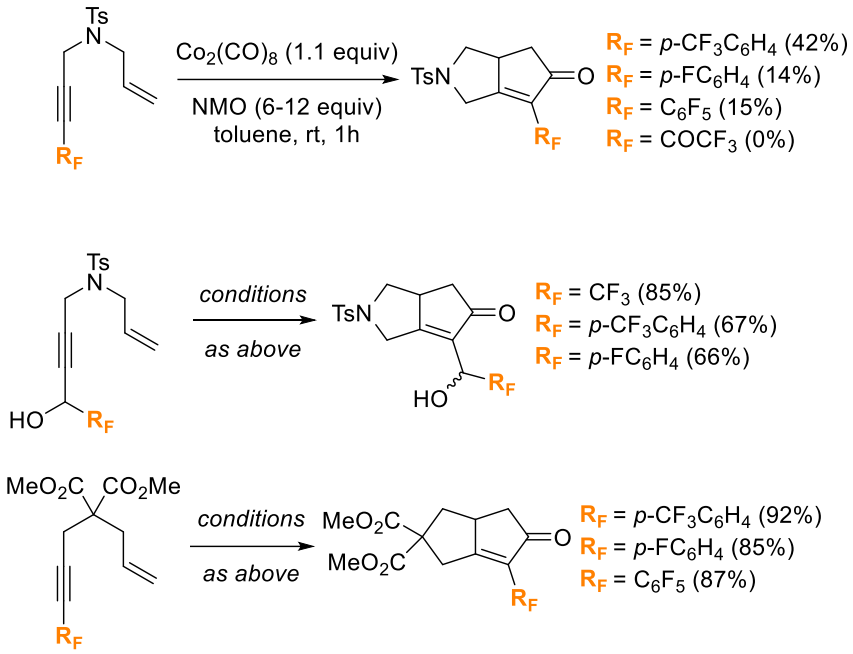
Regarding the intramolecular PKR of fluorinated enynes, only a few examples have been described. The first example was reported in 2001 by Ishizaki and coworkers.[78] In this study, a wide variety of 1,6-enynes bearing fluorine atoms or fluorine-containing groups at the alkenyl or alkynyl positions were synthesized and evaluated as substrates in the intramolecular PKR with dicobalt octacarbonyl [$Co_2(CO)_8$] in CH_2Cl_2 and promoted by NMO. In general, the presence of fluorinated groups on the alkenyl moiety of the 1,6-enyne resulted in low yields (lower than 35%) of the corresponding cyclized products, due to the poor reactivity of the fluorinated olefin (Scheme 6). For example, difluoroalkene-containing compound decomposed and no cyclized product was formed. In this NMO-promoted PKR, monofluoroolefinic enyne afforded the defluorinated cyclopentenone in 37% yield. Similarly, trifluoromethyl-substituted olefin also lost the chlorine atom upon cyclization to give the bicycle ciclopentenone as a single diastereoisomer, albeit in a low 14% yield. The reaction of trifluoromethyl-substituted allylic alcohols afforded the corresponding cyclized products and (31% and 34% yield, respectively) as inseparable diastereoisomeric mixtures. Finally, 1,6-enyne bearing a 4-fluorophenyl group on the olefin, stereoselectively produced *trans*-oriented arylcyclopentenone in 23% yield (Scheme 56).

[78] Ishizaki, M.; Suzuki, D.; Hoshino, O. *J. Fluorine Chem*. **2001**, *111*, 81-90.



Scheme 56. PKR of fluoroolefinic enynes reported by the group of Ishizaki.

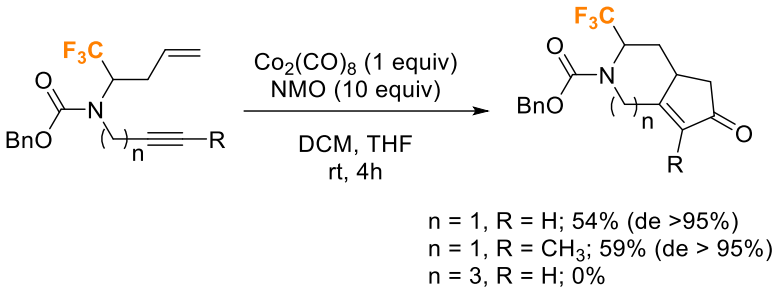
When investigating the intramolecular PKR of enynes bearing fluorine groups on alkynyl moiety, several trends could be observed. Firstly, fluoroaromatic enynes afforded the corresponding cyclized products in low yields (14–42%). However, no cyclized product was observed when using the trifluoromethyl ketone derivative. Secondly, PKR with enynes containing fluorinated propargyl alcohol groups yielded diastereoisomeric mixtures of pyrrolidine ring-fused cyclopentenones in good yields (67–85%) but low diastereoselectivities. Finally, the reaction of dimethyl malonate-derived fluoroaromatic enynes afforded the corresponding cyclopentenone products in higher yields (85–92%). Thus, the reaction of enynes bearing fluorinated groups attached to the alkyne moiety afforded the corresponding cyclized products in moderate to high yields, except for *N*-bridged enynes bearing electron withdrawing groups at the alkyne part and amide type linkage (Scheme 57).



Scheme 57. PKR of enynes bearing fluorinated groups on the alkynyl moiety, reported by the group of Ishizaki.

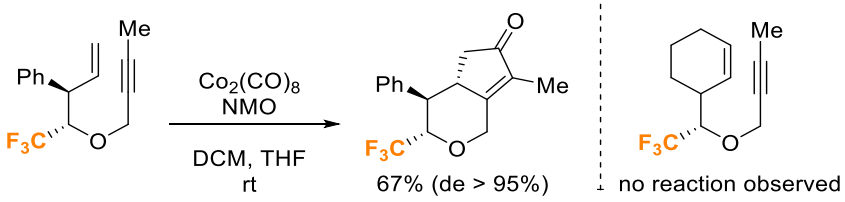
In 2005, Billard and coworkers reported the PKR of α-trifluoromethylated homoallylamine derivatives (Scheme 58).[79] Both 1,7-enynes containing terminal alkyne and methylated alkyne (n=1) underwent PKR in the presence of 1 equiv of $Co_2(CO)_8$ and 10 equiv of NMO, yielding bicyclic derivatives in moderate yields and high diastereoselectivity (*de* >95%). The observed diastereoselectivity was rationalized considering two transition states of the PKR, and assuming the CF_3 group occupies an axial position due to the steric and electrostatic repulsions that occur in the equatorial position. Consequently, in the most favorable transition state there is no steric hindrance between the CF_3 group and the ethylenic hydrogen, leading to the observed diastereoisomer. On the other hand, the use of 1,9-enyne (n=3) did not afford the corresponding bicyclic compound since the double and triple bonds are too distant.

[79] Ferry, A.; Billard, T.; Langlois, B. R. *Synlett* **2005**, *6*, 1027-1029.



Scheme 58. Intramolecular PKR of 1,7-enynes reported by the group of Billard.

In a following paper by Billard and coworkers, the PKR of oxygen-containing 1,7-enynes was assayed, affording trifluoromethylated oxygenated bicyclic enones (Scheme 59). [80] Under classical stoichiometric conditions [reaction with $Co_2(CO)_8$ followed by the addition of NMO], and starting from the pure *anti* diastereoisomer of 1,7-enyne, the expected bicyclic ciclopentenone was obtained in good yield and high diastereoselectivity (de >95%). An attempt to extend the PKR to the formation of a fused tricyclic structure, starting from cyclohexene containing 1,7-enyne, was unsuccessful and no tricyclic product was formed.



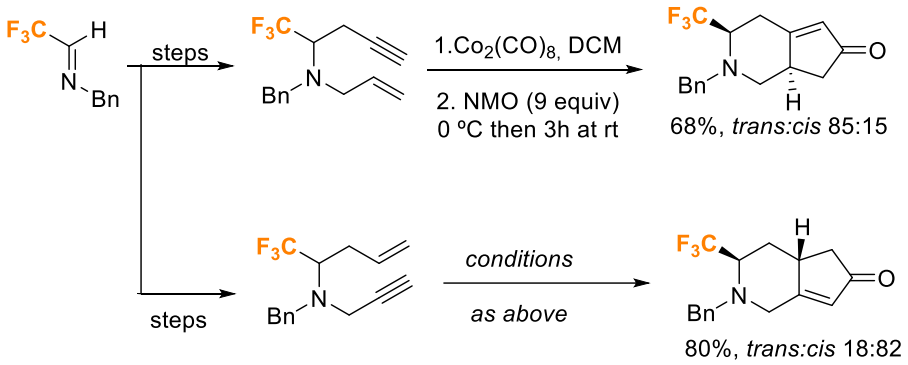
Scheme 59. Intramolecular PKR of 1,7-enynes reported by the group of Billard.

Bonnet-Delpon and coworkers reported the one-pot synthesis of several CF_3-containing *N*-tethered amines in good yields (54-86%, over 2 steps).[81] These products were subjected to

[80] Harthong, S.; Billard, T.; Langlois, B. R. *Synthesis* **2005**, 13, 2253-2263.

[81] Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem*. **2005**, 1258-1265.

metathesis reactions in the presence of Grubbs catalyst affording the corresponding CF_3-containing dehydropiperidine derivatives in excellent yields. Additionally, this enynes were evaluated as substrates in the intramolecular PKR, yielding the corresponding CF_3-containing heterobicyclic derivatives in 68% (85:15 ratio of *trans*/*cis* stereoisomers) and 80% yield (18:82 ratio of *trans/cis* stereoisomers), respectively (Scheme 60).

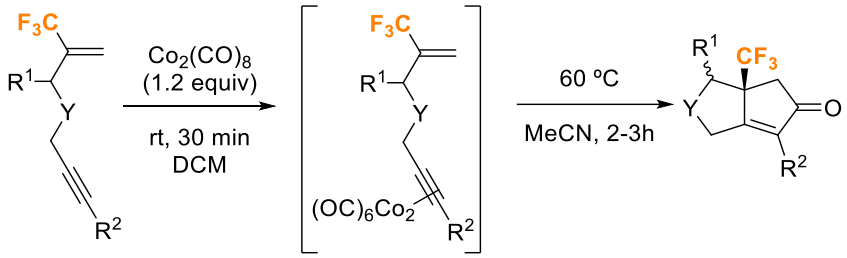


Scheme 60. Intramolecular PKR of 1,7-enynes by the group of Bonnet-Delpon.

Ichikawa and coworkers described an attractive route to synthesize pyrrolidine ring-fused fluorinated cyclopentenone analogs via intramolecular PKR starting from 2-bromo-3,3,3-trifluoroprop-1-ene.[82]

To this end, *N*-propargyl-*N*-[2-(trifluoromethyl)allyl] amides were treated with dicobalt octacarbonyl to afford the cobalt alkyne complex, which was then heated in CH_3CN. Under these conditions, trifluoromethylated cyclopentenone was obtained in high yield (81%) and diastereoselectivity (*anti*/*syn*=94:6) (Scheme 61). The cyclization of internal alkyne substrate yielded pyrrolidine ring-fused cyclopentenone in similar yield but lower diastereoselectivity. Finally, *N*-propargyl-*N*-[2-(trifluoromethyl)allyl] ether, containing an ether linkage instead of the aforementioned sulfonamide linkage, gave furan ring-fused cyclopentenone in both lower yield (53%) and lower diastereoselectivity.

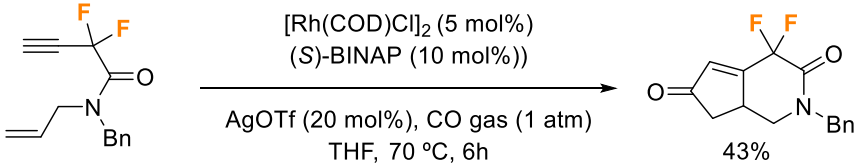
[82] Nadano, R.; Ichikawa, J. *Chem. Lett*. **2007**, *36*, 22-23.



Y = NTs; R^1 = Ph; R^2 = H; 81%; *anti/syn* 94:6
Y = NTs; R^1 = Ph; R^2 = Et; 85%; *anti/syn* 83:17
Y = NTs; R^1 = Pr; R^2 = H; 71%; *anti/syn* 86:14
Y = O; R^1 = Ph; R^2 = H; 53%; *anti/syn* 64:36

Scheme 61. Intramolecular PKR of 1,6-enynes reported by the group of Ichikawa.

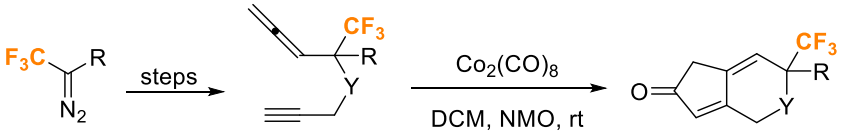
A catalytic PKR of fluorinated 1,7-enyne amides using catalytic amounts of $[Rh(COD)Cl]_2$ was reported in 2008 by Hammond and coworkers.[83] The authors concluded that the reaction was highly sensitive to experimental parameters such as solvent, concentration, temperature, catalyst and silver salt. Under standard reaction conditions, no reaction was observed in the absence of a silver salt, and the best results were obtained in the presence of AgOTf (20 mol%), giving the corresponding *gem*-difluorinated bicyclic lactam in 43% yield (Scheme 62). This reaction was limited to unsubstituted alkynes, as the PKR did not occur with a phenyl-substituted alkyne. Unfortunately, no asymmetric induction was observed.



Scheme 62. Intramolecular Rh(I)-catalyzed PKR reported by the group of Hammond.

[83] Arimitsu, S.; Bottom, R. L.; Hammond, G. B. *J. Fluorine Chem*. **2008**, *129,* 1047-1051.

In 2011, Osipov and coworkers investigated the cobalt-mediated PKR of allenynes in order to synthesize trifluoromethylated nitrogen- and sulfur-based bicyclic compounds (Scheme 63).[84] Using this methodology, the corresponding cyclopentenones were isolated in generally good yields, except for sulfur-containing derivatives, due to the oxidation of the sulfide under the reaction conditions. In contrast, the phosphorus analog was obtained in 45% yield, which could be explained by favorable electronic and steric effects of phosphonate group.

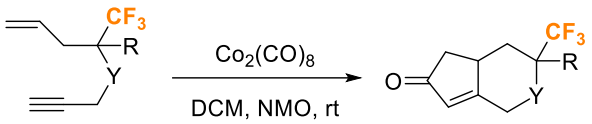


Y = NMe; R = CO_2Me; 52%
Y = NMe; R = $P(O)(OEt)_2$; 48%
Y = S; R = CO_2Me; 5%
Y = S; R = $P(O)(OEt)_2$; 45%

Scheme 63. Intramolecular PKR of allenynes reported by the group of Osipov.

In the same work, the authors also evaluated the PKR of CF_3-substituted enynes. In this case, bicyclic products were formed as mixtures of separable diastereoisomers, which could be isolated in higher yields than the products of the corresponding reaction with allenynes (Scheme 64).

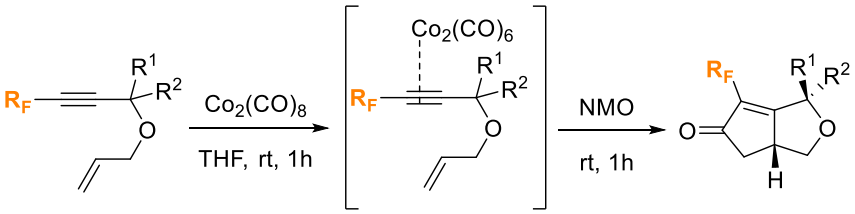
[84] Vorobyeva, D. V.; Mailyan, A. K.; Peregudov, A. S.; Karimova, N. M.; Vasilyeva, T. P.; Bushmarinov, I. S.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Tetrahedron* **2011**, *67*, 3524-3532.



Y = NMe; R = CO_2Me; 68%; *syn/anti* 83:17
Y = NMe; R = $P(O)(OEt)_2$; 81%; *syn/anti* 35:65
Y = S; R = CO_2Me; 40%; *syn/anti* 62:38
Y = S; R = $P(O)(OEt)_2$; 59%; *syn/anti* 75:25

Scheme 64. Intramolecular PKR of 1,7-enynes reported by the group of Osipov.

In 2012, Konno and coworkers studied the intramolecular PKR using fluorine-containing 1,6-enynes (Scheme 65.[85] The PKR of fluorinated propargyl allyl ether afforded the corresponding *cis* bicyclic product in moderate yield and high diastereoselectivity (*dr* >20:1). Other fluorinated allyl propargyl ethers, afforded the corresponding bicyclic PK-adducts in moderate chemical yields but in a highly *cis*-selectivity. Astonishly, a subtle change of the fluoroalkyl group from a CF_3 group to a CHF_2 group completely inhibited the reaction.



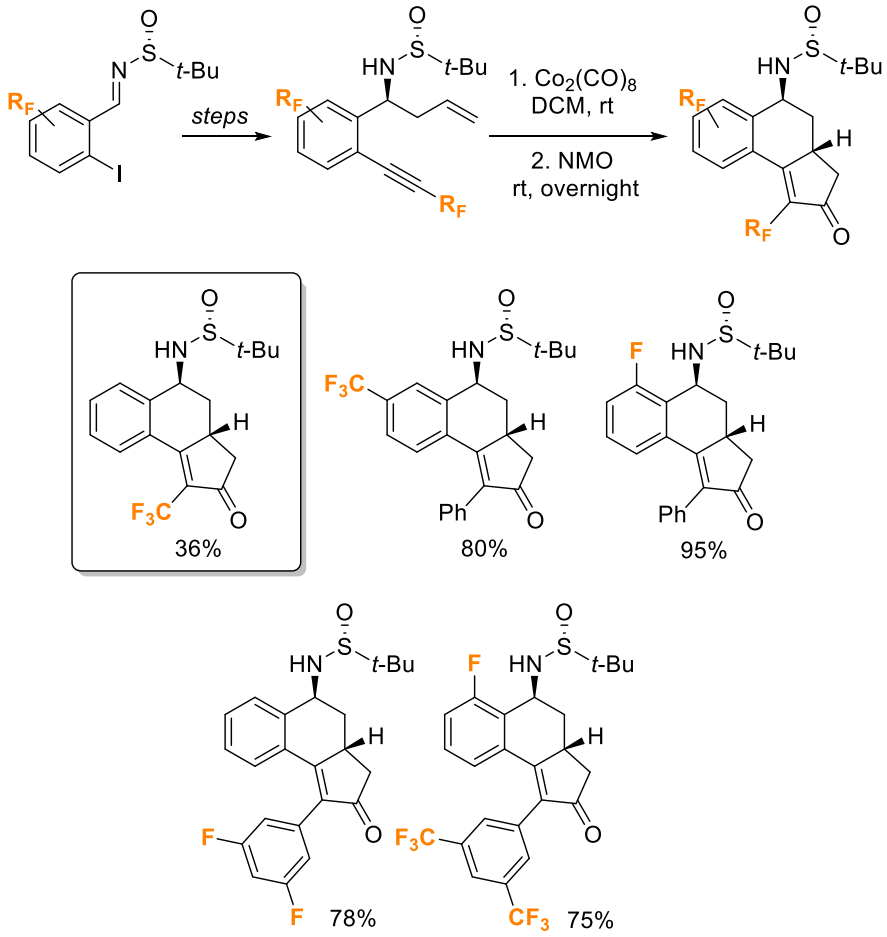
R_F = CF_3; R^1 = *n*-Hex; R^2 = H; 50%
R_F = CF_3; R^1 = $PhCH_2CH_2$; R^2 = H; 45%
R_F = CF_3; R^1 = *c*-Hex; R^2 = H; 35%
R_F = CF_3; R^1 = Et_2CH; R^2 = H; 51%
R_F = CF_3; R^1, R^2 = $-(CH_2)_5-$; 28%
R_F = CHF_2; R^1 = *n*-Hex; R^2 = H; 0%

Scheme 65. Intramolecular PKR of fluorine-containing 1,6-enynes reported by Konno's group.

[85] Konno, T.; Kida, T.; Tani, A.; Ishihara, T. *J. Fluorine Chem*. **2012**, *144*, 147-156.

Within the frame of a broader study, our group reported a single example of an intramolecular PKR using an Ellman's imine-derived CF_3-containing enyne, bearing the trifluoromethylethynyl group at the *ortho* position. [86] One of the key steps in the preparation of the starting 1,n-enynes was a highly diastereoselective allylation reaction of chiral Ellman's sulfinylimines. Based on this strategy, chiral 1,7-enynes were prepared in three steps from sulfinylimines derived of *o*-iodobenzaldehydes. A variety of fluorinated compounds bearing fluorine or fluoroalkyl groups attached to the aryl moieties were efficiently prepared (Scheme 66). In this report, the suitability of enynes bearing CF_3-substituted alkyne moieties (R = CF_3) to participate in intramolecular PK reactions was also demonstrated. Furthermore, several other substrates bearing fluorine at different positions were included. The process took place with moderate to high chemical yields and diastereoselectivities. This transformation can be performed on a multigram scale, and is characterized by a broad substrate scope, functional group compatibility, and high chemo- and diastereoselectivity.

[86] Fustero, S.; Lázaro, R.; Aiguabella, N.; Riera, A.; Simón-Fuentes, A.; Barrio, P. *Org. Lett*. **2014**, *16*, 1224-1227.

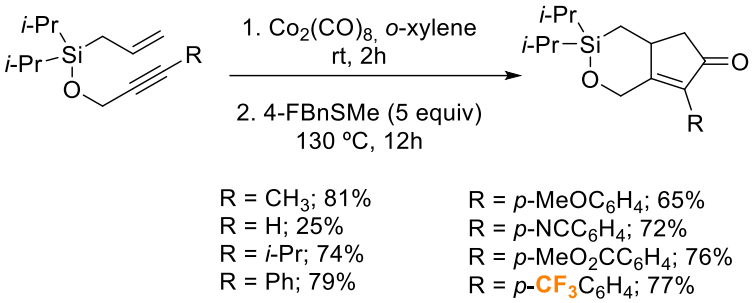


Scheme 66. Diastereoselective PKR with enantioenriched fluorinated enynes.

Martínez-Solorio and coworkers reported an intramolecular PKR of Si–O tethered 1,7-enynes, affording cyclopentaoxasilinones with high diastereoselectivity.[87] In contrast to previous silicon-based tethers, which reacted in low yields and resulted in unexpected byproducts, this transformation could be performed on a multigram scale and showed a

[87] Gallagher, A. G.; Tian, H.; Torres-Herrera, O. A.; Yin, S.; Xie, A. X.; Lange, D. M.; Wilson, J. K.; Mueller, L. G.; Gau, M. R.; Carroll, P. J.; Martínez-Solorio, D. *Org. Lett*. **2019**, *21*, 8646-8651.

wide substrate scope and functional group compatibility, as well as high and diastereoselectivity.[88,89] In this work, Si–O tethered 1,7-enynes underwent the PKR after treatment with 1.05 equiv of $Co_2(CO)_8$ using 4-fluorobenzyl(methyl)sulfide (4-FBnSMe) as an additive, which is commercially available and can be easily recovered by flash chromatography. Under the aforementioned conditions, cyclopentaoxasilinone was isolated in 81% yield. A systematic study of the scope showed that unsubstituted enyne only afforded the desired product in 25% yield. In contrast, isopropyl and phenyl substituted enynes yielded cyclopentaoxasilinones in 74 and 79% yield, respectively. Furthermore, electron-withdrawing *para*-substituted arenes were obtained in good yields and demonstrate excellent functional group compatibility; MeO- (65%), –CN (72%), $-CO_2Me$ (76%) and fluorinated groups such as *p*-$CF_3C_6H_4$ (77%) (Scheme 67).

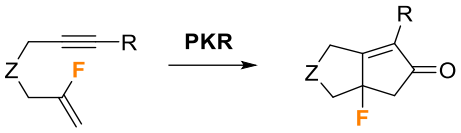


Scheme 67. Intramolecular PKR reported by Martinez-Solorio's group.

Concerning the intramolecular PKR with fluorine atoms or fluorinated groupings at the vinylic position, very few examples have been described to date. In this context, our group recently explored the reactivity of 1,n-enynes bearing a vinyl fluoride moiety as the olefin counterpart in the intramolecular PKR (Scheme 68).

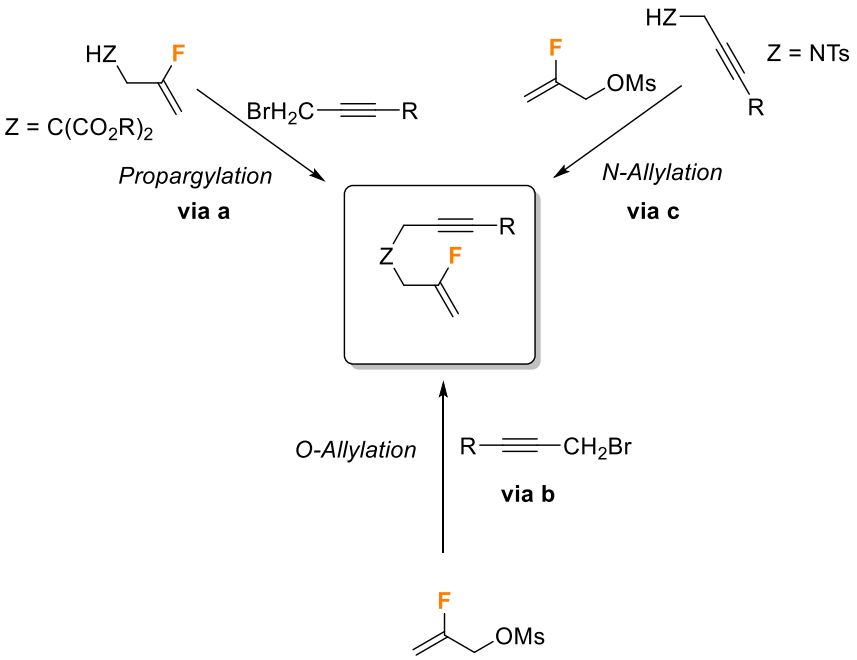
[88] Dobbs, A. P.; Miller, I. J.; Martinovic, S. *Beilstein J. Org. Chem*. **2007**, *3*, No. 21, doi:10.1186/1860-5397-3-21.

[89] Ishaq, S.; Porter, M. J. *Synth. Commun*. **2006**, *36*, 547-557.



Scheme 68. Fluorine substitution at the olefinic counterpart.

The study of the behavior of this kind of compounds in the PK reaction started with fluorinated enynes derived from malonates and those containing heteroatoms as linkers. The synthesis of the starting fluorinated enynes was accomplished following various approaches (Scheme 69).

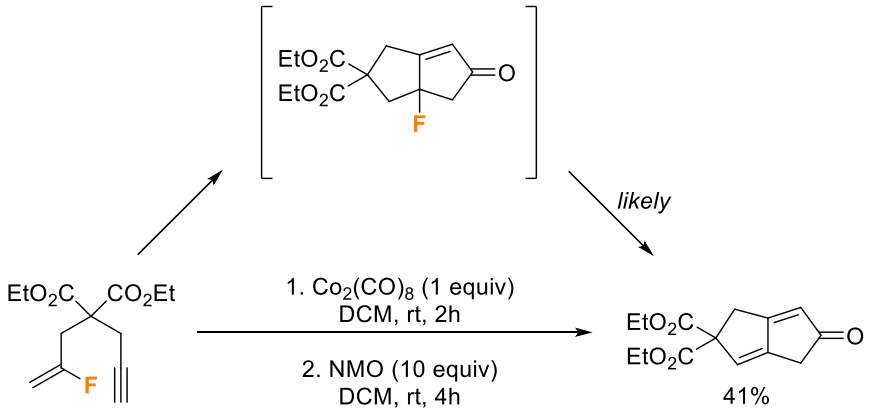


Scheme 69. Synthesis of fluorinated enynes.

The first of these (*via a*) was based on a report by Hammond and coworkers, in which they detailed the Markonikov hydrofluorination of alkynes using HF·DMPU coupled with a gold

catalyst.[90] Accordingly, the appropriate propargylmalonate derivatives were fluorinated to give fluoroalkene intermediates, which were then converted into malonate-based enynes (Z= CO_2R) through a simple propargylation procedure. In addition, the fluoroallyl alcohol was employed as a starting material to obtain the corresponding propargyl ethers (Z= O) by Williamson's synthesis using propargyl bromides in moderate yields (*via b*). Activation of the fluoroallyl alcohol by conversion into the corresponding mesylate proved sufficient for the synthesis of *N*-tethered substrates (Z= NTs), through simple nucleophilic substitution (*via c*).

It is noteworthy that under standard PK reaction conditions, malonate fluoroenyne evolves to a diene product. The formation of this compound is possible by elimination of HF from the PK product, meaning that the fluoro-PKR does initially take place and that the desired product could be isolated by avoiding the subsequent elimination reaction. This hypothesis was confirmed when the less basic DMSO was used as the promoter instead of NMO, allowing the successful isolation of the desired compound (Scheme 70). [91]

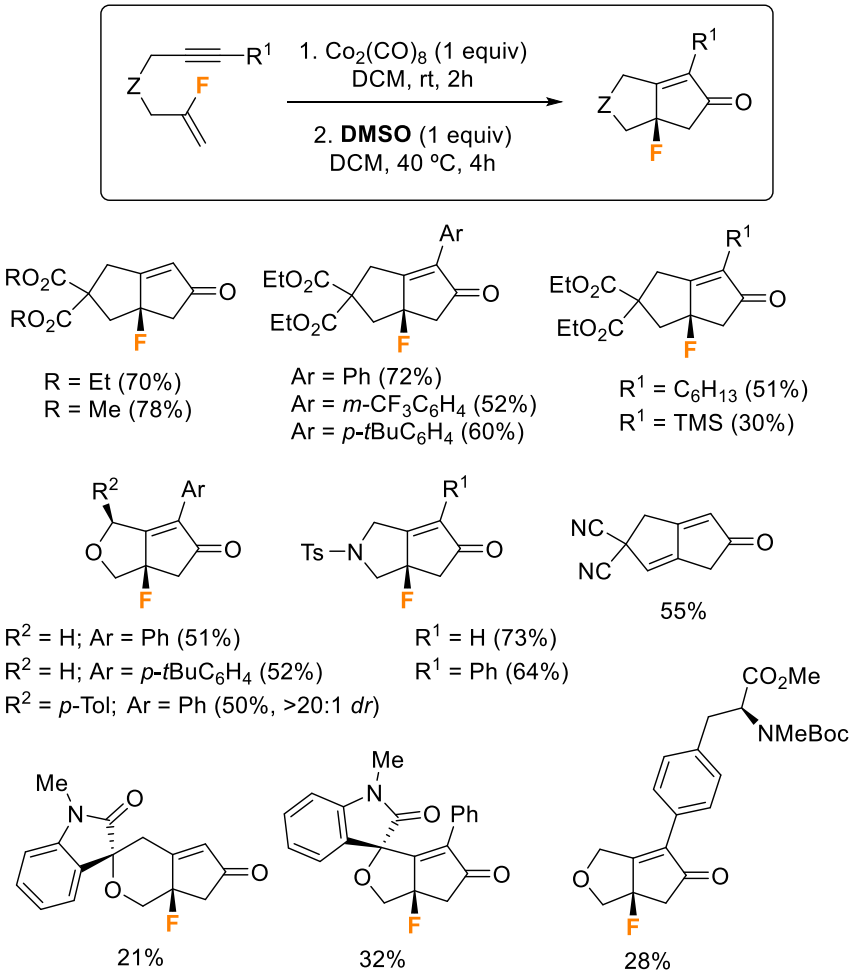


Scheme 70. Fluorine-containing substrates in PKR: Preliminary results.

[90] Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2014**, *136*, 14381-14384.

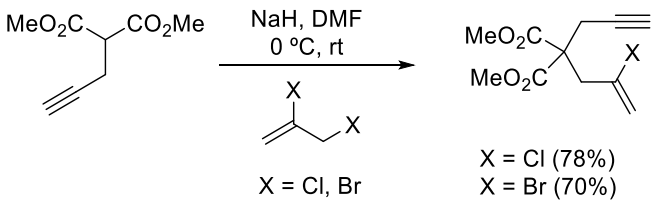
[91] Román, R.; Mateu, N.; López, I.; Medio-Simón, M.; Fustero, S.; Barrio, P. *Org. Lett.* **2019**, *21*, 2569-2573.

Under the optimized conditions, using stoichiometric $Co_2(CO)_8$ and DMSO as the promoter, the process worked well and moderate to good yields were obtained for derivatives bearing aryl substituents at the propargyl moiety, regardless of their electronic nature. Alkyl-substituted derivatives also afforded similar chemical yields as for aromatic substituents; however, TMS-substituted derivative was obtained in a significant lower yield. Regarding the use of linkers other than malonates, while heteroatomic ones (*i.e.* ethers or sulphonamides) were well-tolerated, when malononitrile was used as the tether, the elimination product was exclusively obtained under a variety of reaction conditions tested. More complex biorelevant examples such as isatin derivatives were also suitable substrates, affording the corresponding spirocyclic derivatives, albeit in low yield (Scheme 71). In the case of thioethers and sulfones no reaction was observed, and the starting materials were recovered in all cases.



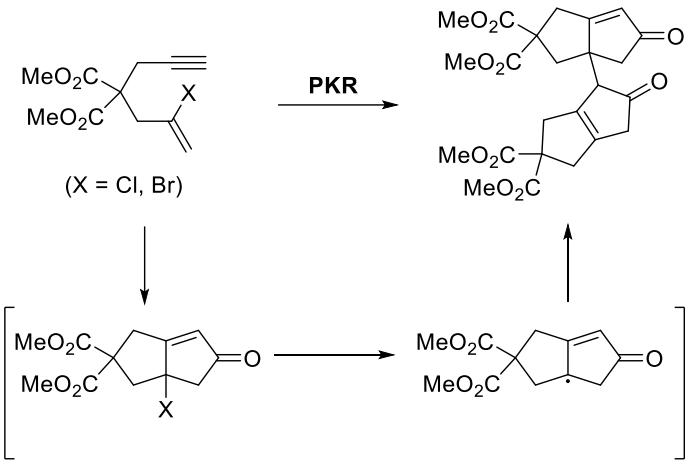
Scheme 71. Pauson-Khand reaction for fluorinated enynes by Fustero's group: scope and limitations.

As a comparison, the same authors also explored the reactivity of the corresponding chloro- and bromoenynes as olefinic counterparts for the intramolecular PKR (Scheme 72).



Scheme 72. Synthesis of chloro- and bromo- analogues.

Disappointingly, the formation of corresponding PKR adducts could not be ascertained in the crude reaction mixtures. Instead, the major isolated species was dimerized product. The presence of the cyclopentenone core in the final product allowed us to envision that PKR product would indeed be formed as an intermediate, and then evolved into product (Scheme 73).



Scheme 73. Dimerization pathway.

In order to rationalize the formation of this unexpected product the authors suggested three factors that may favour the formation of radical: first the inherent weakening the C-X bond through the halide series C-F > C-Cl > C-Br > C-I; second the tertiary position of the halide and third the presence of stoichiometric amounts of cobalt.

5. [2+2+2]-Cycloadditions

Cyclotrimerization of alkynes is an atom-economical and straightforward method for the construction of substituted benzene derivatives.[92] In 1948, Reppe *et al*. reported the Ni-catalyzed cyclization of acetylene and identified benzene amongst the cycloadducts.[93] Yamazaki reported the pioneering work of cobalt complex-mediated cycloaddition of phenylacetylene, and opened the way of transition metal-mediated or catalyzed [2+2+2]-cycloaddition of alkynes in organic synthesis leading to aromatic, heteroaromatic and polycyclic compounds.[94]

These types of compounds are important in nature, as most molecules that possess polycyclic and heterocycle systems are usually biologically active. Therefore, this type of reaction is a useful way to obtain molecules of a certain complexity from simpler and more accessible molecules.

The [2+2+2]-cycloaddition reaction can be classified into three types: an intermolecular reaction of three alkynes, a semi-intramolecular one of a diyne and an unsaturated function such as a monoalkyne, and an intramolecular one of a enediyne or triyne. Since control of the regioselectivity is difficult in the intermolecular version, from a synthetic point of view semi- and intramolecular cycloadditions are the most interesting alternatives.

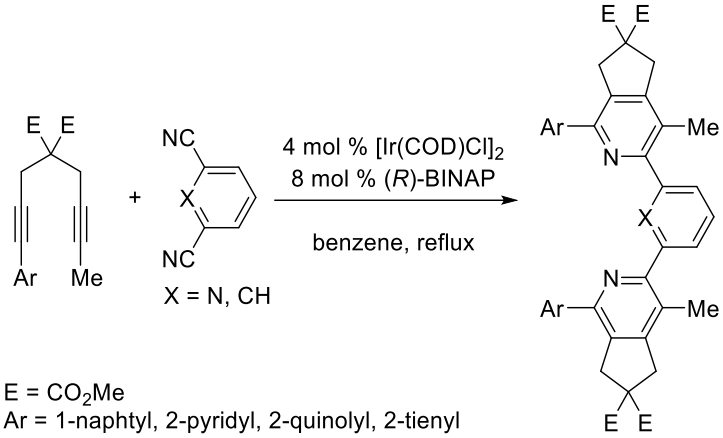
[92] a) Schore, N. E. In Comprehensive Organometallic Chemistry II; Hegedus, L. S., Ed.; Pergamon Press: Oxford, **1999**, *Vol. 12*, 703-739; b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92; c) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901-2916.

[93] Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Ann. Chem*. **1948**, *560*, 1-92.

[94] a) Yamazaki, H.; Hagihara, N. *J. Organomet. Chem.* **1967**, *7*, 22-23; b) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549-4552.

The semi-intramolecular ring formation can occur between enynes, that have extensively studied by Tanaka,[95] or diynes[96] and compounds containing a triple bond.

The groups of Takeuchi and Pérez Castells independently studied the [2+2+2]-cycloadditions reactions catalyzed by transition metals of diynes with nitriles,[97] heterocumulenes[98] or electron-deficient alkenes, which lead respectively to pyridines (Scheme 74), pyridones (Scheme 75), or cyclohexadienes (Scheme 76).



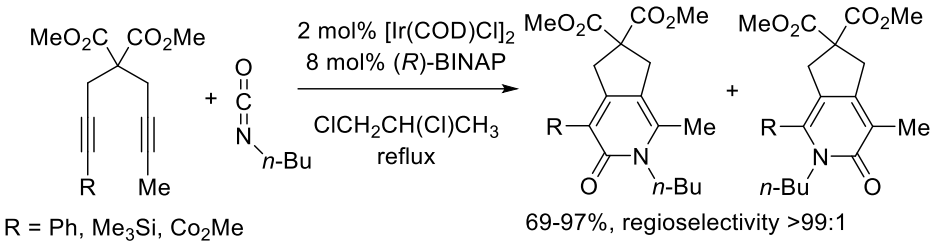
Scheme 74. Intermolecular $[Ir(COD)Cl]_2$ catalyzed [2+2+2]-cycloadditions of diynes and nitriles.

[95] Suzuki, S.; Nishigaki, S.; Shibata, Y.; Tanaka, K. *Org. Lett*. **2018**, *20*, 7461-7465; b) Yoshizaki, S.; Nakamura, Y.; Masutomi, K.; Yoshida, T.; Noguchi, K.; Shibata, Y.; Tanaka, K. *Org. Lett*. **2016**, *18*, 388-391; c) Masutomi, K.; Sakiyama, N.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 13031-1303; d) Tanaka, K.; Otake, Y.; Sagac, H.; Noguchi, K.; Hirano, M. *Ang. Chem. Int. Ed*. **2008**, *47*, 1312-1316.

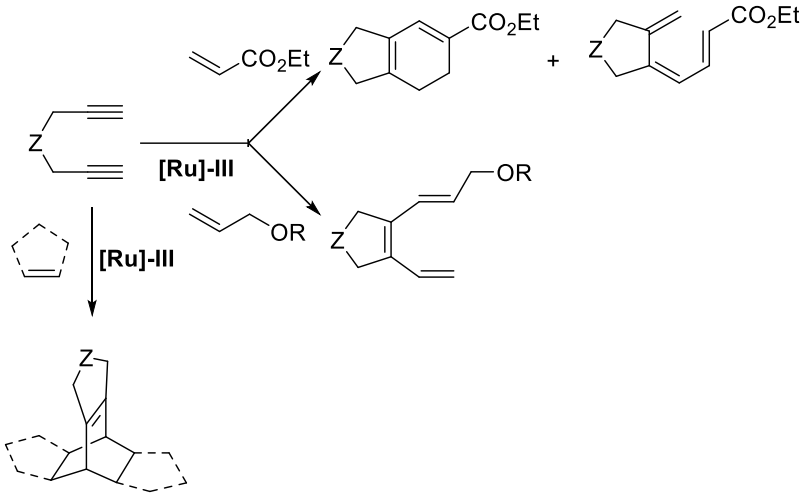
[96] Alvarez, S.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem*. **2015**, *80*, 2436-2442.

[97] Onodera, G.; Shimizu, Y.; Kimura, J.; Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 10515-10531.

[98] Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem*. **2012**, *77*, 908-920.



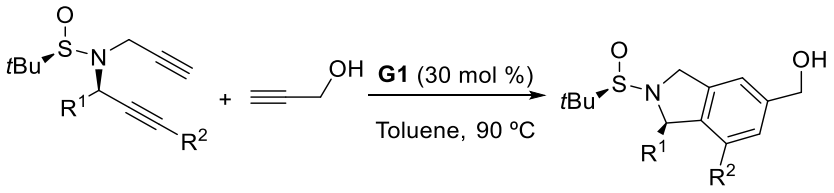
Scheme 75. Intermolecular $[Ir(COD)Cl]_2$ catalyzed [2+2+2]-cycloadditions of diynes and heterocumulenes.



Scheme 76. Ru (III) catalyzed intermolecular [2+2+2]-cycloaddition of diynes with deficient alkenes. Z= $C(CO_2Bn)_2$, NTs, O.

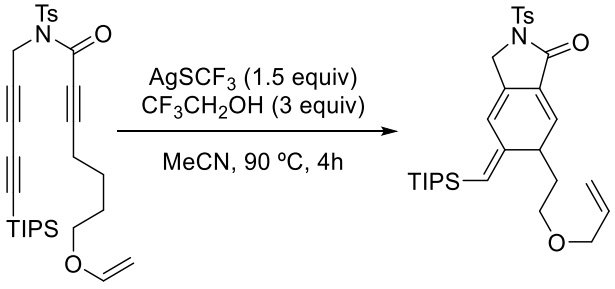
Chiral diynes derived from propargylamines obtained by diastereoselective addition of terminal alkynes to Ellman´s imines, undergo an intermolecular [2+2+2]-cycloaddition when reacted with alkynes leading to the corresponding benzene derivatives (Scheme 77) .[99]

[99] a) Bauer, R. A.; DiBiasi, C. M.; Tan, D. S. *Org. Lett.* **2010**, *12*, 2084-2087; b) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-D.; Hou, X.-L. *Synlett*, **2006**, 1272-1274.



Scheme 77. Intramolecular [2+2+2]-cycloaddition of chiral propargyl amines.

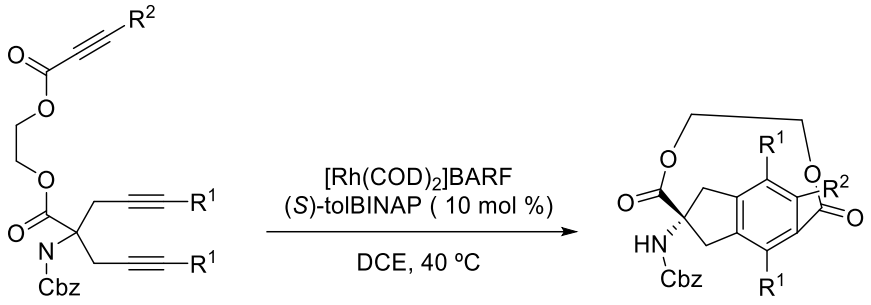
The intramolecular version of the reaction can occur between different molecules with double and/or triple bonds using transition metal complexes as catalyst. The cycloadditions of endiynes[100] and triynes[101] represent an attractive method for generating substituted derivatives of cyclohexadienes (Scheme 78) and benzene rings (Scheme 79), as well as larger cycles.



Scheme 78. Cyclohexadiene generation by [2+2+2]-cycloaddition catalyzed by $AgSCF_3$.

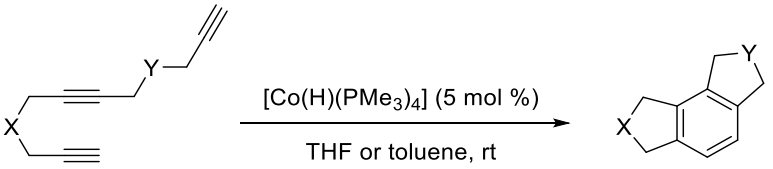
[100] a) Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem*. **2015**, *80*, 9781-9793; b) Ventre, S.; Simon, C.; Rekhroukh, F.; Malacria, M.; Amatore, M.; Aubert, C.; Petit, M. *Chem. Eur. J*. **2013**, *19*, 5830-5835; c) Dachs, A.; Pla-Quintana, A.; Parella, T.; Solà, M.; Roglans, A. *Chem. Eur. J*. **2011**, *17*, 14493-14507; d) Dachs, A.; Roglans, A.; Solà, M. *Organometallics* **2011**, *30*, 3151-3159; e) Geny, A.; Gaudrel, S.; Slowinski, F.; Amatore, M.; Chouraqui, G.; Malacria, M.; Aubert, C.; Gandon, V. *Adv. Synth. Catal*. **2009**, *351*, 271-275; f) Shibata, T.; Kurokawa, H.; Kanda, K. *J. Org. Chem*. **2007**, 72, 6521-6525; g) Eckenberg, P.; Growth, U. *Synlett.* **2003**, 2188-2192.

[101] a) Shibata, T.; Fusamae, T.; Takano, H.; Sugimura, N.; Kanyiva, K. S. *Asian J. Org. Chem*. **2019**, *8*, 970-977; b) Karmakar, R.; Mamidipalli, P.; Salzman, R. M.; Hong, S.; Yun, S. Y.; Guo, W.; Xia, Y.; Lee, D. *Org. Lett*. **2016**, *18*, 3530-3533.



Scheme 79. Synthesis of substituted benzenes by [2+2+2]-cycloaddition catalyzed by $[Rh(cod)_2]BARF$.

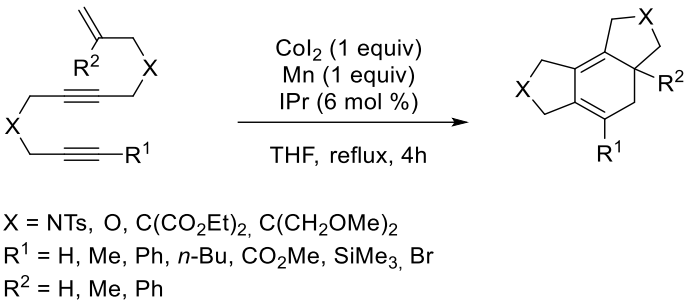
Intramolecular [2+2+2]-cycloadditions can also form heterocycles, from triynes with substituents containing heteroatoms. In the scientific literature have been reported cycloadditions of triynes (Scheme 80) and endiynes with amine and ether type linkages, forming oxa- and aza-five membered heterocycles.



X = O, NTs, $C(CH_2OMe)_2$
Y = O, NTs, CH_2

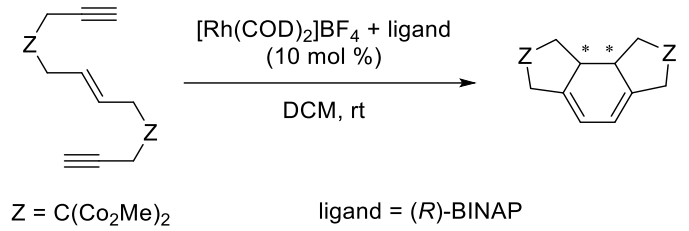
Scheme 80. Tricyclic compounds from triynes.

In the case of the endiynes, many heterocycles have been obtained with substituents in the position β to the heteroatom, which after cycling, becomes a chiral center. The reaction for these endiynes is stereoselective. The stereochemistry of the formed chiral center depends on the configuration of the double bond (Scheme 81).



Scheme 81. [2+2+2]-Cycloaddition of endiynes catalyzed by CoI_2/Mn/IPr.

The enantioselective [2+2+2]-cycloadditions of endiynes (yne-ene-yne) catalyzed by Rhodium (I) chiral complexes of catalyze enantioselective have also been described (Scheme 82).



Scheme 82. Enantioselective [2+2+2]-cycloaddition of endiynes catalyzed by Rh(I) chiral complexes.

Results and Discussion

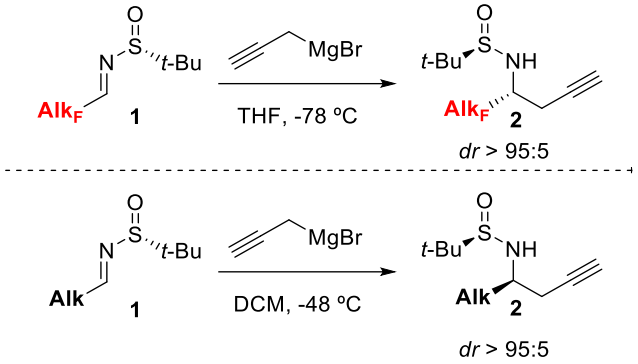
Summary

The results obtained in this thesis report, as well as its discussion, are divided into two different blocks. In the first part, the synthesis of chiral homopropargyl amides used as starting substrates for the subsequent formation of 1,7-enyne and 1,7,13-triyne derivatives. These compounds are of great importance as they are the starting materials in cycloaddition reactions. The second block of results is focused on cycloaddition reactions, which were carried out with these precursors using different transition metals as catalysts.

1. Synthesis of the starting materials

Synthesis of chiral fluorinated and non-fluorinated homopropargyl amides

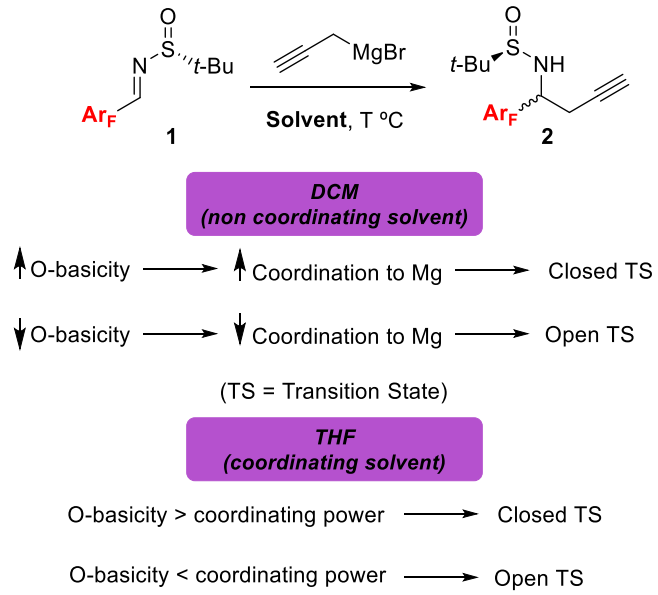
The preparation of the chiral homopropargyl amides was carried out by diastereoselective addition of propargylmagnesium bromide to fluorinated and non-fluorintated Ellman´s imines. A marked effect of the solvent in the diastereoselectivity was observed when switching from fluorinated to non-fluorinated derivatives in the alkyl series. Thus, a coordinating solvent such as THF was required to achieve a high diastereoselectivity in the addition of propargylmagnesium bromide to fluoroalkyl imines; however, the opposite was found in the case of alkyl imines, where high diastereoselectivities were reached using a non-coordinating solvent such as DCM (Scheme 83). The major diastereoisomer was opposite in each case. The diastereomeric ratio (*dr*) was established by ^{1}H- and ^{19}F-NMR spectra and the absolute configuration was determined by X-ray analysis.



Scheme 83. Influence of solvent on the diastereoselectivity with different Ellman's imines.

The aromatic series of Ellman´s imines (Ar_F) had a different behavior. The pentafluoroaryl and tetrafluoroaryl imines showed a complete reversal of diastereoselectivity when using coordinating or non-coordinating solvents, being THF at -78 °C and DCM at -48 °C the optimal conditions to control the diastereoselectivity, while imines having three or less fluorine atoms in the benzene ring behave as the non-substituted phenyl imine and high diastereoselectivity was achieved only in the presence of non-coordinating solvents. The results were interpreted on the basis of the generally accepted models proposed to rationalize the facial selectivity in the addition of organometallics to imines, where coordination of N and O atoms to the metal play a crucial role. In this scenario, the presence of fluorine atoms affects the basicity of the coordinating atoms of the sulfinyl imines, which may in turn affect the facial control of the selectivity by directing the reaction mainly through either an open or a coordinated transition state. The O basicity in fluoroalkyl imines would be poor and thus, a coordinating solvent can compete with the O of the sulfinyl imine for the coordination to Mg. Thus, the reaction takes place through the open transition state. On the contrary, the O-basicity of alkyl, phenyl and trifluoroaryl imines would be strong and compete with the coordinating solvent for the coordination to magnesium making the reaction take place through the two competitive open and coordinate transition states resulting therefore in poor diastereoselectivities while in the presence of non-coordinating solvents the coordinated transition state dominates the addition. The O-basicity of pentafluoroaryl- and tetrafluoroarylimines would be in the border and it would be relatively poor and, therefore, a coordinating solvent can compete with the O of the sulfinyl imine for

the coordination to Mg. Alternatively, with a non-coordinating solvent, the O-basicity would favor the coordination to Mg. Thus, good diastereoselectivities can be reached in both types of solvents (Scheme 84). The major diastereoisomer was always (*R*, *R*$_S$) in coordinating solvents and (*S*, *Rs*) in non-coordinating solvents in agreement with the established models.

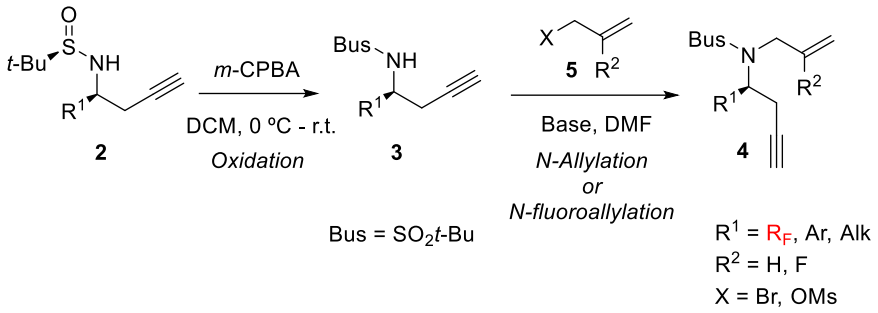


Scheme 84. Influence of solvent and O-basicity on the diastereoselectivity with aromatic fluorinated Ellman's imines.

Synthesis of chiral fluorinated and non-fluorinated 4-aza-1,7-enynes

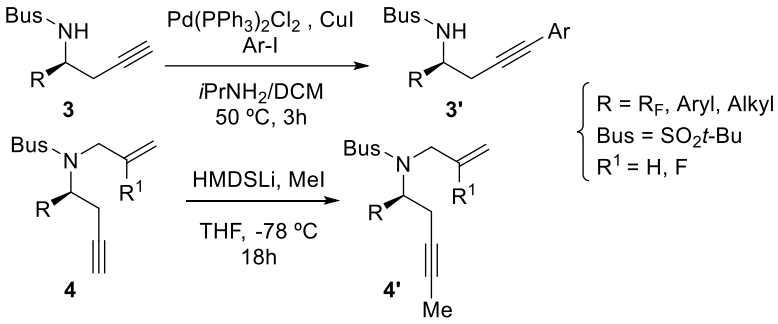
With an efficient method to form a wide array of homopropargylsulfinyl amides in hand, we subsequently prepare aza-1,7-enynes to be used as substrates both in the RCEYM and intramolecular Pauson-Khand reactions. The homopropargyl sulfinylamides were poor substrates for *N*-allylation reaction with both allyl bromide and 2-fluoroallylmethane sulfonate. However, we found that after oxidation of the sulfinyl group with *m*-CPBA the corresponding homopropargyl sulfonamides successfully underwent *N*-allylation through

the reaction with the corresponding bromide or 2-fluoroallylmethane sulfonate in basic conditions and at room temperature to give aza 1,7-enynes generally in good chemical yields (Scheme 85).



Scheme 85. General synthesis of aza 1,7-enynes.

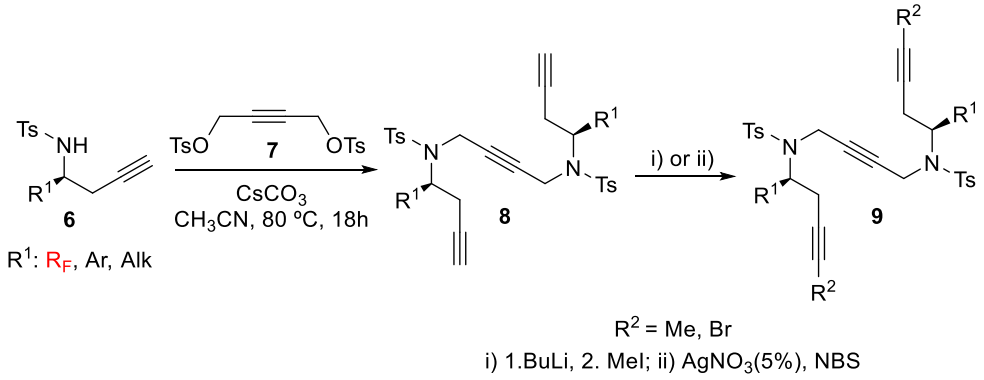
With the goal of exploring the scope and limitations of the Pauson-Khand reaction, we next synthesized *N*-bridged-1,7-enynes bearing an internal triple bond. At this end, we introduced an aryl group at the triple bond of homopropargyl sulfinylamides *via* Sonogashira reaction. In this way, the corresponding homopropargyl sulfinamides were obtained in moderate to good yields. These derivatives were then subjected to the same oxidation/*N*-allylation sequence mentioned previously to prepare the target 4- aza-8-aryl-1,7-enynes. Similarly, we attempted the synthesis of bearing a methyl substituent at the triple bond. We opted to directly methylate the triple bond in terminal enynes using HMDSLi and methyl iodide (MeI), following an adapted previously described procedure [19] (Scheme 86).



Scheme 86. Different strategies employed to obtain internal alkyne compounds.

Synthesis of chiral fluorinated and non-fluorinated N-bridged-1,7,13-triynes

The required *N*-bridged-1,7,13-triynes were obtained by assembly of two units of a given chiral homopropargyl amide linked by a unit of 2-butyne. *N*-Tosyl homopropargyl amides resulted, in this case, more appropriate substrates than the *N*-sulfonyl derivatives. These compounds tend to react better with the 2-butyn-1,4-diol ditosylate and then afford the corresponding *N*-bridged-1,7,13-triynes (Scheme 87).

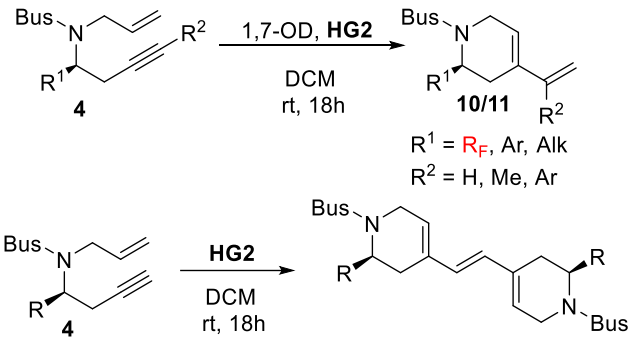


Scheme 87. Synthesis of *N*-bridged-1,7,13-triynes.

2. Cycloadditions Reactions.

Monocyclic compounds: RCEYM reaction of fluorinated and non-fluorinated 4-aza-1,7-enynes

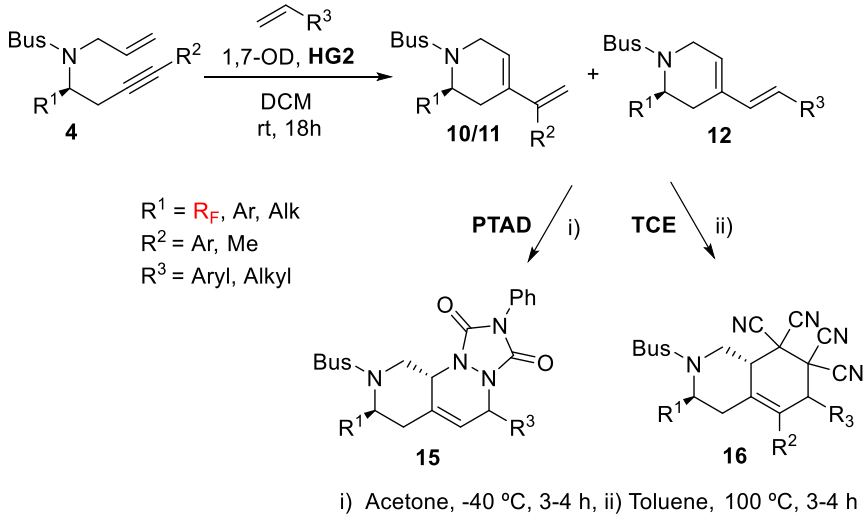
Enynes successfully took part in a ruthenium-catalyzed intramolecular RCEYM reaction yielding the corresponding enantioenriched tetrahydropyridine-based 1,3-diene using **HG2** as the best catalyst. The reaction only took place in the presence of 1,7-octadiene (1,7-OD), which acts as an *in situ* source of ethylene. In the absence of 1,7-octadiene the formation of tetrahydropyridine-based 1,3-diene was not observed, but a triene resulting from a homo cross metathesis was formed (Scheme 88).



Scheme 88. Importance of using 1,7-OD as an ethylene source in metathesis of 1,7-enynes.

Next, a ruthenium-catalyzed domino cross enyne metathesis/ring-closing metathesis (RCEYM/CM) of enynes and different alkenes was assayed. In this case, took place the formation of a mixture of products easily separable by flash chromatography: one of them was tetrahydropyridine-based 1,3-diene substituted at the diene system formed presumably via a ring-closing enyne metathesis (RCEYM) followed by a cross metathesis (CM) reaction, and, the other was the simple RCEYM product previously obtained. Overall, an array of 32 new fluorinated and non-fluorinated compounds having the basic core of tetrahydropyridine-1,3-diene were prepared with moderate to good yields. Then, a Diels-

Alder reaction was assayed with different substituted 1,3-dienes and PTAD and TCE as dienophiles (Scheme 89).

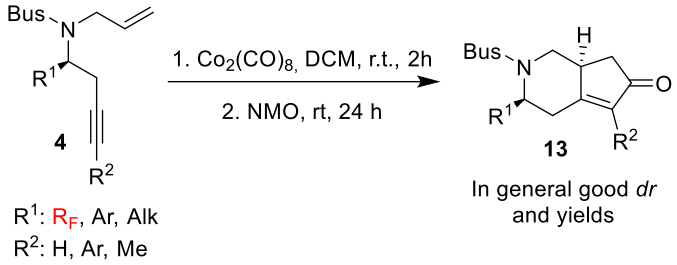


Scheme 89. Domino cross metathesis of 1,7-enynes and DA with TCE and PTAD.

Bicyclic compounds: Intramolecular fluoro Pauson-Khand reaction with fluorinated and non-fluorinated enynes

With a variety of chiral 1,7-enynes in hand, the Pauson-Khand cyclisation was explored to obtain bicyclic adducts bearing stereodefined substitutions in various positions. The structure of these adducts is similar to those of monoterpenic alkaloids that possess a piperidine heterocycle fused with a five-membered carbocyclic ring and that are of utmost interest since they present important biological properties. Thus, for example, *tecomanine* and *incarvilline*, which exhibit hypoglucemic and analgesic activity respectively, are representative examples of this group of alkaloids. Treatment of the starting enynes with 1.2 equivalents of $Co_2(CO)_8$ resulted in their full conversion to the corresponding cobalt intermediates that, upon treatment with *N*-methylmorpholine- *N*-oxide (NMO), underwent an efficient intramolecular PKR to afford the corresponding bicyclic derivatives as single

diastereoisomers. The yields were moderate to good, and high diastereoselectivity was observed in almost all cases. In general, substrates with substituted olefin components or longer fluoroalkyl chains resulted in lower yields and higher diastereoselectivities. When the PKR was carried out with an isomeric mixture of *E*/*Z* of enynes, only two diastereoisomers were obtained, indicating that the reaction took place stereospecifically. The isomers were separable by column chromatography, and their stereochemistry was determined according to NOESY experiments as well as previous literature reports involving similar substrates. Enynes bearing an internal alkyne gave both higher yields and diastereoselectivities (Scheme 90).

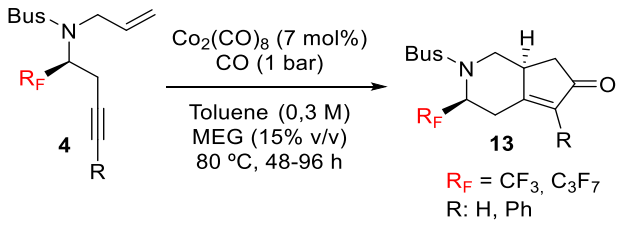


Scheme 90. PKR of 1,7-enynes containing both internal and terminal alkynes.

Furthermore, the introduction a vinyl fluoride moiety on the Pauson-Khand cyclisation (fluoro-PKR) was tested in this study. To this end, the *N*-allylation reaction of the homopropargyl sulfonamide was carried out with 2-fluoroallyl mesylate to afford the corresponding 2-fluoro-4-aza-1,7-enyne. To the cyclisation of this enyne derivative, DMSO was used as promoter instead of NMO (Scheme 91). It is worth noting that this transformation involves the asymmetric construction of a carbon-fluorine quaternary stereogenic center, a goal that constitutes remarkable interest in organic synthesis.

Scheme 91. Fluoro-PKR of 2-fluoro-aza-1,7-enynes.

The use of 1,7-enynes in a catalytic version of the PKR was also explored, for which a new synthetic protocol recently reported was selected. This procedure is based on a biphasic system of ethylene glycol (MEG) in toluene, and usually results in an enhancement of yield and selectivity for the PK adducts, as well as simplifying the purification of the products. By applying these reaction conditions (7 mol % catalyst, low CO pressure, and 15% v/v of ethylene glycol in toluene) to the different substituted enynes, the corresponding bicyclic derivatives were obtained (Scheme 92). Unfortunately, after several attempts, the catalytic version procedure was unsuccessful in the case of the fluoro-PKR.

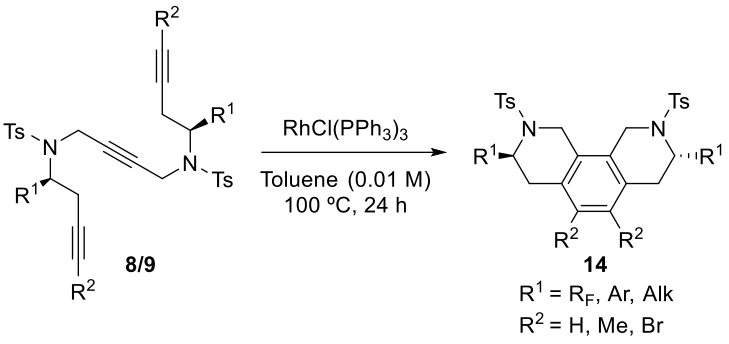


Scheme 92. Catalytic PKR of fluorinated 1,7-enynes.

Tricyclic compounds: [2+2+2]-cycloadditions of chiral N-bridged-1,7,13-triynes

An array of chiral *N*-bridged-1,7,13-triynes was cyclized under rhodium complexes catalyst to tricyclic compounds having the structure of a benzene ring embedded by two chiral piperazines. The versatility of this strategy regarding the scope of triynes is exemplified by the preparation of one enantiomeric pair of triynes by means of a stereodivergent synthesis

of homopropargyl amides and their conversion in the corresponding enantiomeric cycloadducts. This fact is noteworthy because a facile access to both enantiopure cycloadducts is always desirable in compounds with potential bioactivity. Besides, the procedure also permitted the access to a series of cycloadducts with different substitution patterns by simple derivatizations of the starting triynes. The developed method allowed the preparation of cycloadducts having central chirality but taking advantages of the superior reactivity of triynes in [2+2+2]-cycloadditions (Scheme 93). This strategy is not usual in the context of the [2+2+2]-cycloaddition reactions since the reported approaches to compounds with central chirality employ sp^2 hybridized substrates, which are less efficient that sp substrates in this kind of reactions.



Scheme 93. [2+2+2]-Cycloaddition of *N*-bridged-1,7,13-triynes.

Discusión de Resultados

Resumen

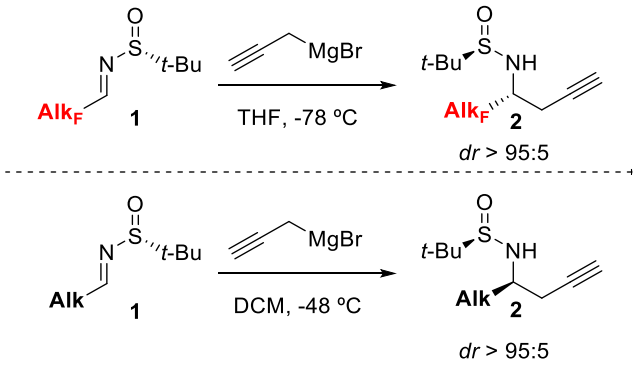
Los resultados obtenidos en esta memoria de Tesis, así como su discusión, se han dividido en dos bloques bien diferenciados. En el primero de ellos, se estudia la síntesis de las homopropargilamidas quirales utilizadas como sustratos de partida para la posterior formación de compuestos tipo 1,7-enino y 1,7,13-triino. Estos compuestos son de gran importancia puesto que van a ser los precursores y reactivos de partida en las reacciones de cicloadición que se estudiarán a continuación. El segundo bloque se refiere al estudio de las diferentes reacciones de cicloadición, llevadas a cabo con estos precursores utilizando metales de transición como catalizadores del proceso.

1. Síntesis de los sustratos de partida

Síntesis de homopropargilamidas quirales fluoradas y no fluoradas.

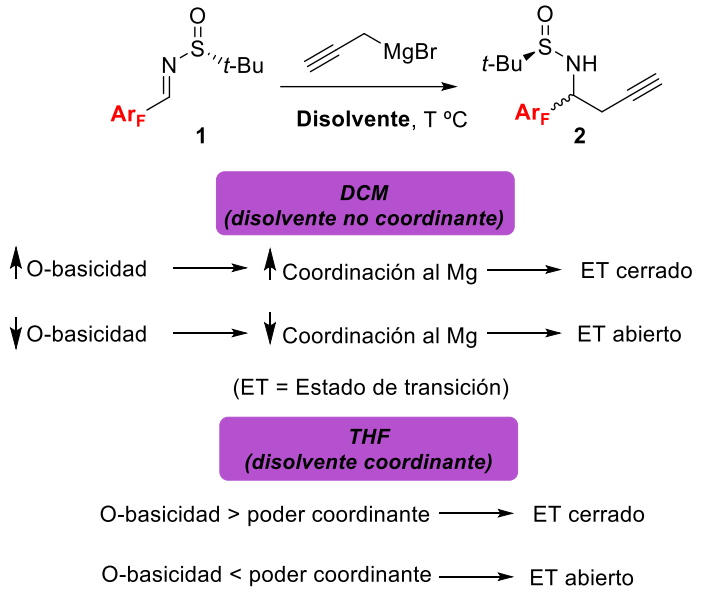
La preparación de homopropargilamidas quirales se llevó a cabo mediante una reacción de propargilación diastereoselectiva de iminas de Ellman fluoradas y no fluoradas. La diastereoselectividad de esta reacción depende de forma muy acusada del disolvente. Con aldiminas sustituidas con grupos fluoroalquilo, como el grupo trifluorometilo, la diastereoselectividad máxima se alcanza con disolventes coordinantes como el THF mientras que con aldiminas sustituidas con grupos alquilo y grupos arilo fluorados y no fluorados las diastereoselectividades altas se obtienen cuando se utilizan disolventes no coordinantes como el diclorometano (Esquema 83). El diastereoisómero mayoritario fue el contrario para cada caso. La relación diastereoisomérica (*dr*) fue establecida a través de los

espectros de ^{1}H- y ^{19}F-NMR y la configuración absoluta fue determinada por análisis de rayos X.



Esquema 83. Influencia del disolvente en la diastereoselectividad con diferentes iminas de Ellman.

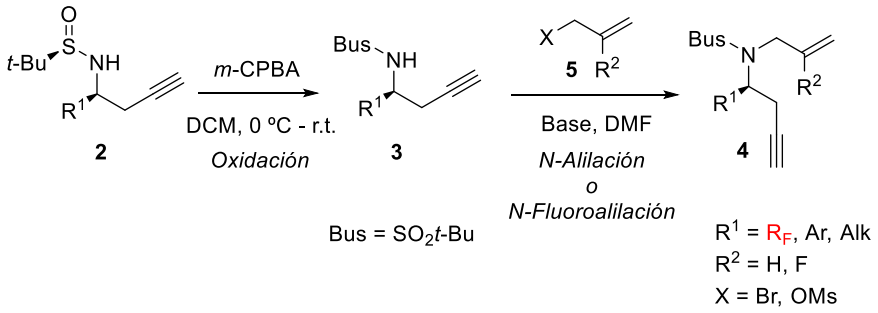
Para el caso de las aril aldiiminas sustituidas con grupos perfluorofenilo y tetrafluorofenilo se obtuvieron también altas diastereoselectividades tanto en disolventes coordinantes (DCM) como no coordinantes (THF) y, por tanto, fue posible realizar una propargilación estereodivergente. En todos los casos el diastereoisómero mayoritario fue diferente en función del disolvente empleado. Los resultados se racionalizaron en base a los modelos que explican la selectividad facial y que están basados en la coordinación de los átomos de O del grupo sulfinilo y del N de la imina al metal del reactivo organometálico empleado en la reacción de adición. La basicidad de los átomos de N y O está modulada por el sustituyente de la aldiimina. Los grupos fluoroalquilo y los grupos perfluorofenilo y tetrafluorofenilo disminuyen la basicidad de los átomos de N y O favoreciendo la competición del disolvente coordinante con el metal del reactivo organometálico y la adición del mismo siguiendo el modelo abierto o no coordinado. Por el contrario, si los sustituyentes de la aldiimina son grupos alquilo, arilo no fluorado o con un número de átomos de flúor inferior a cuatro, la basicidad de los átomos de N y O son suficientes para coordinar con el metal y esta se produce a través de un estado de transición cerrado, el cual se favorece todavía más con el empleo de un disolvente no coordinante (Esquema 84). Los resultados experimentales fueron complementados con cálculos DFT que fueron concordantes con los primeros.



Esquema 84. Influencia del disolvente y la basicidad del átomo de oxígeno en la diastereoselectividad con iminas de Ellman con restos aromáticos fluorados.

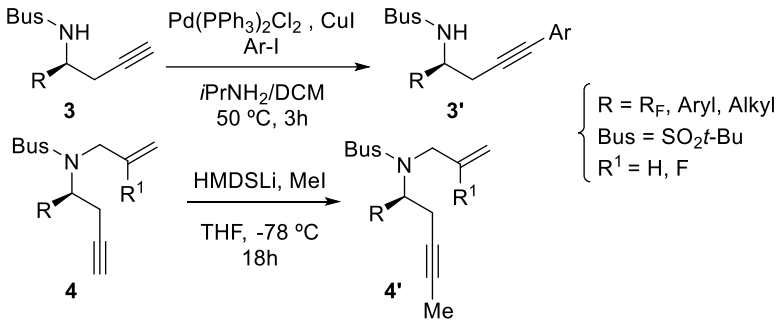
Síntesis de 4-aza-1,7-eninos quirales fluorados y no fluorados.

Una vez se dispuso de un procedimiento eficaz de síntesis de homopropargilamidas el siguiente paso fue la preparación de los correspondientes 1,7-eninos por reacción de *N*-alilación o *N*-fluoroalilación. Las sulfinilamidas no resultaron buenos sustratos para ambas reacciones posiblemente por la baja acidez del grupo sulfinilamida que dificulta la obtención de su base conjugada. Para resolver esta cuestión el grupo sulfinilo se oxidó a sulfonilo y, en este caso, pudieron realizarse con buenos resultados las reacciones de *N*-alilación y *N*-fluoroalilación de las correspondientes sulfonamidas (Esquema 85).



Esquema 85. Síntesis general de aza 1,7-eninos.

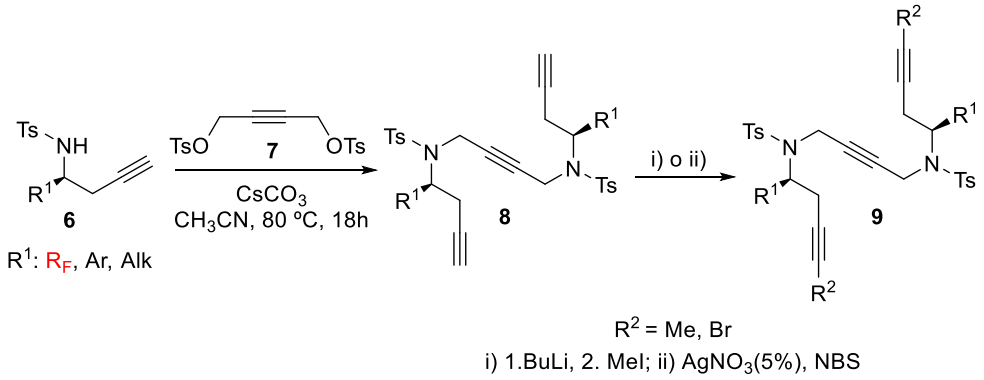
Los 4-aza-1,7-eninos obtenidos se derivaron a su vez a 8-aril-4-aza-1,7-eninos mediante reacciones de Sonogashira y a 8-alquil-4-aza-1,7-eninos mediante metilación de los correspondientes acetiluros generados con hexametildisilazuro de litio (HMDSLi). Por tanto, se dispuso de un amplio rango de 1,7-eninos para las reacciones de cicloadición siguientes (Esquema 86).



Esquema 86. Estrategias empleadas para la obtención de 1,7-eninos con alquinos internos en su estructura.

Síntesis de 5,10-diaza-1,7,13-triinos quirales fluorados y no fluorados

Los 5,10-diaza-1,7,13-triinos se prepararon mediante la conexión de dos unidades de la correspondiente homopropargilamida con un puente de 2-butino. En este caso fue necesario sustituir el grupo sulfonilo de la amida por un grupo tosilo para poder obtener rendimientos aceptables en la reacción de las *N*-tosilamidas con el ditosilato de 2-butin-1,4-diol. También en este caso se llevó a cabo la funcionalización del triple enlace terminal de los triinos para disponer de un mayor rango de sustratos (Esquema 87).



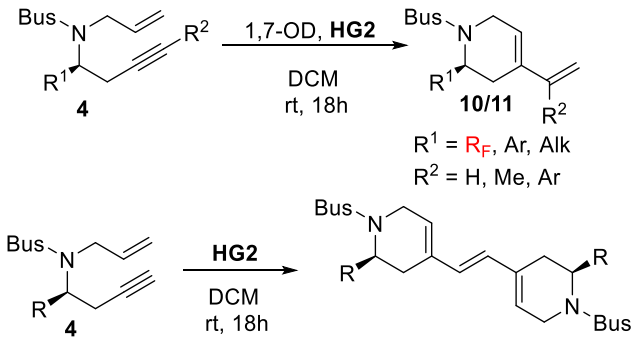
Esquema 87. Síntesis de los 1,7,13-triinos.

2. Reacciones de Cicloadición

Compuestos monocíclicos: Reacciones RCEYM de 4-aza-1,7-eninos fluorados y no fluorados

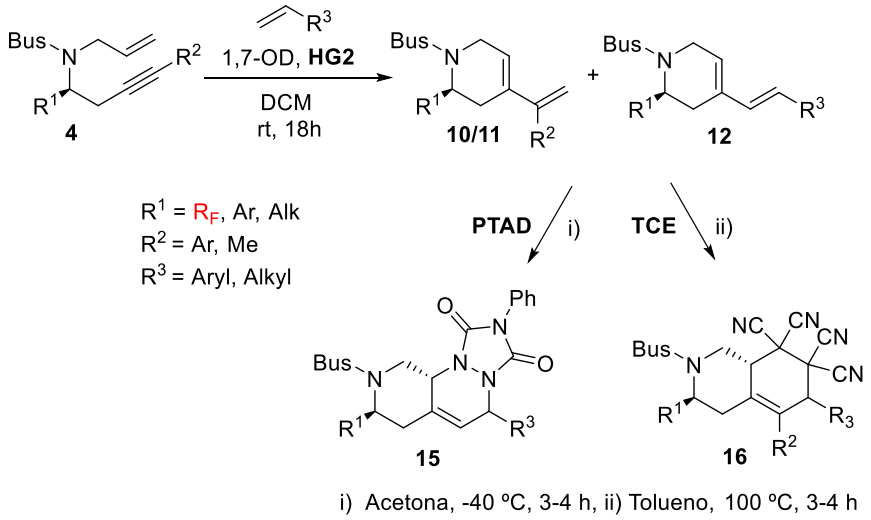
Los eninos sintetizados fueron transformados en vinil dihidropiridinas que contienen un sistema 1,3-diénico mediante una reacción de metátesis para la que el catalizador más eficaz fue el de Hoveyda-Grubbs de segunda generación (**HG2**). La reacción requirió la

utilización de 1,7-octadieno (1,7-OD) como fuente de etileno. En su ausencia se obtiene un trieno resultado de una reacción de homo metátesis cruzada (Esquema 88).



Esquema 88. Importancia del uso de 1,7-OD como fuente de etileno en la metátesis de 1,7-eninos.

Además se llevaron a cabo también reacciones tándem de metátesis de eninos seguidas de metátesis por cierre de anillo combinando los eninos con distintos alquenos derivados del estireno y que condujeron a compuestos con el mismo núcleo de alquenil dihidropiridina pero sustituidas diferentemente sobre el carbono terminal del doble enlace exocíclico en función del alqueno empleado. En conjunto se obtuvieron más de 32 compuestos distintos fluorados y no fluorados con rendimientos de moderados a elevados. Una vez preparados los 1,3-dienos, se llevó a cabo una reacción de Diels-Alder usando TCE y PTAD como dienófilos (Esquema 89).

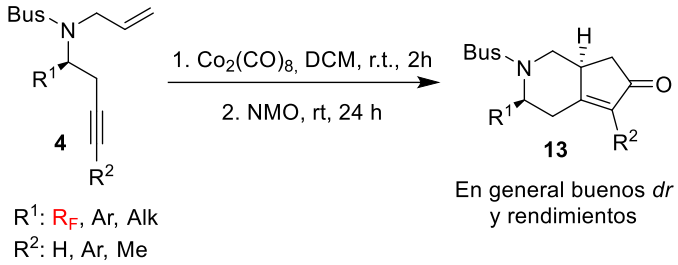


Esquema 89. Metátesis cruzada de 1,7-eninos y diferentes alquenos seguida de DA con TCE y PTAD .

Compuestos bicíclicos: Intramolecular fluoro Pauson-Khand con eninos fluorados y no fluorados.

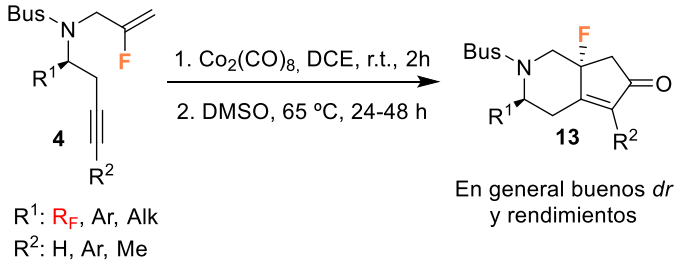
Las reacciones de Pauson-Khand se ensayaron con una amplia variedad de eninos quirales fluorados y no fluorados. La estructura de los heterociclos obtenidos es similar a la de productos naturales bioactivos que son alcaloides monoterpénicos y poseen un anillo de piperidina fusionado con un anillo de ciclopentenona. La *tecomanina* y la *incarvillina*, que tienen actividad como hipoglucemiantes, son ejemplos de este grupo de compuestos. La novedad aportada por los compuestos preparados en este trabajo reside en la incorporación de átomos de flúor o grupos fluorados en distintas posiciones de la estructura. La reacción para el caso de la reacción de Pauson-Khand con grupos fluorados en el conector (*linker*) pero no en el doble ni el triple enlace, tuvo lugar empleando $Co_2(CO)_8$ como catalizador y *N*-óxido de *N*-metilmorfolina (NMO) como promotor. La reacción fue completamente diastereoselectiva y tuvo lugar tanto con eninos con triples enlaces terminales como sustituidos con grupos alquilo y arilo. La reacción también tuvo lugar con

eninos sustituidos en el doble enlace tanto en la posición interna como en posición terminal. En el caso de estereoisomería E/Z, se obtuvieron solamente dos diastereoisómeros, siendo esto un indicativo de la estereoespecificidad de la reacción. Los isómeros obtenidos se pudieron separar por columna cromatográfica y su estereoquímica fue determinada a través de experimentos NOESY y datos de sustratos similares descritos previamente en la literatura existente. Los eninos con un alquino interno reaccionaron con diastereoselectividades y rendimientos elevados (Esquema 90).



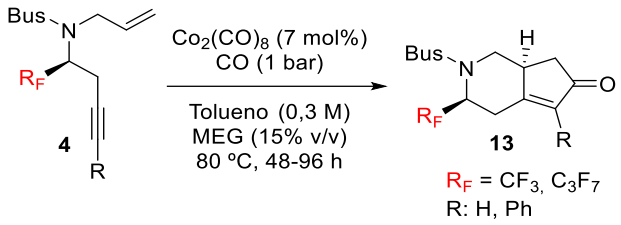
Esquema 90. PKR de 1,7-eninos conteniendo alquinos terminales e internos.

También se estudió la influencia en la ciclación de eninos la introducción de un resto vinilfluorado en su estructura. Para ello se llevó a cabo la *N*-alilación de homopropargil sulfonamida con 2-fluoroalil mesilato y se obtuvo el correspondiente 2-fluoro-4-aza-1,7-enino. Para el caso de 2-fluoro-4-aza-1,7-eninos (fluoro-PKR) fue necesario sustituir el promotor por DMSO ya que, en caso contrario, se obtiene el producto de la eliminación de HF (Esquema 91). Es importante señalar que la fluoro-PKR implica la construcción de un centro estereogénico cuaternario carbono-flúor que es una característica estructural de difícil consecución en síntesis orgánica.



Esquema 91. Fluoro-PKR de 2-fluoro-aza-1,7-eninos.

Además, se llevó a cabo también la versión catalítica de la reacción utilizando un sistema bifásico de etilenglicol/tolueno que permite optimizar los rendimientos y simplificar la purificación de los productos finales (Esquema 92). El procedimiento resultó eficiente para un número representativo de las reacciones de Pauson-Khand desarrolladas en este trabajo, pero no para el caso de la reacción de tipo fluoro Pauson-Khand.

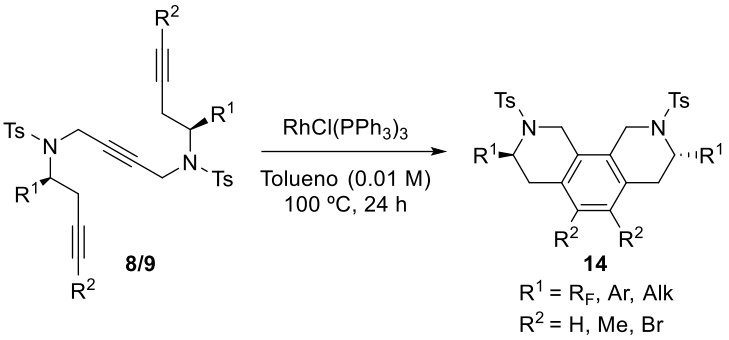


Esquema 92. PKR catalítica de diferentes 1,7-eninos fluorados.

Compuestos tricíclicos: Cicloadiciones [2+2+2] de 5,10-diaza-1,7,13-triinos quirales

Un número amplio de 1,7,13-triinos lineales con puente de nitrógeno ciclan a compuestos tricíclicos que tienen una estructura de benceno fusionado con dos anillos de piperazina quirales utilizando catalizadores de rodio. La estrategia seguida es versátil en cuanto que faculta la disponibilidad de una variedad de triinos. Por ejemplo, se pueden preparar fácilmente una pareja de triinos quirales enantioméricos que al ser ciclados dan acceso a los dos enantiómeros de los compuestos tricíclicos finales. Puesto que los compuestos finales poseen elementos estructurales que se asocian a la actividad biológica como son a los anillos de tetrahidroisoquinolina, la posibilidad de acceso a los dos enantiómeros sin variar el procedimiento de síntesis es una herramienta interesante. Además, la posibilidad demostrada con distintos ejemplos de introducción de sustituyentes adicionales sobre el triino como son grupos metilo o átomos de bromo dando acceso a diferentes tipos de sustitución en el anillo de benceno del producto final muestra la utilidad del procedimiento diseñado. El método permite el acceso a compuestos que tienen quiralidad central utilizando como sustratos de partida triinos que son los sustratos que presentan el mejor

perfil de reactividad en las cicloadiciones [2+2+2] (Esquema 93). Esta estrategia es novedosa puesto que la aproximación más usual en este contexto para introducir estereocentros en los cicloaductos es utilizar sustratos con carbonos sp^2 que son menos activos que los sp en este tipo de reacciones.



Esquema 93. Cicloadición [2+2+2] de 1,7,13-triinos.

Scientific Article 1:

On the diastereoselectivity of the addition of propargylic magnesium reagents to fluorinated aromatic sulfinyl imines

On the diastereoselectivity of the addition of propargylic magnesium reagents to fluorinated aromatic sulfinyl imines

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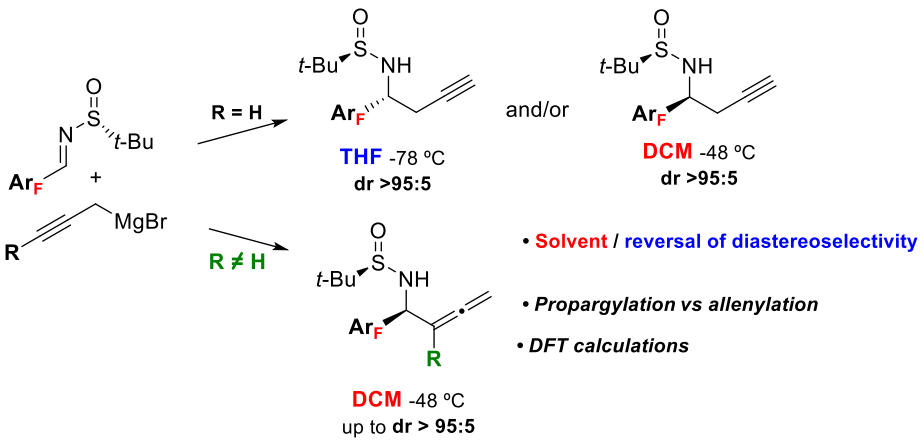
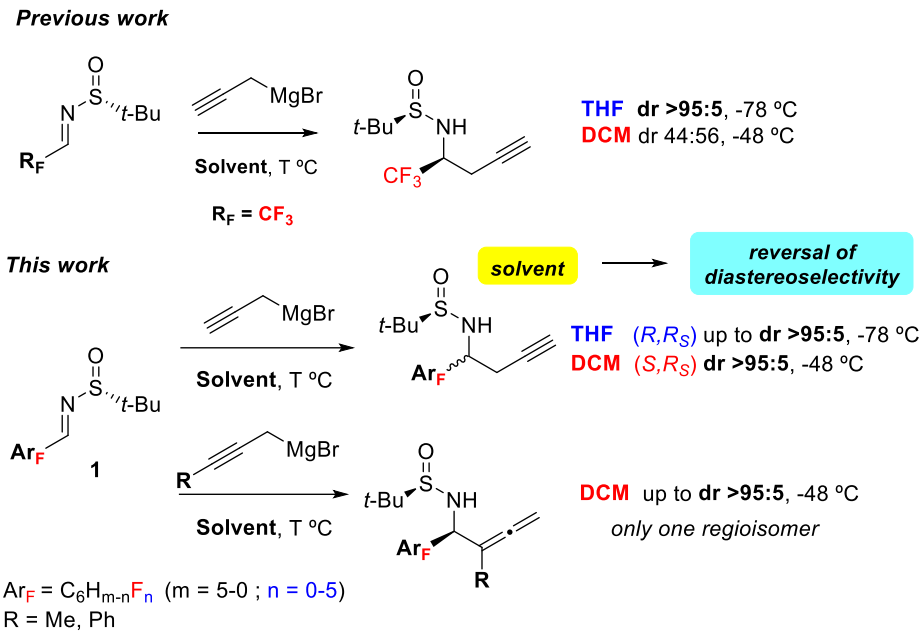
General information, synthesis of compounds, spectral data of the obtained compounds, copies of NMR spectra, computational methods and cartesian coordinates of optimized structures.



ABSTRACT: The addition of propargyl magnesium bromide to fluorinated aromatic sulfinyl imines gave homopropargyl amines with total regio- and diastereoselection. Complete reversal of diastereoselectivity can be achieved in some cases using coordinating (THF) or non-coordinating (DCM) solvents. Substituted propargylic magnesium reagents have been also tested towards fluorinated aryl sulfinyl imines affording chiral homoallenyl amines with good yields and selectivity control. DFT calculations helped to rationalize the origin of the experimental regio- and diastereoselectivities observed in each case.

Enantiomerically pure amines are interesting chiral building blocks, which can be used in the synthesis of pharmaceutical drugs and in organometallic catalysis.[1] The stereoselective 1,2-addition of organometallics to imines represents one of the most direct approaches for the synthesis of chiral amines,[2] which is closely associated to the use of chiral *N*-sulfinyl imines due to their efficiency and availability. Among *N*-sulfinyl imines, *N*-*tert*-butylsulfinyl imines,[3] extensively developed by Ellman, play an important role in this field due to their high chiral induction ability. The propargylation/allenylation of imines represents an interesting reaction leading to homopropargyl or homoallenyl amines, which requires both regio- and stereocontrol.[4] Boron, tin, copper, silver, zinc and indium reagents are usually employed to perform these synthetic reactions;[5] however, magnesium reagents can also be efficient to afford homopropargylamines.[6] Although the diastereoselective 1,2-addition of organometallic compounds to sulfinyl imines is a well-established procedure occurring with good yields and high diastereoselection,[7] the outlook is highly dependent on the reaction conditions. Solvent effects on stereoselectivity, including enantio- and diastereoselectivity, are well documented in the literature, and several examples of dual stereocontrol have been reported.[8,9] However, these studies are generally limited to showing the change in stereoselectivity in the presence of different solvents, bypassing a rationalization of the stereocontrol.

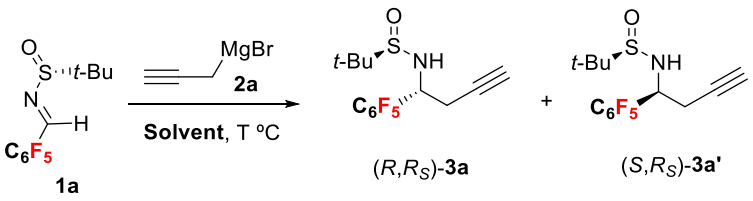
Continuing with our interest in organofluorine chemistry, which has important applications in pharmaceutical chemistry, agrochemistry and materials science,[10] we noticed that the introduction of the trifluoromethyl group has received continuous attention,[11] while aryl fluorinated groups such as tetrafluoro- and, in particular, pentafluoro-benzene derivatives have been disregarded, in spite of their interesting reactivity mainly associated to the possibility to perform nucleophilic substitution reactions.[12] In a recent study, we found that the addition of propargyl magnesium bromide to alkylfluorinated sulfinyl imines



Scheme 1. Previous work relevant to this report.

was completely regioselective affording the corresponding homopropargylic amines without detection of allenic derivatives.[6] For sulfinyl imines bearing a fluoroalkyl group (i.e. CF_3) elevated diastereoselectivity (*dr* >95:5) was observed in THF, while a poor diastereoselection was obtained in dichloromethane (DCM) (*dr* 44:56) (Scheme 1). With these precedents in mind, we report our findings in the diastereoselective propargylation reaction of aryl fluorinated sulfinyl imines **1**, under different reaction conditions, paying attention to the solvent effect. Rationalization of the results is supported by theoretical calculations which help to clarify in which way to the diastereoselectivity is achieved.

Table 1. Optimization study on the diastereoselective 1,2-addition of propargyl magnesium bromide to aromatic sulfinyl imine **1a**.



entry	solvent	additive	T (°C)	yield[b] (%)	*dr*[c]
1	THF	-----	-48	**3a**, 99	67.33
2	Et_2O	-----	−48	**3a**, 65	67.33
3	DME	-----	−48	**3a**, 50	80:20
4	Me-THF	-----	−78	**3a**, 99	67.33
5	THF	-----	−78	**3a**, 67	>95:5
6	Toluene	-----	−48	**3a'**, 78	12:88
7	DCM	-----	−48	**3a'**, 80	>5:95
8	DCM	$BF_3{\cdot}OEt_2$	−48	**3a'**, 41	33:67
9	Toluene	$BF_3{\cdot}OEt_2$	−48	**3a'**, 41	12:88
10	THF	$BF_3{\cdot}OEt_2$	-48	**3a'**, 99	33:67
11	Et_2O	$BF_3{\cdot}OEt_2$	−48	**3a'**, 14	33:67
12	DME	$BF_3{\cdot}OEt_2$	-48	**3a'**, 84	20:80

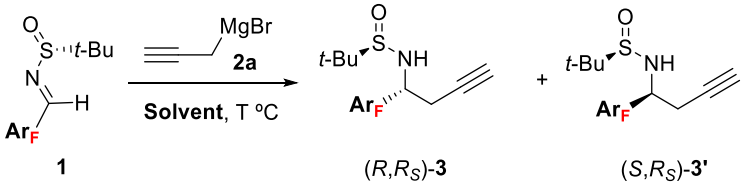
[a] Reaction conditions: Magnesium propargyl bromide (1.5 equiv), solvent (0.1 M), 18 h. [b] Isolated yield after column chromatography. [c] Determined by ^{19}F NMR; *dr* refers to **3a**:**3a'**ratio.

Our study began with the reaction of pentafluoroaryl sulfinyl imine **1a** with propargyl magnesium bromide (**2a**) as model substrates, using representative examples of coordinating (THF, DME, Me-THF, Et_2O) and non-coordinating solvents (DCM, toluene) at −48 °C. The results of addition to (*R*)-*tert*-butylsulfinyl imine (**1a**) are summarized in Table 1. Among coordinating solvents (Table 1, entries 1–5), THF was the optimal solvent in terms of conversion. Despite DME afforded product (*R*,R_S)−**3a** with higher diastereoselectivity than THF (20:80 vs 33:67), the freezing point of DME hampers working below −58 °C, and therefore, the possibility of increasing diastereoselectivity. Interestingly, lowering the temperature to −78 °C in THF, the diastereoselectivity of **3a** was increased up to >95:5. When performing the reaction in non-coordinating solvents, such as toluene, the opposite diastereomer (*S*,R_S)−**3a'** was obtained with good yield and moderate diastereoselectivity (12:88) (Table 1, entry 6) unlike previously reported for fluoroalkyl substituted imines (i.e. CF_3, *dr* 44:56).[6] Noteworthy, when the addition of propargylmagnesium **2a** to imine **1a** was conducted in DCM, homopropargyl amine **3a'** was attained in good yield and high

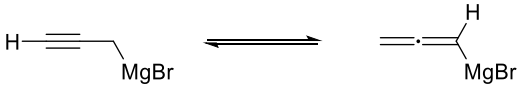
diastereoselectivity (*dr* >5:95) (Table 1, entry 7). The addition of a Lewis acid had no beneficial effect on the diastereoselectivity but resulted in lower yield, probably due to the reactivity of the Grignard reagent with $BF_3{\cdot}Et_2O$ (Table 1, entries 8−12). These results show that a complete reversal of diastereoselectivity can be achieved using coordinating or non-coordinating solvents, i.e. THF at −78 °C or DCM at −48 °C. The major diastereomer was obtained for each solvent and was distinguishable by ^{19}F NMR. Although the influence of solvents in diastereoselectivity in 1,2-addition of propargylic reagents to sulfinyl imines is well documented, a total reversion of the diastereoselection associated to a change in the solvent is unusual and never related with the presence or absence of fluorinated groups in the imine.[6,9]

With the optimized reaction conditions in hand, we decided to test the propargylation reaction in THF at −78 °C and DCM at −48 °C for different aromatic sulfinyl imines **1** in which the number of fluorine atoms in the benzene ring was modulated. When testing the reaction with sulfinyl imine **1b** having a C_6HF_4 substituent, the results were similar to those obtained for sulfinyl imine **1a**. However, when the reactions were carried out with sulfinyl imines bearing less than four fluorine atoms, the diastereoselectivity in THF showed a progressive erosion. Conversely, the high diastereoselectivity for sulfinyl imines **1a–f** was preserved in DCM as solvent. The absolute configuration was assigned based on X−ray analysis of crystals of compounds **3c** and **3c'**, which revealed the formation of (R,R_S)−**3c'** in THF and (S,R_S)−**3c** in DCM. These results suggest the existence of a correlation between the presence or absence of fluorine atoms in the sulfinyl imine and the type of solvent for the propargylation reaction.

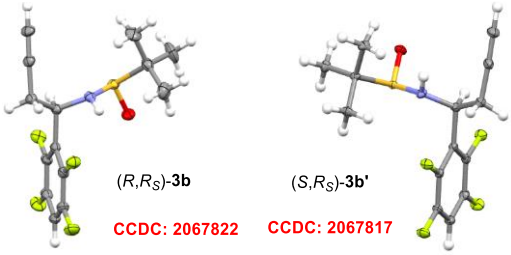
Table 2. Diastereoselective 1,2-addition of propargyl magnesium bromide to aromatic sulfinyl imines **1**.



Metallotropic rearrangement



propargylmagnesium **allenylmagnesium**



entry	Ar_F	solvent	T (°C)	yield[b] (%)	*dr*[c]
1	C_6F_5	THF	−78	**3a**, 67	>95:5
2	C_6F_5	DCM	−48	**3a'**, 80	>5:95
3	2,3,5,6-C_6HF_4	THF	−78	**3b**,[d] 61	>95:5
4	2,3,5,6-C_6HF_4	DCM	−48	**3b'**,[d] 68	>5:95
5	2,4,6-$C_6H_2F_3$	THF	−78	**3c**, 84	67:33
6	2,4,6-$C_6H_2F_3$	DCM	−48	**3c'**, 89	>5:95
7	2,6-$C_6H_3F_2$	THF	−78	**3d**, 51	67:33
8	2,6-$C_6H_3F_2$	DCM	−48	**3d'**, 70	>5:95
9	2-C_6H_4F	THF	−78	**3e**, 72	58:62
10	2-C_6H_4F	DCM	−48	**3e'**, 86	>5:95
11	C_6H_5	THF	−78	**3f**, 76	45:55
12	C_6H_5	DCM	−48	**3f'**, 80	>5:95

[a] Reaction conditions: **2a** (1.5 equiv), solvent (0.1 M), 18 h. [b] Isolated yield after column chromatography. [c] Determined by ^{19}F NMR; *dr* refers to **3**:**3'** ratio. [d] X-ray analysis (see, SI for more details).

The above results can be understood on the basis of the generally accepted models proposed to rationalize the facial selectivity in the addition of organometallics to imines, where coordination of N and O atoms to the metal play a crucial role.[12] In this scenario, the presence of fluorine atoms affects the basicity of the coordinating atoms of the sulfinyl imines, which may in turn affect the facial control of the selectivity. A natural bond orbital (NBO)[13] analysis of charges of the different atoms in the sulfinyl imines revealed that charges on N, O and C atoms of sulfinyl imines can be correlated with the number of fluorine atoms in the benzene ring (Table S1, Supporting Information). Similar charges were found for the pairs formed by sulfinyl imines **1f** and **1e**, **1d** and **1c**, and **1b** and **1a**, respectively, following similar trends as experimentally shown in Table 2. Therefore, the O basicity in imines **1b** and **1a** having four and five fluorine atoms in the benzene ring would be relatively poor and thus, a coordinating solvent can compete with the O of the sulfinyl imine for the coordination to Mg. Alternatively, with a non-coordinating solvent, the O basicity would favor the coordination to Mg.

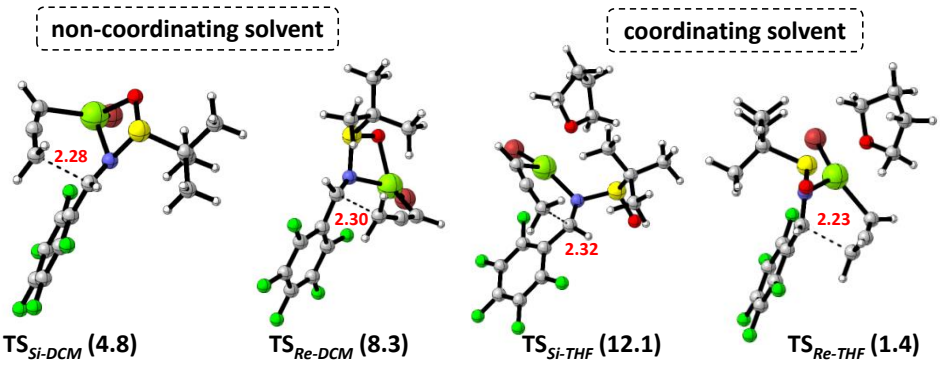


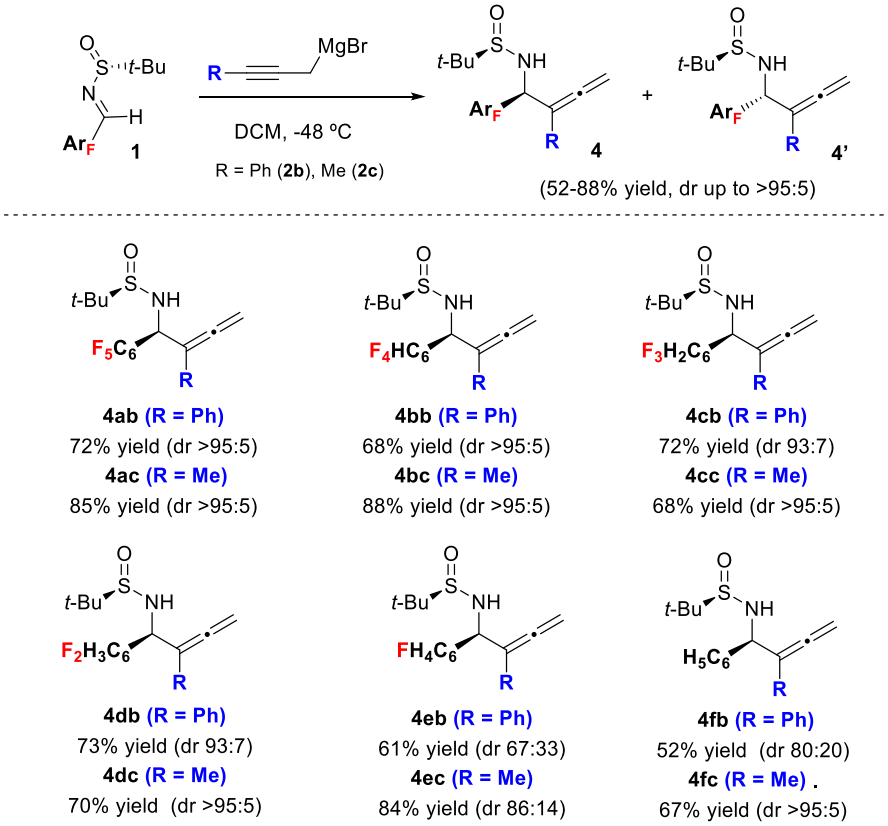
Figure 1. Optimized transition state structures at wB97XD/6−311G(2d,2p) for coordinating and non-coordinating solvents for and 1a. C···C bond forming distances are displayed in red. Relative activation energies are given in brackets in kcal/mol.

In order rationalize the observed diastereoselectivity, a computational study at wB97XD/6−311G(2d,2p) level of theory was carried out with Gaussian 16.[14] The alkylation

reaction of sulfinyl imines has been studied with MeMgBr but theoretical studies on propargylation have not been reported.[15] The reaction of the starting propargyl bromide with magnesium gives the corresponding propargyl reagent **2a**, which after metallotropic rearrangement, is converted into the allenyl magnesium reagent **2a'**.[4] DFT calculations showed the allenyl intermediate is 4.6 kcal/mol more stable than the propargyl magnesium **2a**. Thus, **2a'** will be the reactive specie that by addition to the sulfinyl imine **1a** will afford homopropargyl amines **3a** or **3a** ´through a S_E2´ process. In the case of the reaction in non-coordinating solvents, the coordination of organomagnesium reagent **2a'** to sulfinyl imine **1a** is exergonic and N, S, O and Mg are nearly coplanar (N−S−O−Mg dihedral angle 2.2°). A six-membered TS ring with the coordination of the magnesium atom to both the nitrogen and oxygen atoms of the imine facilitates the nucleophilic attack at the less hindered *Si* face for imines with the R_S configuration, as described for indium-promoted propargylation of chiral sulfinyl imines.[5f] The calculated energy barrier of the TS for the attack from the *Si* or *Re* face are 4.8 and 8.3 kcal/mol, respectively. The difference in energy between the two transition states leading to the *S* and *R* products is 6.4 kcal/mol, which suggests that the *S*–product is mainly formed, in agreement with the observed diastereoselectivity (>5:95). Meanwhile, in the presence of a coordinating solvent (THF), the coordination of the magnesium atom to both the nitrogen of the imine and oxygen of a THF molecule is favored. In this scenario, the energy barrier of the TS for the attack from the *Re* face is 1.4 kcal/mol, whereas a higher barrier (12.1 kcal/mol) was found for the *Si* face attack. Therefore, the *R*−product is mainly formed in complete agreement with the experimental formation of the (R,R_S)−diastereomer in THF. The plausible TS structures are shown in Figure 1. The distances between the imine carbon and the CH_2 of the allenyl magnesium reagent are 2.28 Å ($TS_{Si\text{-}DCM}$), 2.30 Å ($TS_{Re\text{-}DCM}$), 2.32 Å ($TS_{Si\text{-}THF}$) and 2.23 Å ($TS_{Re\text{-}THF}$). The shortest distance corresponds to the TS with the lowest barrier ($TS_{Re\text{-}THF}$) in accordance with Hammond's postulate.

Next, we extended the study to disclose the behavior of representative examples of propargylic Grignard reagents in the addition to aryl fluorinated sulfinyl imines **1** (Scheme 2) The addition of organomagnesium **2b** to imine **1a** resulted in total regioselectivity yielding

allene **4ab** as the only regioisomer. The result is significant since, for this type of additions, the obtention as single regioisomers of homoallenyl amines substituted at the α position in the allenic moiety, is not frequent.[16] High diastereoselectivity (>95:5) for the chiral homoallenyl amines was attained in DCM at −48 °C; however, diastereoselection was moderate in THF at −78 °C (*dr* 20:80). The major diastereomer attained was different for each solvent. For the rest of the sulfinyl imines of the series, high diastereoselectivities were also reached for the corresponding homoallenyl amines when non-coordinating DCM was used as solvent at −48 °C, with the sole exception of sulfinyl imine **1e**, having monofluorophenyl as substituent. Regarding the diastereoselectivity, organomagnesium **2c** behaved similarly to **2b** but in general yields were higher. On the contrary, THF had a deleterious effect in the diastereoselection in all cases.



Scheme 2. 1,2-Addition of substituted-propargyl magnesium bromides to fluorophenyl sulfinyl imines.

The regioselectivity with propargylic magnesium reagents can be ascribed to differences in the rate of equilibration of the corresponding propargylic and allenylic magnesium reagents.[17] DFT calculations show a barrier of 6.4 and 5.3 kcal/mol for the transition states connecting the propargylic and allenylic magnesium species for **2b** and **2c**, respectively. These results suggest that isomerization is not fast and the regioselectivity is governed by the addition of propargylic magnesium reagent.[18] Consistent with this mechanism,[4] allenylic magnesium reagents afford propargylic products and propargylic magnesium reagents provide allenylic products (Figure 2). DFT calculations in DCM show that the relative energy for the addition of the propargylic magnesium reagent is lower than that of the allenylic magnesium (1.5 vs 4.0 kcal/mol). This points out that the propargylic magnesium addition is a more favorable process compared to the allenylic magnesium addition, indicating that the homoallenyl amine is the only product, which is consistent with experimental results, where homopropargylic amines are not detected in the reaction media. The calculated energy for the TS also accounts for the findings in the diastereoselectivity of the allenylation reaction.

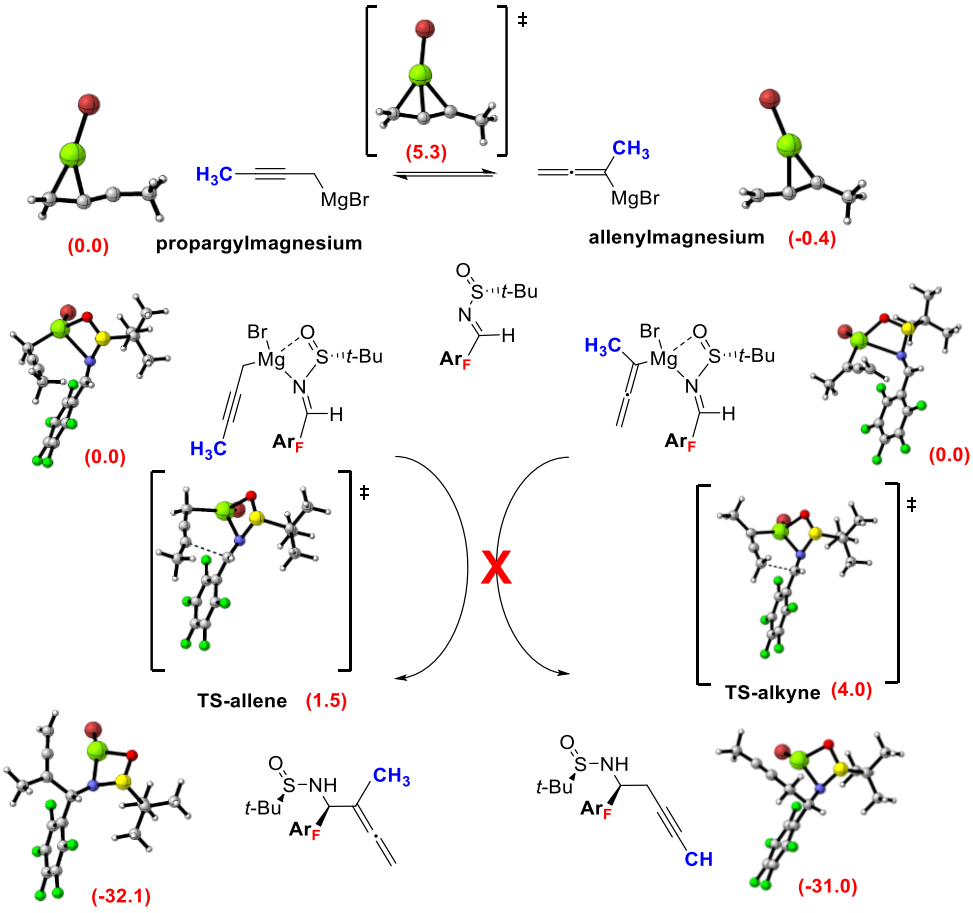


Figure 2. Proposed pathways for propargylation and allenylation of imine **1a** and optimized structures (for **1a** and **2c**) at wB97XD/6−311G(2d,2p) in DCM. Relative activation energies are given in brackets in kcal/mol.

In conclusion, we have disclosed that propargylation or allenylation of aryl fluorinated sulfinyl imines **1** can be performed in a regio- and diastereoselective way through S_E2' reaction of propargyl or propargylic magnesium reagents, respectively. A marked dependence of the diastereoselectivity with the solvent and the basicity of the sulfinyl imine was observed. Coordinating solvents and high diastereoselectivities were compatible only with the less basic sulfinyl imines of the series meanwhile non-coordinating solvent allows good diastereoselection in all cases. Propargylic magnesium

reagents showed a different behavior affording homoallenyl amines **4** as single regioisomers in non-coordinating solvents. DFT calculations helped to rationalize the experimental findings and to elucidate the mechanism supporting that coordination of N and O atoms (from the sulfinyl group or from the solvent) to the metal, plays a crucial role in determining the diastereoselectity of the propargylation/allenylation reaction. Further studies to extend its scope and complete its limitations are under progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, NMR data, DFT calculations data, and X-ray crystal structures (PDF).

Accession Codes

CCDC 2067817 and 2067822 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

[1] a) Nugent, T. C. Chiral Amine Synthesis, Wiley-VCH, Weinheim, 2008; b) Yin, Q.; Shi, Y.; Wang, J.; Zhang, X. Direct catalytic asymmetric synthesis of □-chiral primary amines. *Chem. Soc. Rev.* **2020**, *49*, 6141–6153; c) Ghislieri, D.; Turner, N. J. Biocatalytic Approaches to the Synthesis of Enantiomerically Pure Chiral Amines. *Top. Catal*. **2014**, *57*, 284–300.

[2] Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev*. **1998**, *98*, 1407–1438.

[3] a) Lin, G.-Q.; Xu, M-H.; Zhong, Y.-W.; Sun, X.-W. An Advance on Exploring *N-tert*-Butanesulfinyl Imines in Asymmetric Synthesis of Chiral Amines. *Acc. Chem. Res*. **2008**, *41*, 831–840; b) Ellman, J. A.; Timothy, D. O.; Tang, T. P. *N-tert*-butanesulfinyl imines: versatile intermediates for the asymmetric synthesis of amines. *Acc. Chem. Res*. **2002**, *35*, 984−995; c) Ellman, J. A.; Liu, G.; Cogan, D. A. Catalytic Asymmetric Synthesis of *tert*-Butanesulfinamide. Application to the Asymmetric Synthesis of Amines. *J. Am. Chem. Soc*. **1997**, *119*, 9913−9914.

[4] Wisniewska, H. N.; Jarvo, E. R. Enantioselective Propargylation and Allenylation Reactions of Ketones and Imines. *J. Org. Chem*. **2013**, *78*, 11629–11636.

[5] a) Thalma, Th.; Zhaman, F.; Hyland C. J. T.; Pyne S. G. Allenylation and Propargylation Reactions of Ketones, Aldehydes, Imines, and Iminium Ions Using Organoboronates and Related Derivatives. *Synthesis* **2017**, *49*, 1461−1480; b) Fandrick, D. R.; Hart, C. A.; Okafor, I. S.; Mercadante, M. A.; Sanyal, S.; Masters, J. T.; Sarvestani, M.; Fandrick, K. R.; Stockdill, J. L.; Grinberg, N.; Gonnella, N.; Lee, H.; Senanayake, C. H. Copper-Catalyzed Asymmetric Propargylation of Cyclic Aldimines. *Org. Lett*. **2016**, *18*, 6192–6195. c) García-Muñoz, M. J.; Foubelo, F.; Yus, M. Stereoselective Synthesis of 2-(2-Aminoalkyl)- and 1,3-Disubstituted Tetrahydro-1H-pyrido[4,3-b]- Benzofuran and Indole Derivatives. *J. Org. Chem*. **2016**, *81*, 10214–10226; d) Yamashita, Y.; Cui, Y.; Xie, P.; Kobayashi, S. Zinc Amide Catalyzed Regioselective Allenylation and Propargylation of Ketones with Allenyl Boronate. *Org. Lett*. **2015**, *17*, 6042−6045; e) Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. Silver-Catalyzed Enantioselective Propargylation Reactions of *N*-Sulfonylketimines. *Org. Lett*. **2015**, *17*, 5340–5343; f) García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. Indium-Promoted Diastereo- and Regioselective Propargylation of Chiral Sulfinylimines. *Eur. J. Org. Chem*. **2013**, 1287–1295; g) Acharya, H. P.; Kei Miyoshi, K.; Kobayashi, Y. Mercury-Free Preparation and Selective Reactions of Propargyl (and Propargylic) Grignard Reagents. *Org. Lett*. **2007**, *9*, 3535–3538.

[6] a) Llobat, A.; Sedgwick, D. M.; Cabré, A.; Román, R.; Mateu, N.; Escorihuela, J.; Medio-Simón, M.; Soloshonok, V. A.; Han, J.; Riera, A.; Fustero, S. Asymmetric Synthesis of Fluorinated Monoterpenic Alkaloid Derivatives from Chiral Fluoroalkyl Aldimines via the Pauson-Khand Reaction. *Adv. Synth. Catal*. **2020**, *362*, 1378–1384; b) Llobat, A.; Román, R.; Mateu, N.; Sedgwick, D. M.; Barrio, P.; Medio-Simón, M.; Fustero, S. The Fluoro Pauson-Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C-F Stereogenic Center. *Org. Lett*. **2019**, *21*, 7294–7297.

[7] Foubelo, F.; Yus, M. Chiral *N-tert*-Butylsulfinyl Imines: New Discoveries. *Chem. Rec*. **2021** doi.org/10.1002/tcr.202000122.

[8] a) Liu, S.; Zhu, L.; Zhang, T.; Zhong, K.; Li, S.-J.; Bai, R.; Lan, Y. How Solvents Control the Chemoselectivity in Rh-Catalyzed Defluorinated [4 + 1] Annulation. *Org. Lett*. **2021**, *23*, 1489–1494; b) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. Control of Diastereoselectivity by Solvent Effects in the Addition of Grignard Reagents to Enantiopure

t-Butylsulfinimine: Syntheses of the Stereoisomers of the Hydroxyl Derivatives of Sibutramine. *Org. Lett*. **2005**, *7*, 2599–2602.

[9] a) Grellepois, F.; Jamaa, A. B.; Gassama, A. Diastereoselective Addition of Organomagnesium and Organolithium Reagents to Chiral Trifluoromethyl *N*-*tert*-Butanesulfinyl Hemiaminals. *Eur. J. Org. Chem*. **2013**, 6694−6701; b) Hashmi, A. S. K.; Schäfer, S.; Bats, J. W.; Frey, W.; Rominger F. Gold Catalysis and Chiral Sulfoxides: Enantioselective Synthesis of Dihydoisoindol-4-ols. *Eur. J. Org. Chem*. **2008**, 4891–4999.

[10] a) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640; b) Yerien, D. E.; Bonesi, S.; Postigo, A. Fluorination methods in drug Discovery. *Org. Biomol. Chem*. **2016**, *14*, 8398–8427; c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem*. **2015**, *58*, 8315–8359; d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320–330.

[11] a) Tang, L.; Yang, Z.; Chang, X.; Jiao, J.; Ma, X.; Rao, W.; Zhou, Q.; Zheng, L. $K_2S_2O_8$-mediated selective trifluoromethylacylation and trifluoromethylarylation of alkenes under Transition-metal-free conditions: synthetic scope and mechanistic studies. *Org. Lett*. **2018**, *20*, 6520−6525; b) Song, P.; Yu, P.; Lin, J.-S.; Li, Y.; Yang, N.-Y.; Liu, X.-Y. Transition-Metal-Free β-C−H Bond Carbonylation of Enamides or Amides with a Trifluoromethyl Group as CO Surrogate for the Synthesis of 1,3-Oxazin-6-ones. *Org. Lett*. **2017**, *19*, 1330−1333; c) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Zhou, Z.-Z.; Hua, H.-L.; Liu, X.-Y.; Liang, Y.-M. Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes. *Org. Lett*. **2014**, *16*, 270−273.

[12] a) Wang, J.; Huang, B.; Gao, Y.; Yang, C.; Xia, W. Direct C–H Multifluoroarylation of Ethers through Hydrogen Atom Transfer Using Photoredox Catalysis. *J. Org. Chem*. **2019**, *84*, 6895–6903; b) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation to Access Fluorinated Building Blocks. *Chem. Rev*. **2015**, *115*, 931–972; c) Lu, F.; Sun, H.; Du, A.; Feng, L.; Li, X. Selective Alkylation and Arylation of C−F Bond with Grignard Reagents. *Org. Lett*. **2014**, *16*, 772−775.

[13] Reed, A. E.; Curtiss, L. A.; Weinhold, F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem. Rev*. **1988**, *88*, 899−926.

[14] Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Mont-gomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

[15] Hennum, M.; Fliegl, H.; Gundersen, L.-L.; Eisenstein, O. Mechanistic Insights on the Stereoselective Nucleophilic 1,2-Addition to Sulfinyl Imines. *J. Org. Chem.* **2014**, *79*, 2514–2521.

[16] a) Cruz-Delgado, B.; Rodríguez, R. I.; Rosado-Abón, A.; Sánchez-Obregón, R.; Yuste, F.; Alemán, J. Stereocontrolled Addition of Scrambling *ortho*-Sulfinyl Carbanions: Easy Access to Homopropargylamines and α-Allenylamines. *Org. Lett*. **2020**, *22*, 2431−2436; b) Li, M.-B.; Grape, E. S.; Bäckvall, J.-E. Palladium-Catalyzed Stereospecific Oxidative Cascade Reaction of Allenes for the Construction of Pyrrole Rings: Control of Reactivity and Selectivity *ACS Catal*. **2019**, *9*, 5184−5190; c) Jin, S. S.; Xu, M.-H. Highly Diastereoselective Indium-Mediated Allenylation of *N*-*tert*-Butanesulfinyl Imino Ester: Efficient Synthesis of Optically Active Allenylglycines *Adv. Synth. Catal*. **2010**, *352*, 3136–3140.

[17] Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. Silver-Catalyzed Enantioselective Propargylation Reactions of *N*-Sulfonylketimines. *Org. Lett*. **2015**, *17*, 5340–5343.

[18] When the addition of **2b** was performed at 30 °C in DCM, allene **4ab** was isolated as the only regioisomer, suggesting that isomerization was not fast.

Supporting Information

On the diastereoselectivity of the addition of propargylic magnesium reagents to fluorinated aromatic sulfinyl imines

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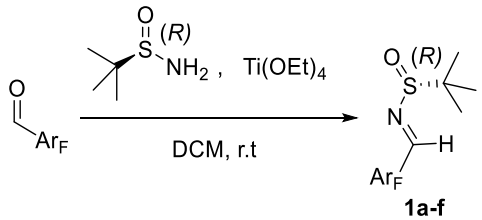
I. General Methods.

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. As a heat source oil baths were used. CH_2Cl_2 (DCM) was used without further purification. The reactions were monitored with the aid of TLC on 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz Bruker Avance III 300 spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points were measured on a Büchi B−540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P−1020 polarimeter at 25 °C.

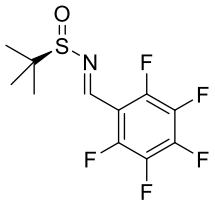
II. General procedure for the condensation of *N*-*tert*-butanesulfinyl aldimines 1.



1a-f

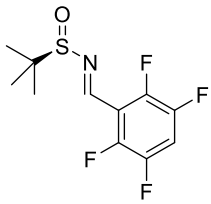
The corresponding aldehyde (5 mmol) was dissolved in DCM (0.1 M) at room temperature in a round-bottomed flask. Titanium tetroxide (IV) (20 mmol) and (*R*)-*tert*-butylsulfinamide (6 mmol) were added and the mixture was stirred at room temperature overnight. Once the reaction was complete (TLC analysis), an aqueous saturated solution of $NaHCO_3$ was added and the mixture was filtered on Celyte® in order to remove the titanium salts. Finally, the filtered organic phase is dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude mixture was purified by column chromatography using deactivated silica gel (*n*-hexane:EtOAc).

(*R*,*E*)-2-Methyl-*N*-((perfluorophenyl)methylene)propane-2-sulfinamide (1a). According to



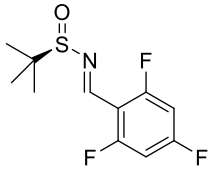
general procedure from 1.00 g (5.1 mmol) of 2,3,4,5,6-pentafluorobenzaldehyde, compound **1a** was obtained as a yellow solid after column chromatography on silica gel using *n*-hexane:EtOAc (4:1) as eluent (1.28 g, 84% yield). Mp: 96–98 °C; $[\alpha]^{25}_{D}$ = –55.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.71 (s, 1H), 1.27 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -139.90 – -140.05 (m, 2F), -147.20 – -147.38 (m, 1F), -160.75 – -160.96 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 151.2, 148.1–144.3 (m, 2C–F), 145.3–141.5 (m, 1C–F), 139.8–135.9 (m, 2C–F), 109.7–109.4 (m, 1C), 58.5, 22.5. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{11}H_{11}F_5NOS$ 300.0403; Found 300.0409.

(*R*,*E*)-2-Methyl-*N*-(2,3,5,6-tetrafluorobenzylidene)propane-2-sulfinamide (1b). According



to general procedure from 500 mg (2.81 mmol) of 2,3,5,6-tetrafluorobenzaldehyde, compound **1b** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (4:1) as eluent (636 mg, 80% yield). Mp: 74–76 °C; $[\alpha]^{25}_{D}$ = –50.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.69 (s, 1H), 7.24–7.13 (m, 1H), 1.20 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -138.03 – -138.17 (m, 2F), -141.02 – -141.16 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 151.9, 147.9–144.19 (m, 2C–F), 147.3–143.7 (m, 2C–F), 114.4 (t, *J* = 10.8 Hz), 109.1 (t, *J* = 22.6 Hz), 58.4, 22.4. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{11}H_{12}F_4NOS$ 282.0579; Found 282.0570.

(*R*,*E*)-2-Methyl-*N*-(2,4,6-trifluorobenzylidene)propane-2-sulfinamide (1c). According to



general procedure, from 500 mg (3.12 mmol) of 2,4,6-trifluorobenzaldehyde, compound **1c** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (4:1) as eluent (612 mg, 72% yield); $[\alpha]^{25}_{D}$ = –64.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.68 (s, 1H), 6.76–6.68 (m, 2H), 1.22 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -99.93 (t, *J* = 9.7 Hz, 1F), -106.89 (d, *J* = 9.7 Hz, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 164.8 (dt, $^{1}J_{CF}$ = 257.0 Hz, $^{3}J_{CF}$ = 15.8 Hz), 162.7 (ddd, $^{1}J_{CF}$ = 257.0 Hz,

$^{3}J_{CF}$ = 15.8 Hz, *J* = 8.5 Hz), 152.3, 101.3 (td, *J* = 25.7, 3.9 Hz), 58.0, 22.5. HRMS (ESI): m/z Calcd for $C_{11}H_{13}F_3NOS$ [M+H$^+$]: 264.0661; Found 264.0664.

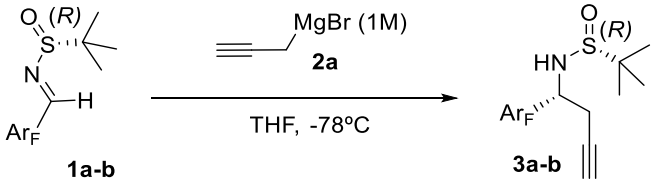
(*R*,*E*)-*N*-(2,6-Difluorobenzylidene)-2-methylpropane-2-sulfinamide (1d). According to general procedure, from 500 mg (3.52 mmol) of 2,6-difluorobenzaldehyde, compound **1d** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (4:1) as eluent (783 mg, 91% yield). Mp: 49–51 °C; $[\alpha]^{25}_{D}$ = −61.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 7.45–7.35 (m 1H), 6.98–6.91 (m, 2H), 1.23 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -110.72 (s, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 163.8 (d, $^{3}J_{CF}$ = 5.8 Hz), 160.3 (d, $^{3}J_{CF}$ = 5.8 Hz), 153.3, 133.7 (t, *J* = 11.0 Hz), 112.2 (d, *J* = 25.2 Hz), 58.0, 22.5. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{11}H_{14}F_2NOS$ 246.0759; Found 246.0758.

(*R*,*E*)-*N*-(2-Fluorobenzylidene)-2-methylpropane-2-sulfinamide (1e). According to general procedure, from 500 mg (4.03 mmol) of 2-fluorobenzaldehyde, compound **1e** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (4:1) as eluent (611 mg, 67% yield); $[\alpha]^{25}_{D}$ = −78.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.76 (s, 1H), 7.86 (td, *J* = 7.6, 1.8 Hz, 1H), 7.39-7.32 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.03–6.97 (m, 1H), 1.13 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -118.18 (s, 1F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 160.4 (d, $^{1}J_{CF}$ = 256.9 Hz), 156.4 (d, *J* = 5.4 Hz), 134.2 (d, *J* = 8.8 Hz), 128.6 (d, *J* = 2.0 Hz), 124.5 (d, *J* = 3.7 Hz), 122.0 (d, *J* = 9.4 Hz), 116.2 (d, *J* = 20.8 Hz), 57.8, 22.6. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{11}H_{15}FNOS$ 228.0853; Found 228.0853.

(*R,E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (1f). Spectroscopic data of compound **1f** were in agreement with those previously reported.[1]

III. General procedure for the diastereoselective propargylation of sulfinyl imines.

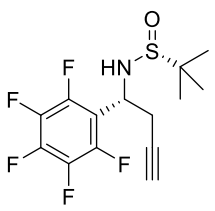
III.a. General procedure for the propargylation reaction to sulfinamides 3 in THF.



First, a 1 M solution of Grignard reagent in diethyl ether was prepared by adding magnesium turnings (214 mg, 11 mmol), mercury chloride (II) (19 mg, 1.7 mol%), two iodine balls and Et_2O (5 mL, 1 M) to a sealed tube under a nitrogen atmosphere. This mixture was cooled to 0 °C and propargyl bromide was added slowly (0.56 mL, 5 mmol). The mixture was then heated an oil bath and stirred at 35 °C for 1.5 h. After this time, the mixture was cooled to room temperature, the stirring stopped, and the solution was used as a reagent in the next step without purification.

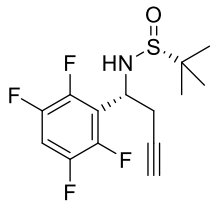
Next, for the asymmetric propargylation, a solution of the corresponding fluorinated imine **1** (1 mmol) in THF (0.1 M) was cooled to –78 °C. The freshly prepared Grignard reagent (1.5 mmol) was slowly added, and the reaction mixture was stirred at this temperature until the reaction was complete (TLC analysis, typically 24 h). The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by flash column chromatography using deactivated silica gel (*n*-hexane:EtOAc).

(*R*$_S$,*R*)-2-Methyl-*N*-(1-(perfluorophenyl)but-3-yn-1-yl)propane-2-sulfinamide (3a).

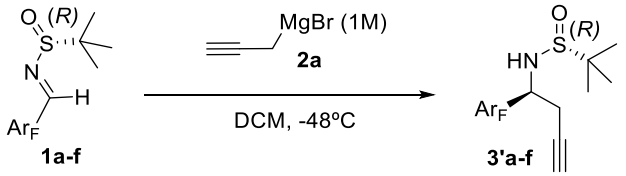


According to general procedure, from 506 mg (0.91 mmol) of **1a**, compound **3a** was obtained as a yellowish oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (383 mg, 67% yield); $[\alpha]^{25}_D$ = +45.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.89–4.80 (m, 1H), 3.99 (d, *J* = 10.6 Hz), 2.81 (ddd, *J* = 16.7, 6.8, 2.6 Hz, 1H), 2.71 (ddd, *J* = 16.7, 8.2, 2.6 Hz, 1H) 1.98 (t, *J* = 2.6 Hz, 1H), 1.18 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.77 – -142.90 (m, 2F), -154.15 – -154.30 (m, 1F), -161.19 – -161.38 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 146.6–143.1 (m, 2C–F), 142.9–139.2 (m, 1C–F), 139.0–135.6 (m, 2C–F), 115.2–114.8 (m, 1C), 78.4, 71.6, 56.7,

51.0, 26.3, 22.3 HRMS (ESI) m/z: [M + H^+] Calcd for $C_{14}H_{15}F_5NOS$ 340.0790; Found 340.0791.

(*R*$_S$,*R*)-2-Methyl-*N*-(1-(2,3,5,6-tetrafluorophenyl)but-3-yn-1-yl)propane-2-sulfinamide (3b).  According to general procedure, from 103 mg (0.37 mmol) of **1b**, compound **3b** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (71 mg, 61% yield). Mp: 82–84 °C; $[\alpha]^{25}_D$ = +51.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.07–6.96 (m, 1H), 4.97–4.88 (m, 1H), 4.04 (d, *J* = 10.5 Hz), 2.84 (ddd, *J* = 16.7, 7.0, 2.6 Hz, 1H), 2.74 (ddd, *J* = 16.7, 7.9, 2.6 Hz, 1H) 1.99 (t, *J* = 2.6 Hz, 1H), 1.22 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) 138.15 – -138.27 (m, 2F), -143.32 – -143.45 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 147.8–144.09 (m, 2C–F), 146.1–142.5 (m, 2C–F), 120.7 (t, *J* = 15.1 Hz, 1C), 105.9 (t, *J* = 22.6 Hz, 1C), 78.7, 71.4, 56.7, 51.4, 26.4, 22.4. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{14}H_{16}F_4NOS$ 322.0879; Found 322.0883.

III.b. General procedure for the propargylation reaction to sulfinamides 3' in DCM.

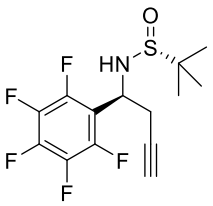


First, a 1 M solution of Grignard reagent in diethyl ether was prepared by adding magnesium turnings (214 mg, 11 mmol), mercury chloride (II) (19 mg, 1.7 mol%), two iodine balls and Et_2O (5 mL, 1 M) to a sealed tube under a nitrogen atmosphere. This mixture was cooled to 0 °C and propargyl bromide was added slowly (0.56 mL, 5 mmol). The mixture was then stirred at 35 °C for 1.5 h. After this time, the mixture was cooled to room temperature, the stirring stopped, and the solution was used as a reagent in the next step without purification.

Next, for the asymmetric propargylation, a solution of the corresponding fluorinated imine **1** (1 mmol) in DCM (0.1 M) was cooled to –48 °C. The freshly prepared Grignard reagent (1.5 mmol) was slowly added, and the reaction mixture was stirred at this temperature until the reaction was complete (TLC analysis, typically 18–24 h). The

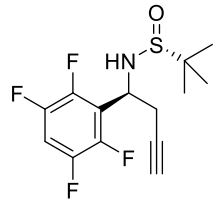
reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by flash column chromatography using deactivated silica gel (*n*-hexane:EtOAc).

(*Rs,S*)-2-Methyl-*N*-(1-(perfluorophenyl)but-3-yn-1-yl)propane-2-sulfinamide (3'a).



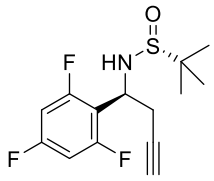
According to general procedure, from 51 mg (0.17 mmol) of **1a**, compound **3'a** was obtained as a yellowish solid after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (46 mg, 80% yield). Mp: 83–85 °C; $[\alpha]^{25}_D$ = –50.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.08–6.97 (m, 1H), 4.99 (q, *J* = 7.8 Hz, 1H), 4.00 (d, *J* = 7.4 Hz), 2.97 (ddd, *J* = 16.6, 6.4, 2.6 Hz, 1H), 2.84 (ddd, *J* = 16.6, 8.2, 2.6 Hz, 1H) 2.04 (t, *J* = 2.6 Hz, 1H), 1.18 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -141.91 – -142.04 (m, 2F), -153.65 – -153.81 (m, 1F), -161.10 – -161.30 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 146.8–143.1 (m, 2C–-F), 142.8–139.5 (m, 2C–F), 136.2–135.7 (m, 1C–F), 114.4–113.9 (m, 1C), 78.3, 72.1, 56.4, 50.9, 26.5, 22.3. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{14}H_{15}F_5NOS$ 340.0790; Found 340.0791.

(*Rs,S*)-2-Methyl-*N*-(1-(2,3,5,6-tetrafluorophenyl)but-3-yn-1-yl)propane-2-sulfinamide (3'b).



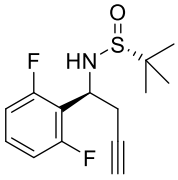
According to general procedure, from 517 mg (0.91 mmol) of **1b**, compound **3'b** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (405 mg, 68% yield). Mp: 58–60 °C; $[\alpha]^{25}_D$ = –49.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.08–6.97 (m, 1H), 5.01 (q, *J* = 7.8 Hz, 1H), 4.04 (d, *J* = 7.8 Hz), 2.97 (ddd, *J* = 16.6, 6.4, 2.6 Hz, 1H), 2.84 (ddd, *J* = 16.6, 8.1, 2.6 Hz, 1H) 2.02 (t, *J* = 2.6 Hz, 1H), 1.16 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -138.28 – -138.41 (m, 2F), -142.64 – -142.77 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 147.7–144.06 (m, 2C–F), 146.2-142.7 (m, 2C–F), 119.9 (t, *J* = 14.7 Hz, 1C), 105.8 (t, *J* = 22.6 Hz, 1C), 78.4, 71.9, 56.4, 51.3, 26.5, 22.3. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{14}H_{16}F_4NOS$ 322.0879; Found 322.0883.

(*R*$_S$,*S*)-2-Methyl-*N*-(1-(2,4,6-trifluorophenyl)but-3-yn-1-yl)propane-2-sulfinamide (3'c).



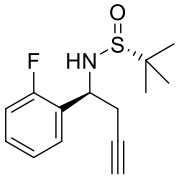
According to general procedure, from 282 mg (0.91 mmol) of **1c**, compound **3'c** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (290 mg, 89% yield); $[\alpha]^{25}_D$ = –53.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.66–6.56 (m, 2H), 4.89 (q, *J* = 7.3 Hz, 1H), 3.97 (d, *J* = 7.3 Hz, 1H), 2.90 (ddd, *J* = 16.6, 6.8, 2.6 Hz, 1H), 2.75 (ddd, *J* = 16.6, 8.0, 2.6 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.10 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -107.66 (t, J_{FF} = 6.7 Hz, 1F), -110.12 (d, J_{FF} = 6.7 Hz, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 162.2 (dt, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 15.9 Hz, C-F), 161.2 (ddd, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 14.8, 11.0 Hz, C-F) 112.8 (td, *J* = 17.1, 4.9 Hz), 101.0–100.2 (m, 1C), 79.1, 71.5, 56.1, 50.3, 26.4, 22.3. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{14}H_{17}F_3NOS$ 304.0974; Found 304.0977.

(*R*$_S$,*S*)-*N*-(1-(2,6-Difluorophenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (3'd).



According to general procedure, from 223 mg (0.91 mmol) of **1d**, compound **3'd** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (179 mg, 70% yield). Mp: 70–72 °C; $[\alpha]^{25}_D$ = –44.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.24–7.14 (m, 1H), 6.87–6.78 (m, 2H), 4.94 (dd, *J* = 14.8, 7.7 Hz, 1H), 4.00 (d, *J* = 7.7 Hz, 1H), 2.93 (ddd, *J* = 16.6, 6.7, 2.6 Hz, 1H), 2.77 (ddd, *J* = 16.6, 8.0, 2.6 Hz, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.09 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -113.52 (s, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 161.0 (d, $^1J_{CF}$ = 248.7 Hz, $^3J_{CF}$ = 8.1 Hz), 129.8 (t, *J* = 10.7 Hz), 116.5 (t, *J* = 16.7 Hz), 111.8 (d, *J* = 26.2 Hz), 79.3, 71.3, 56.1, 50.8, 26.6, 22.3. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{14}H_{17}F_2NOS$ 286.1072; Found 286.1073.

(*R*$_S$,*S*)-*N*-(1-(2-Fluorophenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (3'e).

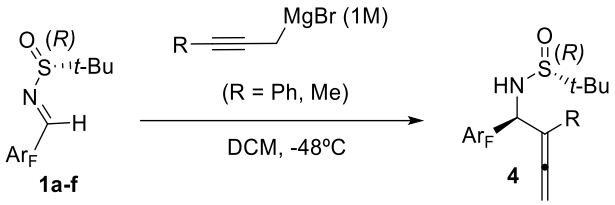


According to general procedure, from 74 mg (0.33 mmol) of **1e**, compound **3'e** was obtained as a white solid after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (76 mg, 86% yield). Mp: 100–102 °C; $[\alpha]^{25}_D$ = –47.6 (c 1.0, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): δ (ppm) 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.25-7.17 (m, 1H), 7.06 (td, *J* = 7.5, 1.2 Hz, 1H), 6.97 (ddd, *J* = 10.6, 8.2, 1.2 Hz, 1H), 4.81 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.95 (d, *J* = 5.1 Hz, 1H), 2.82–2.64 (m, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.15 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -117.85 (s, 1F); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 160.4 (d, $^1J_{CF}$ = 247.3 Hz), 129.5 (d, *J* = 8.4 Hz), 128.7 (d, *J* = 4.1 Hz), 127.6 (d, *J* = 12.5 Hz), 124.1 (d, *J* =3.5 Hz), 115.7 (d, *J* = 21.8 Hz), 79.5, 72.2, 56.0, 51.9, 27.3, 22.5. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{14}H_{18}FNOS$ 268.1166; Found 268.1163.

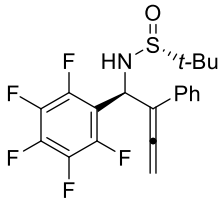
(*Rs,S*)-*N*-(1-(Phenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (3'f). Spectroscopic data of compound **3'f** were in agreement with those previously reported.[1]

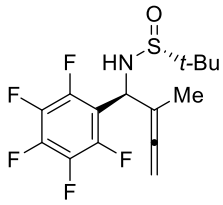
IV. General procedure for the propargylation reaction in DCM.

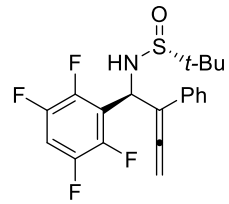


First, a 1 M solution of Grignard reagent in diethyl ether was prepared by adding magnesium turnings (214 mg, 11 mmol), mercury chloride (II) (19 mg, 1.7 mol%), two iodine balls and Et_2O (5 mL, 1 M) to a sealed tube under a nitrogen atmosphere. This mixture was cooled to 0 °C and the corresponding bromide was added slowly (0.56 mL, 5 mmol). The mixture was then heated an oil bath and stirred at 35 °C for 1.5 h. After this time, the mixture was cooled to room temperature, the stirring stopped, and the solution was used as a reagent in the next step without purification.

For the next asymmetric propargylation, a solution of the corresponding fluorinated imine **1** (1 mmol) in DCM (0.1 M) was cooled to –48 °C. The freshly prepared Grignard reagent (1.5 mmol) was slowly added, and the reaction mixture was stirred at this temperature until the reaction was complete (TLC analysis, typically 18–24 h). The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by flash column chromatography using deactivated silica gel (*n*-hexane:EtOAc).

(*R*$_S$,*S*)-2-Methyl-*N*-(1-(perfluorophenyl)-2-phenyl-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4ab).  According to general procedure from 51 mg (0.17 mmol) of **1a**, compound **4ab** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (51 mg, 72% yield); $[\alpha]^{25}_D$ = –90.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38–7.29 (m, 5H), 5.95–5.92 (m, 1H), 5.44–5.32 (m, 2H), 4.19 (d, *J* = 4.8 Hz, 1H), 1.17 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -141.48 – -141.58 (m, 2F), -147.20 – -153.90 (t, *J* = 21.0 Hz, 1F), -161.46 – -161.64 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 207.4, 147.6–144.0 (m, 2C–F), 146.5–143.0 (m, 2C-F), 132.9, 128.8, 127.8, 126.6, 120.5 (t, *J* = 13.8 Hz, C–F), 106.6, 105.7 (t, *J* = 22.6 Hz, C), 83.0, 56.5, 49.0, 22.4. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{20}H_{19}F_5NOS$ 416.1099; Found 416.1102.

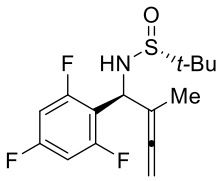
(*R*$_S$,*S*)-2-Methyl-*N*-(2-methyl-1-(perfluorophenyl)-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4ac). According to general procedure from 53 mg (0.18 mmol) of **1a**,  compound **4ac** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (54 mg, 85% yield); $[\alpha]^{25}_D$ = –93.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.20–5.15 (m, 1H), 4.99–4.86 (m, 2H), 4.09 (d, *J* = 6.4 Hz, 1H), 1.73 (t, *J* = 3.1 Hz, 3H), 1.16 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.44 – -142.56 (m, 2F), -147.20 – -154.45 – -154.60 (m, 1F), -161.58 – -161.76 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 205.0, 146.7–143.0 (m , 2C-F), 142.6–142.1 (m, 1C–F), 139.4–135.6 (m, 2C–F), 115.1–114.6 (m ,1C), 99.0, 79.9, 56.4, 52.4, 22.4, 16.2. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{15}H_{17}F_5NOS$ 354.0943; Found 354.0946.

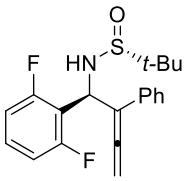
(*R*$_S$,*S*)-2-Methyl-*N*-(2-phenyl-1-(2,3,5,6-tetrafluorophenyl)-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4bb).  According to general procedure from 50 mg (0.18 mmol) of **1b**, compound **4bb** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (48 mg, 68% yield); $[\alpha]^{25}_D$ = –61.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.39–7.28 (m, 5H), 7.01–6.90 (m, 1H), 5.98–5.94 (m, 1H), 5.44–5.32 (m, 2H), 4.22 (d, *J* = 5.3 Hz, 1H), 1.17 (s,

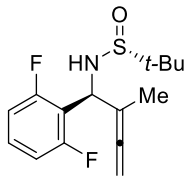
9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -138.64 – -138.76 (m, 2F), -142.19 – -142.32 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 207.3, 147.7–144.0 (m, 2C–F), 146.4–143.0 (m, 2C–F), 132.9, 128.8, 127.8, 126.6, 120.5 (t, *J* = 13.8 Hz, C), 106.6, 105.7 (t, *J* = 22.6 Hz, CH), 83.0, 56.5, 49.0, 22.4. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{20}H_{20}F_4NOS$ 398.1203; Found398.1196.

(*Rs,S*)-2-Methyl-*N*-(2-methyl-1-(2,3,5,6-tetrafluorophenyl)-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4bc). According to general procedure from 50 mg (0.18 mmol) of **1b**, compound **4bc** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (60 mg, 88% yield); $[\alpha]^{25}_D$ = –79.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.06–6.95 (m, 1H), 5.23–5.19 (m, 1H), 4.98–4.86 (m, 2H), 4.15 (d, *J* = 6.9 Hz, 1H), 1.73 (t, *J* = 3.1 Hz, 3H), 1.15 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -138.70 – -138.83 (m, 2F), -143.09 – -143.21 (m, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 205.1, 147.1–144.4 (m, 2C–F), 145.8–143.1 (m, 2C–F), 120.7 (t, *J* = 14.4 Hz, C), 105.3, 99.1, 79.8, 56.4, 52.8, 22.4, 16.2. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{15}H_{18}F_4NOS$ 336.1037; Found 336.1040.

(*Rs,S*)-2-Methyl-*N*-(2-phenyl-1-(2,4,6-trifluorophenyl)-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4cb). According to general procedure, from 55 mg (0.19 mmol) of **1c**, compound **4cb** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (53 mg, 72% yield); $[\alpha]^{25}_D$ = –96.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38–7.26 (m, 5H), 6.61–6.55 (m, 2H), 5.91–5.86 (m, 1H), 5.39–5.28 (m, 2H), 4.16 (d, *J* = 5.1 Hz, 1H), 1.15 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -107.78 (t, J_{FF} = 6.9 Hz, 1F), -109.61 (d, J_{FF} = 6.2 Hz, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 207.5, 162.2 (dt, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 15.8 Hz, C–F), 161.4 (ddd, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 14.8, 10.6 Hz, C–F), 131.7, 128.6, 127.6, 126.6, 113.3 (td, *J* = 16.0, 4.9 Hz), 107.1, 101.0–100.2 (m, 1C), 82.5, 56.3, 48.1, 22.4. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{20}H_{21}F_3NOS$ 380.1298; Found 380.1290.

(*R*$_S$,*S*)-2-Methyl-*N*-(2-methyl-1-(2,4,6-trifluorophenyl)-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide (4cc).  According to general procedure, from 53 mg (0.20 mmol) of **1c**, compound **4cc** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (43 mg, 68% yield); $[\alpha]^{25}_D$ = −153.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.68–6.62 (m, 2H), 5.18–5.13 (m, 1H), 4.96–4.85 (m, 2H), 4.12 (d, *J* = 6.5 Hz, 1H), 1.71 (t, *J* = 3.1 Hz, 3H), 1.15 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -108.31 (t, J_{FF} = 6.6 Hz, 1F), -110.59 (d, J_{FF} = 6.6 Hz, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 205.0, 162.0 (dt, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 15.8 Hz, C–F), 161.2 (ddd, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 14.8, 10.8 Hz, C–F), 113.4 (td, *J* = 16.6, 4.9 Hz), 100.9–100.2 (m, 1C), 99.7, 79.4, 56.2, 51.7, 22.4, 16.2. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{15}H_{19}F_3NOS$ 318.1135; Found 318.1134.

(*R*$_S$,*S*)-*N*-(1-(2,6-Difluorophenyl)-2-phenyl-3λ^5-buta-2,3-dien-1-yl)-2-methylpropane-2-sulfinamide (4db).  According to general procedure, from 55 mg (0.22 mmol) of **1d**, compound **4db** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (59 mg, 73% yield); $[\alpha]^{25}_D$ = −96.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38–7.23 (m, 5H), 7.20–7.12 (m, 1H), 6.82–6.76 (m, 2H), 5.94–5.90 (m, 1H), 5.38–5.26 (m, 2H), 4.21 (d, *J* = 5.8 Hz, 1H), 1.13 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -112.94 (s, 2F); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 207.6, 161.2 (dd, *J* = 250, 7.8 Hz, 2C–F), 133.5, 131.7, 129.6 (t, *J* = 10.7 Hz, 1C), 128.5, 127.4, 126.7, 117.0 (t, *J* = 15.8 Hz, C-F), 111.7 (d, *J* = 26.0 Hz, CH), 82.5, 56.3, 48.6, 22.4. HRMS (ESI) m/z: [M + H$^+$] Calcd for $C_{20}H_{22}F_2NOS$ 362.1380; Found 362.1385.

(*R*$_S$,*S*)-*N*-(1-(2,6-Difluorophenyl)-2-methyl-3λ^5-buta-2,3-dien-1-yl)-2-methylpropane-2-sulfinamide (4dc).  According to general procedure, from 60 mg (0.24 mmol) of **1d**, compound **4dc** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (6:1) as eluent (51 mg, 70% yield); $[\alpha]^{25}_D$ = −128.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.24–7.18 (m, 1H), 6.88–6.82 (m, 2H), 5.22–5.17 (m, 1H), 4.94–4.82 (m, 2H), 4.17 (d, *J* = 7.1 Hz, 1H), 1.69 (t, *J* = 3.1 Hz, 3H), 1.13 (s, 9H); ^{19}F

NMR (282 MHz, $CDCl_3$): δ (ppm) -113.89 (s, 2F); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 205.0, 161.0 (dd, *J* = 250, 8.0 Hz, 2C–F), 129.3 (t, *J* = 10.6 Hz, 1C), 117.1 (t, *J* = 16.3 Hz, C-F), 111.6 (d, *J* = 26.0 Hz, CH), 99.9, 79.2, 56.2, 52.2, 22.4, 16.2. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{15}H_{20}F_2NOS$ 300.1228; Found 300.1228.

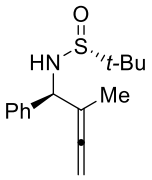
(*R*$_S$,*S*)-*N*-(1-(2-Fluorophenyl)-2-phenyl-3λ^5-buta-2,3-dien-1-yl)-2-methylpropane-2-sulfinamide (4eb). According to general procedure, from 51 mg (0.22 mmol) of **1e**, compound **4eb** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (10:1) as eluent (46 mg, 61% yield); $[\alpha]^{25}_D$ = −81.7 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33–7.29 (m, 2H), 7.23–7.08 (m, 5H), 7.02–6.92 (m, 2H), 5.79–5.75 (m, 1H), 5.31–5.18 (m, 2H), 3.83 (d, *J* = 4.3 Hz, 1H), 1.10 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -117.63 (s, 1F); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 208.4, 160.8 (d, *J* = 250 Hz, C–F), 133.5, 129.5 (d, *J* = 8.4 Hz), 129.4 (d, *J* = 3.6 Hz), 128.6, 127.7 (d, *J* = 12.8 Hz), 127.4, 126.6, 124.1 (d, *J* = 3.6 Hz), 115.5 (d, *J* = 21.9 Hz), 108.4, 82.5, 56.2, 51.0, 22.5. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{20}H_{23}FNOS$ 344.1475; Found 344.1479.

(*R*$_S$,*S*)-*N*-(1-(2-Fluorophenyl)-2-methyl-3λ^5-buta-2,3-dien-1-yl)-2-methylpropane-2-sulfinamide (4ec). According to general procedure, from 53 mg (0.22 mmol) of **1e**, compound **4ec** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (10:1) as eluent (55 mg, 84% yield); $[\alpha]^{25}_D$ = −133.4 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.34–7.22 (m, 2H), 7.14–7.00 (m, 2H), 5.12–5.08 (m, 1H), 4.98–4.88 (m, 2H), 3.88 (d, *J* = 3.7 Hz, 1H), 1.63 (t, *J* = 3.1 Hz, 3H), 1.16 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -118.09 – -118.17 (m, 1F); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 204.9, 161.0 (d, *J* = 250 Hz, C–F), 129.4 (d, *J* = 7.1 Hz), 129.3 (d, *J* = 2.6 Hz), 127.6 (d, *J* = 12.7 Hz), 124.1 (d, *J* = 3.6 Hz), 115.5 (d, *J* = 22.0 Hz), 101.4, 79.2, 56.1, 53.4, 22.6, 16.3. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{15}H_{21}FNOS$ 282.1324; Found 282.1322.

(*R*$_S$,*R*)-*N*-(1,2-Diphenyl-3λ^5-buta-2,3-dien-1-yl)-2-methylpropane-2-sulfinamide (4fb). According to general procedure, from 55 mg (0.26 mmol) of **1f**, compound **4fb** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (10:1) as eluent (44 mg, 52% yield); $[\alpha]^{25}_D$ =

−124.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.36–7.10 (m, 10H), 5.41–5.38 (m, 1H), 5.29–5.17 (m, 2H), 3.88 (d, *J* = 3.5 Hz, 1H), 1.11 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 208.2, 140.2, 133.8, 128.5, 128.5, 128.4, 127.9, 127.3, 126.8, 109.4, 81.9, 57.2, 56.1, 22.6. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{20}H_{24}NOS$ 326.1572; Found 326.1573.

(*R*$_S$,*R*)-2-Methyl-*N*-(2-methyl-1-phenyl-3λ^5-buta-2,3-dien-1-yl)propane-2-sulfinamide



(4fc). According to general procedure, from 76 mg (0.36 mmol) of **1f**, compound **4fc** was obtained as a colorless oil after column chromatography on silica gel using *n*-hexane:EtOAc (10:1) as eluent (64 mg, 67% yield); $[\alpha]^{25}_D$ = −128.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.28–7.23 (m, 5H), 4.91–4.87 (m, 2H), 4.68–4.65 (m, 1H), 3.83 (d, *J* = 2.0 Hz, 1H), 1.50 (t, *J* = 3.0 Hz, 3H), 1.11 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 204.5, 140.0, 128.4, 128.3, 128.0, 102.1, 78.7, 59.3, 55.9, 22.6, 16.2. HRMS (ESI) m/z: [M + H^+] Calcd for $C_{15}H_{22}NOS$ 264.1416; Found 264.1417.

V. X-ray structure of compound 3b (Deposition Number 2067822).

Experimental

Single crystals of $C_{14}H_{15}F_4NOS$ [**CCDC 2067822**] were obtained by slow evaporation method at room temperature using chloroform as solvent. A suitable crystal was selected and mounted on a SuperNova, Single source at offset, Atlas diffractometer. The crystal was kept at 150.00(10) K during data collection. Using Olex2,[2] the structure was solved with the ShelXS[3] structure solution program using Direct Methods and refined with the ShelXL[4] refinement package using Least Squares minimization. Displacement ellipsoids are drawn at the 50% probability level.

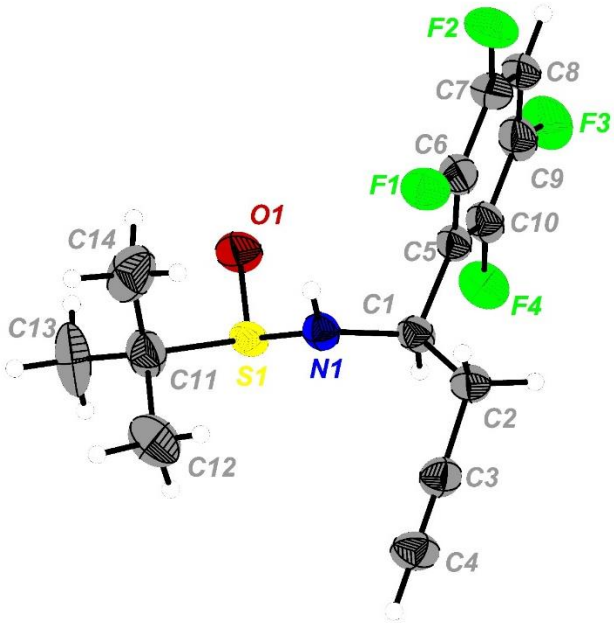


Table S1. Crystal data and structure refinement for CCDC 2067822.

Identification code	CCDC 2067822
Empirical formula	$C_{14}H_{15}F_4NOS$
Formula weight	321.33
Temperature/K	150.4(5)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.8963(3)
b/Å	10.1860(3)
c/Å	10.2163(4)
α/°	90.0
β/°	107.419(4)
γ/°	90.0
Volume/Å^3	784.04(5)
Z	2
ρ_{calc}g/cm^3	1.361
μ/mm^{-1}	2.221
F(000)	332.0
Crystal size/mm^3	0.343 × 0.272 × 0.114
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.072 to 137.984
Index ranges	-9 ≤ h ≤ 9, -12 ≤ k ≤ 12, -12 ≤ l ≤ 11
Reflections collected	14341
Independent reflections	2909 [R_{int} = 0.0352, R_{sigma} = 0.0300]
Data/restraints/parameters	2909/2/196
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0378, wR_2 = 0.0932
Final R indexes [all data]	R_1 = 0.0431, wR_2 = 0.0977

Largest diff. peak/hole / e $Å^{-3}$	0.21/-0.40
Flack parameter	-0.007(10)
Friedel coverage	99%
Flack x	0.007(10)
Hooft y	-0.013(5)
P2(wrong)	$<10^{-99}$

Table S2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for CCDC 2067822. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	3522.0(11)	6708.1(9)	2607.7(8)	33.6(2)
F4	4687(3)	5356(2)	6429(2)	50.3(6)
F1	2501(3)	2462(2)	2698(2)	48.8(6)
F2	248(3)	1452(3)	3927(3)	66.0(8)
F3	2387(4)	4366(3)	7621(3)	62.5(8)
O1	1894(3)	6848(3)	3034(3)	45.9(7)
N1	4058(4)	5140(3)	2522(3)	33.4(7)
C5	3694(5)	3926(4)	4536(4)	33.8(8)
C10	3599(6)	4386(4)	5788(4)	39.1(9)
C1	4966(5)	4525(4)	3852(4)	34.1(8)
C3	7718(5)	4199(4)	3220(5)	39.9(9)
C6	2532(5)	2917(4)	3947(4)	39.5(9)
C9	2411(6)	3876(4)	6411(4)	46.0(11)
C7	1363(5)	2402(4)	4579(5)	45.8(10)
C11	2858(6)	7089(4)	767(4)	48.6(11)
C8	1272(5)	2878(4)	5804(5)	47.7(11)
C2	6338(5)	3519(4)	3664(4)	39.2(9)
C4	8790(6)	4789(4)	2885(5)	46.5(10)
C14	1323(7)	6221(6)	-14(5)	66.2(15)
C12	4480(7)	6912(6)	264(5)	69.5(15)
C13	2295(10)	8533(6)	710(6)	81.0(18)

Table S3. Anisotropic Displacement Parameters ($Å^2×10^3$) for CCDC 2067822. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+…]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	34.7(4)	36.1(4)	34.8(4)	1.8(4)	17.5(3)	-0.4(4)
F4	64.6(15)	46.1(13)	45.6(14)	-8.6(11)	24.8(12)	-6.9(12)
F1	49.3(14)	52.3(14)	45.9(14)	-7.0(11)	15.7(11)	-10.5(11)
F2	55.8(15)	66.2(19)	74.6(18)	7.5(15)	17.3(13)	-25.9(14)
F3	77(2)	72.7(19)	53.9(16)	5.8(14)	43.4(15)	13.5(14)
O1	44.4(14)	52.7(16)	50.1(16)	1.9(15)	28.4(12)	5.7(13)
N1	36.3(16)	35.7(16)	30.7(16)	0.9(13)	13.9(13)	1.2(13)
C5	32.9(18)	35.1(18)	36.3(19)	6.8(16)	14.8(16)	4.6(15)
C10	43(2)	39(2)	41(2)	7.1(18)	21.2(19)	7.3(17)
C1	36(2)	35.6(18)	34.4(19)	2.2(15)	16.4(17)	0.1(15)
C3	37(2)	44(2)	41(2)	-0.3(18)	16.0(18)	4.3(17)
C6	41(2)	40(2)	39(2)	5.2(17)	14.1(17)	2.1(16)
C9	49(3)	52(2)	45(3)	14(2)	27(2)	15(2)
C7	36(2)	44(2)	57(3)	9(2)	15.3(19)	-4.5(18)
C11	57(3)	53(3)	40(2)	10.6(18)	20(2)	6.8(19)
C8	36(2)	58(3)	56(3)	23(2)	25(2)	8.8(18)
C2	36(2)	43(2)	43(2)	5.2(18)	17.7(18)	3.1(17)
C4	41(2)	50(2)	57(3)	-2(2)	27(2)	1.7(18)
C14	61(3)	89(4)	41(2)	-1(2)	4(2)	8(3)
C12	79(3)	95(4)	47(3)	14(3)	38(2)	1(3)
C13	119(5)	61(3)	58(3)	30(3)	19(3)	27(3)

Table S4. Bond Lengths for CCDC 2067822.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.482(2)	C10	C9	1.383(5)
S1	N1	1.662(3)	C1	C2	1.544(5)
S1	C11	1.837(4)	C3	C2	1.472(5)
F4	C10	1.344(5)	C3	C4	1.170(6)
F1	C6	1.350(5)	C6	C7	1.379(5)
F2	C7	1.343(5)	C9	C8	1.376(6)
F3	C9	1.338(5)	C7	C8	1.364(6)
N1	C1	1.473(5)	C11	C14	1.520(7)
C5	C10	1.385(5)	C11	C12	1.526(6)
C5	C1	1.513(5)	C11	C13	1.532(7)
C5	C6	1.390(5)			

Table S5. Bond Angles for CCDC 2067822.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O1	S1	N1	111.37(16)	C7	C6	C5	121.8(4)
O1	S1	C11	105.90(18)	F3	C9	C10	119.0(4)
N1	S1	C11	98.53(17)	F3	C9	C8	120.3(4)
C1	N1	S1	114.9(2)	C8	C9	C10	120.8(4)
C10	C5	C1	121.2(4)	F2	C7	C6	118.3(4)
C10	C5	C6	116.0(3)	F2	C7	C8	120.3(4)
C6	C5	C1	122.8(3)	C8	C7	C6	121.4(4)
F4	C10	C5	119.6(3)	C14	C11	S1	110.7(3)
F4	C10	C9	118.4(3)	C14	C11	C12	111.9(4)

C9	C10	C5	122.0(4)	C14	C11	C13	111.2(4)
N1	C1	C5	112.9(3)	C12	C11	S1	108.0(3)
N1	C1	C2	109.5(3)	C12	C11	C13	111.3(4)
C5	C1	C2	112.2(3)	C13	C11	S1	103.4(3)
C4	C3	C2	177.1(5)	C7	C8	C9	118.0(4)
F1	C6	C5	119.1(3)	C3	C2	C1	109.7(3)
F1	C6	C7	119.1(4)				

Table S6. Torsion Angles for CCDC 2067822.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S1	N1	C1	C5	88.9(3)	C5	C1	C2	C3	-170.3(4)
S1	N1	C1	C2	-145.3(3)	C5	C6	C7	F2	178.2(4)
F4	C10	C9	F3	0.1(5)	C5	C6	C7	C8	1.2(6)
F4	C10	C9	C8	-179.7(4)	C10	C5	C1	N1	-117.2(4)
F1	C6	C7	F2	0.7(6)	C10	C5	C1	C2	118.5(4)
F1	C6	C7	C8	-176.3(4)	C10	C5	C6	F1	177.2(3)
F2	C7	C8	C9	-178.2(4)	C10	C5	C6	C7	-0.4(5)
F3	C9	C8	C7	-179.2(4)	C10	C9	C8	C7	0.5(6)
O1	S1	N1	C1	-79.2(3)	C1	C5	C10	F4	-1.9(6)
O1	S1	C11	C14	-55.3(4)	C1	C5	C10	C9	178.2(3)
O1	S1	C11	C12	-178.0(3)	C1	C5	C6	F1	-1.4(5)
O1	S1	C11	C13	63.9(4)	C1	C5	C6	C7	-178.9(4)
N1	S1	C11	C14	59.9(3)	C6	C5	C10	F4	179.6(3)
N1	S1	C11	C12	-62.8(4)	C6	C5	C10	C9	-0.4(6)
N1	S1	C11	C13	179.1(4)	C6	C5	C1	N1	61.2(4)
N1	C1	C2	C3	63.5(4)	C6	C5	C1	C2	-63.1(5)

C5	C10	C9	F3	-179.9(4)	C6	C7	C8	C9	-1.3(6)
C5	C10	C9	C8	0.3(6)	C11	S1	N1	C1	169.9(3)

Table S7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for CCDC 2067822.

Atom	*x*	*y*	*z*	U(eq)
H1A	5638.4	5232.15	4471.87	41
H8	448.01	2530.47	6225.37	57
H2A	6888.9	3056.96	4540.74	47
H2B	5738.85	2859.15	2968.33	47
H4	9660.65	5267.34	2612.2	56
H14A	1730.49	5309.89	10.25	99
H14B	880.82	6517.29	-968.6	99
H14C	366.81	6275.22	413.08	99
H12A	5480.32	7409.25	857.29	104
H12B	4209.18	7234.84	-679.71	104
H12C	4792.5	5979.41	293.06	104
H13A	1300.73	8622.97	1092.41	121
H13B	1926.56	8833.03	-244.99	121
H13C	3295.96	9065.04	1246.76	121
H1	3250(60)	4590(50)	1970(50)	97

.

VI. X-ray structure of compound 3'b (Deposition Number 2067817).

Experimental

Single crystals of $C_{14}H_{15}F_4NOS$ [**CCDC 2067817**] were obtained by vapour diffusion method using dichloromethane and *n*-hexane (1:1) and slow evaporation in glass vial. A suitable crystal was selected and mounted on a SuperNova, Single source at offset, Atlas diffractometer. The crystal was kept at 150.00(10) K during data collection. Using Olex2,[2] the structure was solved with the ShelXS[3] structure solution program using Direct Methods and refined with the ShelXL[4] refinement package using Least Squares minimization. Displacement ellipsoids are drawn at the 50% probability level.

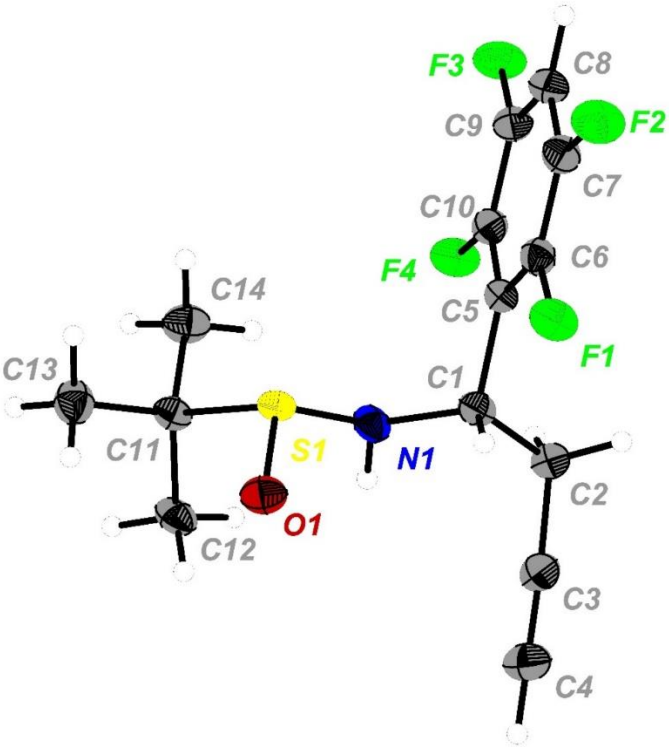


Table S8. Crystal data and structure refinement for CCDC 2067817.

Identification code	CCDC 2067817
Empirical formula	$C_{14}H_{15}F_4NOS$
Formula weight	321.33
Temperature/K	150.00(10)
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	8.87345(12)
b/Å	5.57753(8)
c/Å	15.18268(19)
α/°	90.0
β/°	101.7056(13)
γ/°	90.0
Volume/Å^3	735.793(18)
Z	2
ρ_{calc}g/cm^3	1.450
μ/mm^{-1}	2.372
F(000)	332.0
Crystal size/mm^3	0.297 × 0.165 × 0.067
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.18 to 137.99
Index ranges	-10 ≤ h ≤ 10, -6 ≤ k ≤ 6, -18 ≤ l ≤ 18
Reflections collected	13571
Independent reflections	2686 [R_{int} = 0.0408, R_{sigma} = 0.0263]
Data/restraints/parameters	2686/2/196
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0330, wR_2 = 0.0877
Final R indexes [all data]	R_1 = 0.0342, wR_2 = 0.0891

Largest diff. peak/hole / e $Å^{-3}$	0.30/-0.16
Flack parameter	0.00(2)
Friedel coverage	99%
Flack x	-0.007(10)
Hooft y	-0.013(5)
P2(wrong)	$<10^{-99}$

Table S9. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å2×10^3) for CCDC 2067817. Ueq is defined as 1/3 of the trace of the orthogonalised UIJ tensor.

Atom	x	y	Z	U(eq)
S1	1263.3(7)	2075.0(13)	7843.6(3)	21.78(18)
F1	4575(2)	3228(4)	6268.6(11)	34.6(4)
F2	3720(2)	3291(4)	4482.7(12)	41.0(5)
F3	805(2)	-3727(4)	4576.9(12)	38.8(5)
F4	1643(2)	-3832(4)	6358.7(11)	32.2(4)
O1	2023(2)	3790(4)	8548.6(14)	32.2(5)
N1	2294(3)	-413(5)	7835.4(15)	25.9(5)
C1	3632(3)	-290(6)	7400.3(17)	24.4(6)
C5	3122(3)	-275(5)	6386.3(17)	22.4(6)
C6	3617(3)	1498(5)	5867.7(18)	24.7(6)
C7	3181(3)	1532(6)	4941.6(18)	28.5(7)
C8	2227(3)	-206(6)	4488.9(18)	30.0(6)
C9	1735(3)	-1983(6)	4989.3(18)	27.4(6)
C10	2172(3)	-2034(6)	5917.2(19)	23.9(6)
C2	4663(3)	-2477(6)	7726.4(18)	28.9(7)
C3	5386(3)	-2250(6)	8678(2)	32.1(7)

C4	5926(4)	-1967(7)	9452(2)	39.6(8)
C11	-322(3)	646(5)	8275.5(17)	23.2(6)
C12	298(4)	-538(6)	9182.5(18)	29.5(6)
C13	-1418(3)	2689(6)	8373(2)	32.4(7)
C14	-1090(4)	-1150(6)	7569(2)	32.0(7)

Table S10. Anisotropic Displacement Parameters (Å2×103) for CCDC 2067817. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+…].

Atom	U11	U22	U33	U23	U13	U12
S1	26.0(3)	21.8(3)	16.7(3)	1.2(2)	2.3(2)	-1.9(3)
F1	39.9(9)	33.8(10)	30.9(9)	-2.9(8)	9.1(7)	-13.8(8)
F2	46.7(11)	44.8(12)	31.9(9)	11.2(8)	8.8(8)	-11.4(9)
F3	41.3(10)	43.8(12)	28.5(9)	-6.7(8)	0.0(7)	-15.1(9)
F4	39.4(9)	29.7(9)	26.7(8)	1.0(7)	4.7(7)	-11.5(8)
O1	33.9(10)	30.5(13)	29.8(10)	-7.1(9)	0.4(8)	-6.0(9)
N1	31.4(12)	27.1(14)	21.0(11)	5.1(9)	9.5(9)	2.8(10)
C1	26.5(12)	26.7(16)	20.4(12)	-1.1(11)	5.5(9)	-3.4(11)
C5	21.2(11)	27.5(16)	18.7(12)	-0.2(11)	4.8(9)	1.3(10)
C6	23.0(12)	26.3(18)	25.6(13)	-1.1(10)	6.3(10)	-1.4(10)
C7	28.1(13)	33(2)	25.2(13)	7.1(11)	8.3(10)	1.2(11)
C8	29.0(13)	40.3(18)	20.3(13)	1.8(12)	4.0(10)	1.4(12)
C9	24.4(13)	32.0(17)	24.4(13)	-5.4(12)	1.7(10)	-2.8(11)
C10	22.9(12)	25.7(15)	23.2(13)	0.8(10)	4.4(10)	-0.4(10)
C2	24.6(12)	37(2)	24.3(12)	-0.9(12)	2.3(10)	1.2(12)

C3	25.5(13)	41(2)	28.9(15)	3.0(12)	3.1(11)	1.4(11)
C4	36.4(16)	52(2)	27.8(15)	4.0(14)	-0.1(12)	1.6(15)
C11	27.4(13)	22.7(15)	19.8(12)	0.5(10)	5.3(10)	-2.1(11)
C12	38.8(15)	31.2(16)	20.1(12)	4.7(11)	9.5(11)	2.0(13)
C13	32.4(14)	32(2)	34.6(14)	4.1(12)	10.2(11)	3.4(12)
C14	34.5(15)	30.1(18)	29.7(14)	-1.8(12)	2.3(12)	-8.5(13)

Table S11 Bond Lengths for CCDC 2067817.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.491(2)	C5	C10	1.392(4)
S1	N1	1.664(3)	C6	C7	1.381(4)
S1	C11	1.849(3)	C7	C8	1.376(4)
F1	C6	1.347(3)	C8	C9	1.373(4)
F2	C7	1.346(3)	C9	C10	1.384(4)
F3	C9	1.345(3)	C2	C3	1.463(4)
F4	C10	1.343(3)	C3	C4	1.186(5)
N1	C1	1.473(3)	C11	C12	1.526(4)
C1	C5	1.514(3)	C11	C13	1.525(4)
C1	C2	1.545(4)	C11	C14	1.524(4)
C5	C6	1.390(4)			

Table S12. Bond Angles for CCDC 2067817.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O1	S1	N1	111.80(12)	C9	C8	C7	117.7(2)
O1	S1	C11	106.71(12)	F3	C9	C8	119.9(2)
N1	S1	C11	95.86(13)	F3	C9	C10	118.5(3)
C1	N1	S1	117.3(2)	C8	C9	C10	121.6(3)
N1	C1	C5	110.8(2)	F4	C10	C5	120.5(2)
N1	C1	C2	107.4(2)	F4	C10	C9	118.0(3)
C5	C1	C2	111.4(2)	C9	C10	C5	121.5(3)
C6	C5	C1	121.1(3)	C3	C2	C1	111.2(3)
C6	C5	C10	116.1(2)	C4	C3	C2	176.6(4)
C10	C5	C1	122.8(3)	C12	C11	S1	110.23(19)
F1	C6	C5	119.8(2)	C13	C11	S1	105.0(2)
F1	C6	C7	118.1(2)	C13	C11	C12	110.9(2)
C7	C6	C5	122.1(3)	C14	C11	S1	107.33(18)
F2	C7	C6	118.8(3)	C14	C11	C12	112.2(3)
F2	C7	C8	120.2(2)	C14	C11	C13	110.9(2)
C8	C7	C6	121.1(3)				

Table S13. Torsion Angles for CCDC 2067817.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S1	N1	C1	C5	-75.3(3)	C1	C5	C6	C7	179.3(3)
S1	N1	C1	C2	162.84(18)	C1	C5	C10	F4	1.0(4)
F1	C6	C7	F2	-0.5(4)	C1	C5	C10	C9	-179.5(3)
F1	C6	C7	C8	178.8(3)	C5	C1	C2	C3	169.2(2)

F2 C7 C8 C9	178.8(3)	C5 C6 C7 F2	-179.2(2)
F3 C9 C10 F4	0.1(4)	C5 C6 C7 C8	0.1(4)
F3 C9 C10 C5	-179.5(3)	C6 C5 C10 F4	179.6(2)
O1 S1 N1 C1	-78.4(2)	C6 C5 C10 C9	-0.9(4)
O1 S1 C11 C12	-56.4(2)	C6 C7 C8 C9	-0.5(4)
O1 S1 C11 C13	63.1(2)	C7 C8 C9 F3	-179.8(3)
O1 S1 C11 C14	-178.9(2)	C7 C8 C9 C10	0.3(4)
N1 S1 C11 C12	58.5(2)	C8 C9 C10 F4	-180.0(3)
N1 S1 C11 C13	177.96(19)	C8 C9 C10 C5	0.5(4)
N1 S1 C11 C14	-64.0(2)	C10 C5 C6 F1	-178.1(2)
N1 C1 C5 C6	126.9(3)	C10 C5 C6 C7	0.6(4)
N1 C1 C5 C10	-54.6(4)	C2 C1 C5 C6	-113.7(3)
N1 C1 C2 C3	-69.3(3)	C2 C1 C5 C10	64.8(3)
C1 C5 C6 F1	0.5(4)	C11 S1 N1 C1	171.0(2)

Table S14 Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for CCDC 2067817.

Atom	x	y	z	U(eq)
H1A	4220.77	1212.23	7595.31	29
H8	1918.92	-177.81	3852.08	36
H2A	4033.17	-3955.75	7635.3	35
H2B	5470.56	-2615.51	7364.99	35
H1	2510(40)	-1210(70)	8348(16)	38
H4	6358.76	-1741.01	10072.09	48
H12A	861.91	-1997.97	9091.41	44
H12B	-561.45	-951.47	9470.08	44

H12C	991.46	573.53	9568.43	44
H13A	-870.71	3900.06	8784.8	49
H13B	-2284.86	2061.8	8612.87	49
H13C	-1804.17	3418.83	7782.83	49
H14A	-1445.88	-322.49	6995.27	48
H14B	-1970.65	-1886.65	7764.1	48
H14C	-348.34	-2396.79	7493.96	48

VII. Computational details.

All DFT geometry optimizations were performed with the dispersion-corrected B97D functional[5] and 6-311+G(2d,2p) basis set as implemented within the Gaussian 16 series of programs.[6] Solvent effects were included with the conductor-like polarizable continuum model (CPCM)[7] to mimic the solvent (CH_2Cl_2 or THF) during both geometry optimizations and vibrational analysis. All energies presented for the reactant complex (RC), transition state (TS), and product (P) are given in Hartree. All energies have been corrected with zero-point energies (ZPE). Vibrational frequency calculations were performed at the same level of theory used for optimization. All transition states were verified to have only one negative eigenvalue in the Hessian matrix, describing the motion along the reaction coordinate. In addition, intrinsic reaction coordinate (IRC)[8] calculations were performed at the wB97D/6-311+G(2d,2p) level to verify the expected connections of the first-order saddle points with the local minima Found on the potential energy surface. Natural bond orbital (NBO)[9] analysis of charges was performed at TPSS-D3/def2-TZVPP level of theory.[10,11] Optimized structures were illustrated using CYLview20.3.[12]

VIII. Natural bond orbital (NBO) analysis of charges of the different atoms in sulfinyl imines.

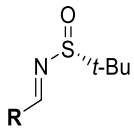
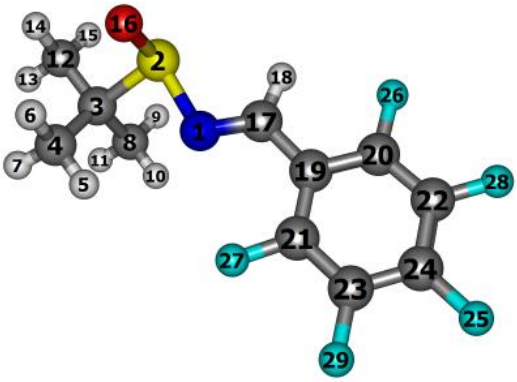


Table S15. NBO charges on different atoms of experimentally studied sulfinyl imines based on TPSS-D3/def2-TZVPP calculations.

Entry		R	S	O	N	C
1	1a	C_6F_5	1.1809	-0.8474	-0.5275	0.0766
2	1b	2,3,5,6-C_6HF_4	1.1808	-0.8478	-0.5243	0.0772
3	1c	2,4,6-$C_6H_2F_3$	1.1805	-0.8530	-0.5367	0.0816
4	1d	2,6-$C_6H_4F_2$	1.1802	-0.8538	-0.5339	0.0824
5	1e	2-C_6H_4F	1.1868	-0.8561	-0.5688	0.1005
6	1f	C_6H_5	1.1863	-0.8569	-0.5658	0.1016

Sulfinyl imine 1a



Summary of Natural Population Analysis:

Natural Population

Natural ----------

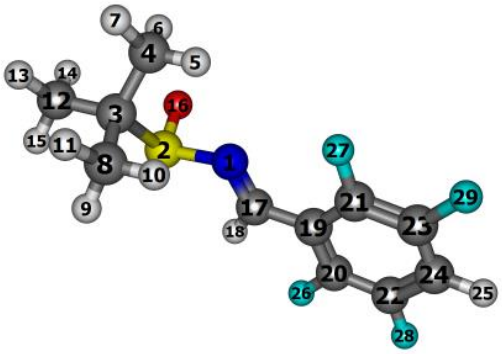
Atom	No	Charge	Core	Valence	Rydberg	Total
N	1	-0.52755	1.99940	5.50854	0.01961	7.52755
S	2	1.18094	9.99904	4.70637	0.11364	14.81906
C	3	-0.15636	1.99943	4.13596	0.02098	6.15636
C	4	-0.60940	1.99935	4.60103	0.00901	6.60940
H	5	0.22397	0.00000	0.77454	0.00149	0.77603
H	6	0.22779	0.00000	0.77047	0.00173	0.77221
H	7	0.20369	0.00000	0.79457	0.00174	0.79631
C	8	-0.60653	1.99936	4.59962	0.00755	6.60653
H	9	0.20244	0.00000	0.79555	0.00202	0.79756
H	10	0.21865	0.00000	0.77967	0.00167	0.78135
H	11	0.21268	0.00000	0.78554	0.00179	0.78732
C	12	-0.60605	1.99937	4.59853	0.00815	6.60605
H	13	0.20997	0.00000	0.78826	0.00176	0.79003
H	14	0.22317	0.00000	0.77532	0.00151	0.77683
H	15	0.20350	0.00000	0.79484	0.00167	0.79650

O	16	-0.84736	1.99990	6.83647	0.01099	8.84736
C	17	0.07656	1.99932	3.89635	0.02777	5.92344
H	18	0.18011	0.00000	0.81322	0.00667	0.81989
C	19	-0.21310	1.99893	4.19613	0.01804	6.21310
C	20	0.34252	1.99846	3.63559	0.02343	5.65748
C	21	0.35462	1.99845	3.62306	0.02387	5.64538
C	22	0.23930	1.99833	3.73735	0.02503	5.76070
C	23	0.24104	1.99837	3.73551	0.02508	5.75896
C	24	0.27950	1.99839	3.69661	0.02550	5.72050
F	25	-0.24398	1.99994	7.23662	0.00742	9.24398
F	26	-0.26552	1.99994	7.25872	0.00686	9.26552
F	27	-0.24256	1.99994	7.23531	0.00731	9.24256
F	28	-0.25102	1.99994	7.24404	0.00704	9.25102
F	29	-0.25102	1.99994	7.24399	0.00708	9.25102

==========

* Total *	-0.00000	45.98582	105.59778	0.41640	152.00000

Sulfinyl imine 1b



Summary of Natural Population Analysis:

Natural Population

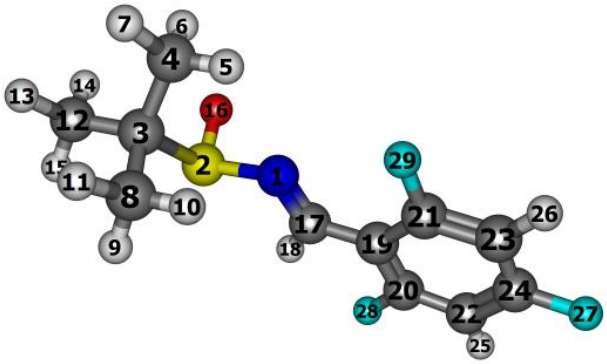
Natural ----------

Atom	No	Charge	Core	Valence	Rydberg	Total
N	1	-0.52432	1.99940	5.50552	0.01940	7.52432
S	2	1.18080	9.99904	4.70662	0.11354	14.81920
C	3	-0.15635	1.99943	4.13594	0.02099	6.15635
C	4	-0.60951	1.99935	4.60115	0.00901	6.60951
H	5	0.22460	0.00000	0.77391	0.00149	0.77540
H	6	0.22765	0.00000	0.77062	0.00173	0.77235
H	7	0.20328	0.00000	0.79498	0.00175	0.79672
C	8	-0.60652	1.99936	4.59964	0.00752	6.60652
H	9	0.20231	0.00000	0.79568	0.00202	0.79769
H	10	0.21907	0.00000	0.77928	0.00165	0.78093
H	11	0.21231	0.00000	0.78589	0.00180	0.78769
C	12	-0.60601	1.99937	4.59849	0.00815	6.60601
H	13	0.20965	0.00000	0.78857	0.00177	0.79035
H	14	0.22303	0.00000	0.77545	0.00152	0.77697
H	15	0.20334	0.00000	0.79499	0.00168	0.79666
O	16	-0.84778	1.99990	6.83690	0.01098	8.84778

C	17	0.07725	1.99932	3.89577	0.02766	5.92275
H	18	0.17984	0.00000	0.81349	0.00667	0.82016
C	19	-0.20065	1.99893	4.18410	0.01761	6.20065
C	20	0.33312	1.99842	3.64586	0.02260	5.66688
C	21	0.34220	1.99842	3.63418	0.02521	5.65780
C	22	0.30021	1.99840	3.67778	0.02360	5.69979
C	23	0.30231	1.99844	3.67545	0.02380	5.69769
C	24	-0.28618	1.99900	4.27453	0.01265	6.28618
H	25	0.25047	0.00000	0.74807	0.00146	0.74953
F	26	-0.27038	1.99994	7.26376	0.00668	9.27038
F	27	-0.24710	1.99994	7.24010	0.00706	9.24710
F	28	-0.26823	1.99994	7.26161	0.00667	9.26823
F	29	-0.26841	1.99994	7.26172	0.00674	9.26841

* Total *	-0.00000	43.98657	99.62005	0.39338	144.00000

Sulfinyl imine 1c



Summary of Natural Population Analysis:

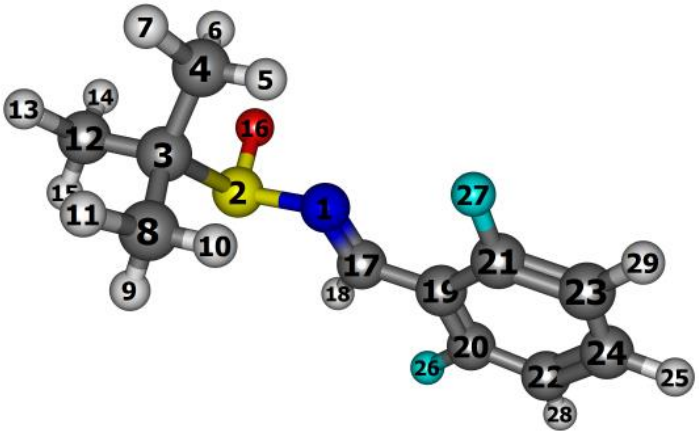
Natural Population

Natural ----------

Atom	No	Charge	Core	Valence	Rydberg	Total
N	1	-0.53669	1.99940	5.51790	0.01939	7.53669
S	2	1.18053	9.99904	4.70635	0.11408	14.81947
C	3	-0.15723	1.99943	4.13670	0.02110	6.15723
C	4	-0.60942	1.99936	4.60103	0.00903	6.60942
H	5	0.22430	0.00000	0.77419	0.00151	0.77570
H	6	0.22743	0.00000	0.77081	0.00176	0.77257
H	7	0.20186	0.00000	0.79637	0.00177	0.79814
C	8	-0.60613	1.99936	4.59922	0.00756	6.60613
H	9	0.20181	0.00000	0.79614	0.00205	0.79819
H	10	0.21898	0.00000	0.77934	0.00168	0.78102
H	11	0.21079	0.00000	0.78739	0.00182	0.78921
C	12	-0.60561	1.99937	4.59808	0.00816	6.60561
H	13	0.20837	0.00000	0.78984	0.00179	0.79163
H	14	0.22290	0.00000	0.77557	0.00153	0.77710
H	15	0.20280	0.00000	0.79550	0.00169	0.79720

O	16	-0.85303	1.99990	6.84219	0.01093	8.85303
C	17	0.08156	1.99932	3.89156	0.02757	5.91844
H	18	0.17716	0.00000	0.81595	0.00689	0.82284
C	19	-0.24232	1.99887	4.22625	0.01719	6.24232
C	20	0.42325	1.99855	3.55602	0.02217	5.57675
C	21	0.43353	1.99854	3.54504	0.02288	5.56647
C	22	-0.34303	1.99893	4.33144	0.01265	6.34303
C	23	-0.33947	1.99896	4.32803	0.01249	6.33947
C	24	0.40405	1.99854	3.57468	0.02273	5.59595
H	25	0.24854	0.00000	0.75005	0.00141	0.75146
H	26	0.24797	0.00000	0.75065	0.00137	0.75203
F	27	-0.27832	1.99994	7.27183	0.00655	9.27832
F	28	-0.28461	1.99994	7.27814	0.00653	9.28461
F	29	-0.25999	1.99994	7.25317	0.00688	9.25999
* Total *		-0.00000	41.98740	93.63945	0.37314	136.00000

Sulfinyl imine 1d



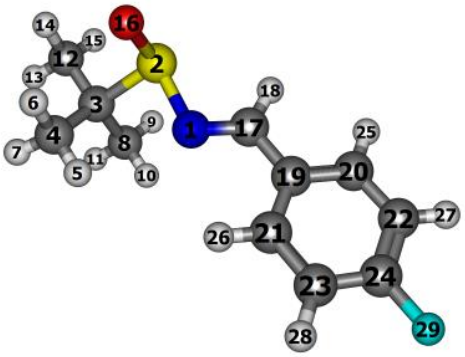
Summary of Natural Population Analysis:

Natural Population

Atom	No	Natural Charge	Core	Valence	Rydberg	Total
N	1	-0.53394	1.99941	5.51543	0.01910	7.53394
S	2	1.18025	9.99904	4.70671	0.11399	14.81975
C	3	-0.15723	1.99943	4.13668	0.02113	6.15723
C	4	-0.60954	1.99936	4.60116	0.00903	6.60954
H	5	0.22500	0.00000	0.77349	0.00151	0.77500
H	6	0.22724	0.00000	0.77099	0.00176	0.77276
H	7	0.20131	0.00000	0.79691	0.00178	0.79869
C	8	-0.60611	1.99936	4.59922	0.00753	6.60611
H	9	0.20166	0.00000	0.79630	0.00204	0.79834
H	10	0.21948	0.00000	0.77886	0.00166	0.78052
H	11	0.21029	0.00000	0.78788	0.00183	0.78971
C	12	-0.60553	1.99937	4.59800	0.00816	6.60553
H	13	0.20792	0.00000	0.79027	0.00181	0.79208
H	14	0.22275	0.00000	0.77572	0.00154	0.77725

H	15	0.20259	0.00000	0.79570	0.00170	0.79741
O	16	-0.85383	1.99990	6.84301	0.01091	8.85383
C	17	0.08242	1.99932	3.89086	0.02740	5.91758
H	18	0.17701	0.00000	0.81614	0.00685	0.82299
C	19	-0.23216	1.99889	4.21566	0.01761	6.23216
C	20	0.41033	1.99853	3.56952	0.02162	5.58967
C	21	0.41863	1.99852	3.55915	0.02370	5.58137
C	22	-0.28274	1.99908	4.27033	0.01334	6.28274
C	23	-0.27862	1.99910	4.26610	0.01341	6.27862
C	24	-0.15005	1.99925	4.13767	0.01313	6.15005
H	25	0.21752	0.00000	0.78145	0.00103	0.78248
F	26	-0.29127	1.99994	7.28505	0.00627	9.29127
F	27	-0.26628	1.99994	7.25966	0.00667	9.26628
H	28	0.23176	0.00000	0.76697	0.00127	0.76824
H	29	0.23114	0.00000	0.76756	0.00130	0.76886
* Total *		0.00000	39.98844	87.65247	0.35909	128.00000

Sulfinyl imine 1e



Summary of Natural Population Analysis:

Natural Population

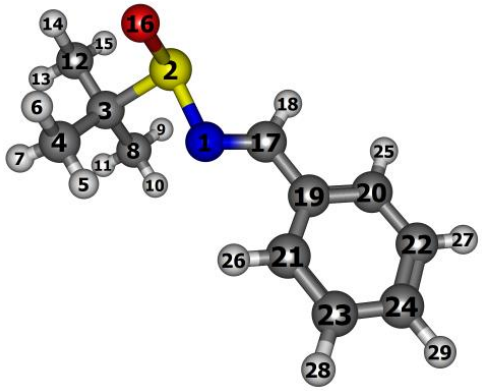
Natural ----------

Atom	No	Charge	Core	Valence	Rydberg	Total
N	1	-0.56879	1.99939	5.54981	0.01960	7.56879
S	2	1.18683	9.99904	4.69913	0.11499	14.81317
C	3	-0.15785	1.99942	4.13724	0.02118	6.15785
C	4	-0.60803	1.99936	4.59966	0.00901	6.60803
H	5	0.21824	0.00000	0.78013	0.00163	0.78176
H	6	0.22855	0.00000	0.76965	0.00180	0.77145
H	7	0.20194	0.00000	0.79627	0.00179	0.79806
C	8	-0.60540	1.99936	4.59846	0.00758	6.60540
H	9	0.20211	0.00000	0.79583	0.00206	0.79789
H	10	0.21684	0.00000	0.78148	0.00167	0.78316
H	11	0.21040	0.00000	0.78777	0.00183	0.78960
C	12	-0.60567	1.99937	4.59812	0.00817	6.60567
H	13	0.20786	0.00000	0.79033	0.00181	0.79214
H	14	0.22327	0.00000	0.77520	0.00153	0.77673
H	15	0.20285	0.00000	0.79544	0.00171	0.79715
O	16	-0.85610	1.99990	6.84528	0.01091	8.85610

C	17	0.10053	1.99930	3.87314	0.02702	5.89947
H	18	0.15530	0.00000	0.83757	0.00713	0.84470
C	19	-0.13575	1.99909	4.11843	0.01823	6.13575
C	20	-0.14344	1.99918	4.13158	0.01269	6.14344
C	21	-0.13538	1.99915	4.12301	0.01322	6.13538
C	22	-0.26750	1.99908	4.25523	0.01319	6.26750
C	23	-0.26039	1.99909	4.24849	0.01281	6.26039
C	24	0.37958	1.99853	3.60014	0.02175	5.62042
H	25	0.21105	0.00000	0.78754	0.00141	0.78895
H	26	0.23229	0.00000	0.76613	0.00158	0.76771
H	27	0.22854	0.00000	0.77008	0.00137	0.77146
H	28	0.22853	0.00000	0.77013	0.00134	0.77147
F	29	-0.29043	1.99994	7.28417	0.00632	9.29043

* Total *	-0.00000	37.98921	81.66546	0.34532	120.00000

Sulfinyl imine 1f



Summary of Natural Population Analysis:

Natural Population

Natural ----------

Atom	No	Charge	Core	Valence	Rydberg	Total
N	1	-0.56578	1.99939	5.54678	0.01961	7.56578
S	2	1.18627	9.99904	4.69976	0.11493	14.81373
C	3	-0.15787	1.99942	4.13724	0.02120	6.15787
C	4	-0.60817	1.99936	4.59980	0.00901	6.60817
H	5	0.21888	0.00000	0.77948	0.00164	0.78112
H	6	0.22839	0.00000	0.76981	0.00180	0.77161
H	7	0.20138	0.00000	0.79682	0.00180	0.79862
C	8	-0.60547	1.99936	4.59853	0.00758	6.60547
H	9	0.20193	0.00000	0.79601	0.00206	0.79807
H	10	0.21732	0.00000	0.78100	0.00168	0.78268
H	11	0.20988	0.00000	0.78828	0.00184	0.79012
C	12	-0.60559	1.99937	4.59804	0.00818	6.60559
H	13	0.20742	0.00000	0.79076	0.00182	0.79258
H	14	0.22310	0.00000	0.77536	0.00154	0.77690
H	15	0.20265	0.00000	0.79564	0.00171	0.79735

O	16	-0.85690	1.99990	6.84611	0.01089	8.85690
C	17	0.10165	1.99930	3.87201	0.02703	5.89835
H	18	0.15432	0.00000	0.83850	0.00718	0.84568
C	19	-0.12263	1.99909	4.10481	0.01873	6.12263
C	20	-0.15928	1.99916	4.14746	0.01265	6.15928
C	21	-0.15193	1.99914	4.13971	0.01309	6.15193
C	22	-0.20418	1.99923	4.19164	0.01331	6.20418
C	23	-0.19908	1.99923	4.18677	0.01308	6.19908
C	24	-0.17726	1.99924	4.16492	0.01310	6.17726
H	25	0.20605	0.00000	0.79248	0.00146	0.79395
H	26	0.22724	0.00000	0.77116	0.00160	0.77276
H	27	0.20982	0.00000	0.78895	0.00124	0.79018
H	28	0.20979	0.00000	0.78899	0.00121	0.79021
H	29	0.20804	0.00000	0.79078	0.00118	0.79196

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* Total *	-0.00000	35.99024	75.67760	0.33216	112.00000

IX. Cartesian coordinates of optimized structures.

Sulfinyl imine 1a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.342465	-0.039253	0.216642
2	16	0	1.091084	-0.723996	-0.683629
3	6	0	2.345906	0.505719	0.064879
4	6	0	2.368183	0.307130	1.578933
5	1	0	1.422124	0.614701	2.031106
6	1	0	2.549447	-0.744536	1.823001
7	1	0	3.180282	0.908737	2.006624
8	6	0	1.914076	1.912545	-0.354711
9	1	0	1.805373	1.994725	-1.443441
10	1	0	0.968721	2.193435	0.118813
11	1	0	2.680549	2.632838	-0.042914
12	6	0	3.678828	0.099926	-0.579581
13	1	0	4.474504	0.750836	-0.197897
14	1	0	3.934242	-0.935335	-0.332647
15	1	0	3.650373	0.204705	-1.670741
16	8	0	1.370382	-2.076792	-0.045401
17	6	0	-1.412928	-0.144100	-0.485098
18	1	0	-1.417911	-0.536147	-1.510179
19	6	0	-2.739848	0.240098	0.019369
20	6	0	-3.860698	0.050325	-0.811943
21	6	0	-2.988470	0.798512	1.288986
22	6	0	-5.153378	0.381092	-0.419795
23	6	0	-4.276195	1.136736	1.700281
24	6	0	-5.360584	0.929166	0.846262

25	9	0	-6.596086	1.255385	1.241394
26	9	0	-3.697723	-0.477046	-2.042556
27	9	0	-1.991418	1.030196	2.150208
28	9	0	-6.193821	0.179686	-1.242935
29	9	0	-4.482311	1.667347	2.915486

Sulfinyl imine 1b

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.340409	-0.052449	0.221949
2	16	0	1.094104	-0.731373	-0.680845
3	6	0	2.344526	0.504962	0.065041
4	6	0	2.370003	0.306907	1.579111
5	1	0	1.422610	0.608704	2.032364
6	1	0	2.557832	-0.743647	1.823050
7	1	0	3.179076	0.913445	2.005681
8	6	0	1.905363	1.909606	-0.354118
9	1	0	1.792608	1.990492	-1.442566
10	1	0	0.960401	2.186866	0.122308
11	1	0	2.669819	2.633444	-0.045490
12	6	0	3.678275	0.105312	-0.581442
13	1	0	4.471814	0.759362	-0.200588
14	1	0	3.938414	-0.929013	-0.335423
15	1	0	3.647734	0.210472	-1.672520
16	8	0	1.380839	-2.082096	-0.041484
17	6	0	-1.409375	-0.147200	-0.483455
18	1	0	-1.412214	-0.530412	-1.511802
19	6	0	-2.737324	0.237810	0.020676

20	6	0	-3.855051	0.048683	-0.815544
21	6	0	-2.984974	0.795495	1.290735
22	6	0	-5.142972	0.385287	-0.410659
23	6	0	-4.279972	1.129573	1.685257
24	6	0	-5.369498	0.931157	0.846083
25	1	0	-6.371570	1.194430	1.166138
26	9	0	-3.686005	-0.478424	-2.047419
27	9	0	-1.986097	1.025533	2.152651
28	9	0	-6.176594	0.177965	-1.252141
29	9	0	-4.471986	1.661075	2.910214

Sulfinyl imine 1c

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.335417	-0.056567	0.238513
2	16	0	1.090869	-0.741536	-0.660484
3	6	0	2.344662	0.505690	0.061514
4	6	0	2.377625	0.328195	1.578062
5	1	0	1.431417	0.634705	2.030696
6	1	0	2.567026	-0.719102	1.834659
7	1	0	3.188024	0.940971	1.993324
8	6	0	1.902911	1.904778	-0.373087
9	1	0	1.786017	1.971803	-1.462068
10	1	0	0.958734	2.185719	0.102697
11	1	0	2.667424	2.633583	-0.076080
12	6	0	3.676126	0.099331	-0.585057
13	1	0	4.471300	0.758045	-0.215536
14	1	0	3.937106	-0.932083	-0.327888

15	1	0	3.640761	0.191092	-1.677236
16	8	0	1.390524	-2.084432	-0.008261
17	6	0	-1.407966	-0.155641	-0.464899
18	1	0	-1.407459	-0.549153	-1.489640
19	6	0	-2.732998	0.233722	0.027712
20	6	0	-3.861209	0.057755	-0.799409
21	6	0	-3.011430	0.790401	1.294625
22	6	0	-5.159282	0.384078	-0.439676
23	6	0	-4.288244	1.138296	1.714894
24	6	0	-5.338011	0.923682	0.829081
25	1	0	-5.989833	0.223493	-1.116392
26	1	0	-4.453043	1.562087	2.698443
27	9	0	-6.589025	1.255645	1.218749
28	9	0	-3.672184	-0.469102	-2.034440
29	9	0	-2.003527	1.009489	2.155869

Sulfinyl imine 1d

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.332951	-0.069477	0.242257
2	16	0	1.094187	-0.747044	-0.660177
3	6	0	2.343379	0.505381	0.061810
4	6	0	2.378251	0.326514	1.578141
5	1	0	1.430659	0.627606	2.031486
6	1	0	2.572956	-0.720184	1.833294
7	1	0	3.185902	0.942839	1.993648
8	6	0	1.894987	1.902937	-0.370830
9	1	0	1.775704	1.970211	-1.459571

10	1	0	0.950468	2.179399	0.106871
11	1	0	2.656935	2.634854	-0.074740
12	6	0	3.676109	0.105700	-0.586196
13	1	0	4.468967	0.766962	-0.216134
14	1	0	3.941324	-0.925127	-0.330910
15	1	0	3.639603	0.199034	-1.678220
16	8	0	1.401596	-2.089152	-0.009603
17	6	0	-1.404290	-0.158439	-0.464429
18	1	0	-1.402019	-0.542849	-1.492483
19	6	0	-2.730307	0.231431	0.028398
20	6	0	-3.856171	0.055641	-0.801646
21	6	0	-3.008691	0.788003	1.294573
22	6	0	-5.151740	0.384712	-0.435413
23	6	0	-4.289775	1.133287	1.704927
24	6	0	-5.359787	0.927848	0.833125
25	1	0	-6.365302	1.193352	1.145550
26	9	0	-3.660456	-0.472674	-2.038909
27	9	0	-1.997057	1.006748	2.156461
28	1	0	-5.966015	0.215000	-1.131261
29	1	0	-4.430854	1.555804	2.693991

Sulfinyl imine 1e

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.364759	-0.130948	0.260239
2	16	0	1.086566	-0.823530	-0.567465
3	6	0	2.303938	0.507253	0.067891
4	6	0	2.335404	0.438640	1.593080

5	1	0	1.382815	0.760513	2.021360
6	1	0	2.540388	-0.584825	1.923470
7	1	0	3.133426	1.092819	1.967033
8	6	0	1.831012	1.860122	-0.467321
9	1	0	1.719108	1.845479	-1.558766
10	1	0	0.876482	2.151359	-0.018969
11	1	0	2.574922	2.627972	-0.220498
12	6	0	3.648597	0.089086	-0.542762
13	1	0	4.425854	0.791958	-0.219149
14	1	0	3.932884	-0.914596	-0.211324
15	1	0	3.616322	0.101034	-1.638801
16	8	0	1.424641	-2.106184	0.180088
17	6	0	-1.417594	-0.211875	-0.475184
18	1	0	-1.387202	-0.596464	-1.507055
19	6	0	-2.741808	0.199482	0.002132
20	6	0	-3.836070	0.136732	-0.877470
21	6	0	-2.943646	0.655334	1.318804
22	6	0	-5.109732	0.522786	-0.465194
23	6	0	-4.207501	1.041744	1.746309
24	6	0	-5.267131	0.969040	0.842232
25	1	0	-3.686933	-0.219222	-1.894502
26	1	0	-2.095338	0.692768	1.995489
27	1	0	-5.965603	0.480781	-1.130940
28	1	0	-4.386514	1.392236	2.757842
29	9	0	-6.503151	1.347440	1.258240

Sulfinyl imine 1f

Center	Atomic	Atomic	Coordinates (Angstroms)		
Number	Number	Type	X	Y	Z

1	7	0	-0.361295	-0.143824	0.268626
2	16	0	1.090122	-0.832038	-0.562295
3	6	0	2.303043	0.506255	0.066830
4	6	0	2.339212	0.440426	1.592060
5	1	0	1.386001	0.757608	2.022399
6	1	0	2.550576	-0.581443	1.923420
7	1	0	3.134791	1.099522	1.962728
8	6	0	1.821888	1.855921	-0.469062
9	1	0	1.705913	1.838677	-1.560064
10	1	0	0.867642	2.143455	-0.017780
11	1	0	2.563149	2.627737	-0.226473
12	6	0	3.648017	0.093814	-0.546894
13	1	0	4.423032	0.800439	-0.225934
14	1	0	3.937605	-0.908328	-0.215311
15	1	0	3.612774	0.104548	-1.642870
16	8	0	1.437211	-2.111178	0.187450
17	6	0	-1.413277	-0.217076	-0.468448
18	1	0	-1.382079	-0.596646	-1.502258
19	6	0	-2.738996	0.197632	0.007830
20	6	0	-3.827056	0.142711	-0.879361
21	6	0	-2.944897	0.646644	1.325215
22	6	0	-5.099163	0.533289	-0.462605
23	6	0	-4.215300	1.032830	1.738217
24	6	0	-5.294196	0.978995	0.846338
25	1	0	-3.669473	-0.208842	-1.897191
26	1	0	-2.098938	0.677265	2.005536
27	1	0	-5.935832	0.488219	-1.154525
28	1	0	-4.372241	1.375620	2.757585
29	1	0	-6.285100	1.281930	1.174751

RC for *Si* attack in DCM of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	1.752059	0.993972	1.338645
2	6	0	0.168084	0.976086	2.770136
3	6	0	-0.508465	-0.099134	2.991829
4	6	0	-1.144228	-1.244342	3.141462
5	6	0	-0.464268	-1.365487	0.052405
6	7	0	0.694645	-0.824521	0.013671
7	1	0	-0.593773	-2.414239	0.308682
8	16	0	2.004027	-1.808736	0.482680
9	8	0	2.804406	-0.775112	1.253745
10	6	0	-1.687624	-0.640647	-0.252089
11	6	0	-2.908015	-1.284560	-0.032947
12	6	0	-1.737088	0.662058	-0.753997
13	6	0	-4.118286	-0.669696	-0.274392
14	6	0	-2.939964	1.292052	-1.006002
15	6	0	-4.130850	0.626986	-0.762093
16	35	0	2.984442	2.860563	0.251230
17	6	0	2.845665	-2.002998	-1.153502
18	6	0	3.046930	-0.651062	-1.818994
19	1	0	3.605494	0.029918	-1.177971
20	1	0	3.621684	-0.802819	-2.733265
21	1	0	2.099500	-0.185392	-2.083553
22	6	0	1.960228	-2.934008	-1.976311
23	1	0	1.758235	-3.871048	-1.455633
24	1	0	1.014943	-2.462675	-2.243370

25	1	0	2.483257	-3.174884	-2.901855
26	6	0	4.179822	-2.663355	-0.804593
27	1	0	4.039726	-3.618937	-0.297716
28	1	0	4.722853	-2.850674	-1.730925
29	1	0	4.789025	-2.014336	-0.177321
30	1	0	-0.769050	-2.007781	3.811315
31	1	0	-2.095398	-1.429544	2.660040
32	1	0	-0.041888	1.826008	3.419160
33	9	0	-5.256914	-1.302805	-0.043301
34	9	0	-5.278246	1.228102	-0.999210
35	9	0	-2.924366	-2.525256	0.438106
36	9	0	-0.632691	1.333327	-1.031033
37	9	0	-2.962142	2.525526	-1.483921

TS for *Si* attack in DCM of 1a with 2a

Imaginary frequency: -362.8069

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	1.935766	0.978448	1.031645
2	6	0	0.807175	0.950552	2.953043
3	6	0	-0.075306	0.058769	3.020668
4	6	0	-0.928905	-0.969125	2.822759
5	6	0	-0.473307	-1.183641	0.600035
6	7	0	0.720036	-0.722492	0.271613
7	1	0	-0.609878	-2.242822	0.776230
8	16	0	2.012215	-1.770958	0.523472
9	8	0	3.064002	-0.758491	0.971005
10	6	0	-1.685083	-0.490808	0.129041

11	6	0	-2.879861	-1.206445	0.080273
12	6	0	-1.733346	0.832060	-0.297301
13	6	0	-4.058501	-0.653717	-0.377023
14	6	0	-2.903404	1.408759	-0.757673
15	6	0	-4.069076	0.664835	-0.800020
16	35	0	2.752482	2.860665	-0.352488
17	6	0	2.454561	-2.199635	-1.222586
18	6	0	2.655936	-0.936672	-2.043990
19	1	0	3.437770	-0.307977	-1.619939
20	1	0	2.961162	-1.224264	-3.050788
21	1	0	1.738444	-0.355316	-2.117334
22	6	0	1.307121	-3.054682	-1.751670
23	1	0	1.106449	-3.912688	-1.107819
24	1	0	0.392751	-2.473064	-1.864963
25	1	0	1.583323	-3.436228	-2.734880
26	6	0	3.746546	-3.007096	-1.104569
27	1	0	3.609381	-3.903506	-0.498300
28	1	0	4.055016	-3.319992	-2.102454
29	1	0	4.546817	-2.407281	-0.673132
30	1	0	-0.651830	-1.949528	3.191381
31	1	0	-1.988888	-0.769627	2.744820
32	1	0	1.160571	1.608153	3.734179
33	9	0	-2.903470	-2.470564	0.496957
34	9	0	-5.172026	-1.371119	-0.411575
35	9	0	-5.189312	1.211526	-1.237748
36	9	0	-2.912746	2.672567	-1.154536
37	9	0	-0.653180	1.606925	-0.271049

PRODUCT for *Si* attack in DCM of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	2.221079	0.606913	1.256093
2	6	0	0.679391	1.482991	3.341757
3	6	0	0.081226	0.488502	3.032821
4	6	0	-0.620642	-0.746915	2.693747
5	6	0	-0.463193	-1.180705	1.206702
6	7	0	0.820327	-0.796832	0.661370
7	1	0	-0.568945	-2.264982	1.216033
8	16	0	1.939639	-1.957246	0.468345
9	8	0	3.204152	-1.156817	0.867364
10	6	0	-1.582275	-0.669652	0.313139
11	6	0	-2.516304	-1.545714	-0.217455
12	6	0	-1.694017	0.658234	-0.071792
13	6	0	-3.510355	-1.137811	-1.090690
14	6	0	-2.675107	1.096940	-0.941737
15	6	0	-3.589857	0.193077	-1.454204
16	35	0	3.115901	2.876001	0.948192
17	6	0	2.119627	-2.142623	-1.366917
18	6	0	2.381984	-0.790856	-2.008459
19	1	0	3.324784	-0.365676	-1.665598
20	1	0	2.440363	-0.914244	-3.090821
21	1	0	1.574287	-0.091359	-1.791136
22	6	0	0.796000	-2.737878	-1.839057
23	1	0	0.549146	-3.656446	-1.303070
24	1	0	-0.020390	-2.026956	-1.710730
25	1	0	0.869124	-2.980861	-2.899717

26	6	0	3.279421	-3.110342	-1.583244
27	1	0	3.097287	-4.069029	-1.094462
28	1	0	3.400674	-3.297050	-2.651229
29	1	0	4.211072	-2.694699	-1.200844
30	1	0	-0.203028	-1.540002	3.315576
31	1	0	-1.673406	-0.652707	2.961404
32	1	0	1.161332	2.385254	3.637837
33	9	0	-2.467073	-2.844561	0.091762
34	9	0	-4.379012	-2.014081	-1.581330
35	9	0	-4.535205	0.602640	-2.287553
36	9	0	-2.746767	2.376849	-1.286663
37	9	0	-0.836669	1.567775	0.392115

RC for *Re* attack in DCM of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	-2.095113	1.332956	0.402503
2	6	0	-1.080424	1.065005	2.257687
3	6	0	-0.245928	0.104134	2.480627
4	6	0	0.578434	-0.909065	2.643881
5	6	0	0.169037	-1.194897	-1.135451
6	7	0	-0.894131	-0.609008	-0.756357
7	1	0	0.159116	-2.053101	-1.803639
8	16	0	-2.419814	-1.091634	-1.346055
9	8	0	-3.236096	0.053696	-0.780086
10	6	0	1.480768	-0.774374	-0.650833
11	6	0	2.463196	-1.743153	-0.471756
12	6	0	1.798657	0.539053	-0.314621

13	6	0	3.702737	-1.437583	0.053102
14	6	0	3.037719	0.868719	0.197345
15	6	0	3.987001	-0.123814	0.388943
16	35	0	-2.665424	3.631879	-0.397325
17	6	0	-2.813948	-2.570840	-0.281662
18	6	0	-2.742421	-2.206267	1.190624
19	1	0	-3.439059	-1.405902	1.434677
20	1	0	-3.024992	-3.085235	1.771181
21	1	0	-1.738244	-1.906800	1.487430
22	6	0	-1.838779	-3.682944	-0.649222
23	1	0	-1.781415	-3.845778	-1.726813
24	1	0	-0.840450	-3.498179	-0.255390
25	1	0	-2.196743	-4.607935	-0.196962
26	6	0	-4.240654	-2.922204	-0.709045
27	1	0	-4.295100	-3.184950	-1.765839
28	1	0	-4.565649	-3.786104	-0.129228
29	1	0	-4.928190	-2.101539	-0.509431
30	1	0	1.628591	-0.829046	2.390286
31	1	0	0.239655	-1.842714	3.076280
32	1	0	-1.201858	1.780006	3.072896
33	9	0	2.195931	-3.009626	-0.772111
34	9	0	4.610869	-2.382064	0.239217
35	9	0	5.168277	0.185970	0.884702
36	9	0	3.327666	2.123445	0.498998
37	9	0	0.934220	1.519829	-0.519746

TS for *Re* attack in DCM of 1a with 2a

Imaginary frequency: -346.1914

Center	Atomic	Atomic	Coordinates (Angstroms)		

Number	Number	Type	X	Y	Z
1	12	0	-1.707010	1.186986	0.260833
2	6	0	-0.968204	0.609129	2.320738
3	6	0	-0.307615	-0.456164	2.372707
4	6	0	0.326346	-1.624472	2.118277
5	6	0	0.293554	-1.305374	-0.163957
6	7	0	-0.752974	-0.600948	-0.522863
7	1	0	0.317240	-2.377761	-0.295192
8	16	0	-2.169664	-1.163964	-1.220471
9	8	0	-3.020753	0.067260	-0.912543
10	6	0	1.628222	-0.673310	-0.170857
11	6	0	2.748941	-1.500520	-0.141775
12	6	0	1.871347	0.694240	-0.229498
13	6	0	4.038395	-1.010777	-0.175112
14	6	0	3.153912	1.210846	-0.262172
15	6	0	4.242252	0.357336	-0.235283
16	35	0	-2.167654	3.595540	-0.086798
17	6	0	-2.943843	-2.527869	-0.213458
18	6	0	-3.272059	-2.066219	1.193417
19	1	0	-3.913787	-1.186491	1.176973
20	1	0	-3.808578	-2.866345	1.705224
21	1	0	-2.378999	-1.832109	1.766209
22	6	0	-2.009634	-3.734026	-0.242709
23	1	0	-1.617052	-3.925426	-1.243218
24	1	0	-1.180719	-3.625780	0.453139
25	1	0	-2.573406	-4.616964	0.059776
26	6	0	-4.220482	-2.820752	-1.009022
27	1	0	-3.998450	-3.142405	-2.027139
28	1	0	-4.757291	-3.628443	-0.510618

29	1	0	-4.873212	-1.949732	-1.046931
30	1	0	1.400485	-1.681587	2.223390
31	1	0	-0.212414	-2.550117	2.287663
32	1	0	-1.316856	1.251729	3.115112
33	9	0	2.584479	-2.819759	-0.061636
34	9	0	5.074120	-1.836217	-0.145786
35	9	0	5.469716	0.845379	-0.262756
36	9	0	3.343719	2.520267	-0.316602
37	9	0	0.875368	1.584756	-0.258258

PRODUCT for *Re* attack in DCM of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	-2.024246	0.209499	-0.219732
2	6	0	0.480012	2.361783	-1.081365
3	6	0	-0.944980	2.679260	-1.029076
4	6	0	-2.121675	2.907204	-0.955783
5	6	0	0.847290	1.442630	0.107109
6	7	0	0.050877	0.217641	0.171443
7	1	0	0.563471	1.993696	1.002319
8	16	0	0.297441	-0.895894	-0.999033
9	8	0	-1.163621	-1.130240	-1.478646
10	6	0	2.341260	1.193021	0.247696
11	6	0	2.865299	1.059980	1.528047
12	6	0	3.234225	1.007692	-0.797218
13	6	0	4.191844	0.760280	1.769794
14	6	0	4.570559	0.706827	-0.587392
15	6	0	5.052647	0.580950	0.701230

16	35	0	-4.313261	0.441874	0.669293
17	6	0	0.686473	-2.459737	-0.081321
18	6	0	-0.402944	-2.770371	0.930774
19	1	0	-1.365754	-2.920228	0.443234
20	1	0	-0.144229	-3.689658	1.457988
21	1	0	-0.492716	-1.972611	1.668142
22	6	0	2.030289	-2.232088	0.602518
23	1	0	2.797494	-1.907225	-0.103168
24	1	0	1.942909	-1.491218	1.395033
25	1	0	2.364553	-3.169683	1.048158
26	6	0	0.786815	-3.543381	-1.152570
27	1	0	1.555790	-3.306708	-1.889697
28	1	0	1.054557	-4.489450	-0.680263
29	1	0	-0.163575	-3.675595	-1.667949
30	1	0	-3.155975	3.155301	-0.905517
31	1	0	1.058650	3.285792	-1.038958
32	1	0	0.699627	1.883191	-2.033530
33	9	0	6.327408	0.292150	0.912550
34	9	0	4.640908	0.635191	3.012120
35	9	0	2.065105	1.193564	2.586473
36	9	0	5.387184	0.535182	-1.619454
37	9	0	2.837156	1.094738	-2.069103

RC for *Si* attack in THF of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.305457	1.969138	-1.216155
2	7	0	-0.164330	0.737919	-0.639880

3	8	0	-0.660448	2.682255	-2.344182
4	6	0	1.020257	0.951419	-1.054390
5	1	0	1.204419	1.807815	-1.703601
6	6	0	2.199201	0.180738	-0.664814
7	6	0	2.208941	-1.175937	-0.372722
8	6	0	3.401541	0.869354	-0.526474
9	6	0	3.343803	-1.822900	0.067265
10	6	0	4.551391	0.248544	-0.079122
11	6	0	4.518827	-1.103130	0.221743
12	12	0	-1.119260	-1.057832	0.301214
13	8	0	-2.984338	-0.270746	0.781290
14	6	0	-4.114626	-0.097815	-0.094298
15	6	0	-5.173172	-1.076663	0.417642
16	6	0	-4.712359	-1.422227	1.851340
17	6	0	-3.539858	-0.482477	2.092429
18	1	0	-5.201758	-1.967794	-0.204500
19	1	0	-2.751237	-0.878890	2.724806
20	1	0	-5.495502	-1.278172	2.591721
21	1	0	-4.378807	-2.456494	1.906602
22	1	0	-6.159793	-0.619661	0.402058
23	1	0	-4.444404	0.940262	-0.011644
24	1	0	-3.866464	0.483217	2.485735
25	1	0	-3.778457	-0.297768	-1.106285
26	6	0	-1.165209	3.144654	0.242758
27	6	0	-2.069854	4.303506	-0.181798
28	1	0	-2.099717	5.032023	0.628822
29	1	0	-1.692250	4.797186	-1.075408
30	1	0	-3.091460	3.968027	-0.367896
31	6	0	0.274938	3.604110	0.404540
32	1	0	0.286809	4.450615	1.092349

33	1	0	0.903884	2.824724	0.833516
34	1	0	0.695061	3.940181	-0.543103
35	6	0	-1.699031	2.479080	1.502455
36	1	0	-2.737386	2.176139	1.382200
37	1	0	-1.105459	1.615584	1.799054
38	1	0	-1.655769	3.208886	2.312605
39	35	0	-1.901979	-2.497354	-1.610212
40	6	0	1.589259	0.699781	2.697453
41	1	0	1.290858	1.616093	3.191568
42	1	0	2.629946	0.599063	2.413886
43	6	0	0.728338	-0.273495	2.486622
44	6	0	-0.136478	-1.187383	2.191079
45	1	0	-0.285214	-1.967542	2.937983
46	9	0	1.111556	-1.905935	-0.561627
47	9	0	3.448037	2.170793	-0.784476
48	9	0	5.673448	0.933831	0.070059
49	9	0	5.609183	-1.709201	0.647260
50	9	0	3.320888	-3.117686	0.333766

TS for *Si* attack in THF of 1a with 2a

Imaginary frequency: -355.8269

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.101403	1.938963	-1.312504
2	7	0	-0.099495	0.802764	-0.493841
3	8	0	-0.215086	2.729292	-2.211897
4	6	0	1.040362	1.258378	-0.009311
5	1	0	1.242377	2.320915	-0.060906

6	6	0	2.276497	0.450167	-0.013085
7	6	0	2.359642	-0.897582	-0.327698
8	6	0	3.485870	1.089670	0.257808
9	6	0	3.558147	-1.584397	-0.365931
10	6	0	4.698785	0.432915	0.228786
11	6	0	4.735640	-0.916146	-0.083665
12	12	0	-0.967432	-1.077293	0.027058
13	8	0	-2.963672	-0.507837	0.075989
14	6	0	-3.836899	-0.505429	-1.082288
15	6	0	-5.171907	-1.026695	-0.582146
16	6	0	-5.170294	-0.578481	0.878690
17	6	0	-3.724565	-0.804782	1.272739
18	1	0	-5.200030	-2.114406	-0.644285
19	1	0	-3.539500	-1.844818	1.547054
20	1	0	-5.426622	0.478840	0.957235
21	1	0	-5.854363	-1.147911	1.502800
22	1	0	-6.003614	-0.623722	-1.154602
23	1	0	-3.900130	0.521585	-1.441489
24	1	0	-3.362916	-0.149498	2.061456
25	1	0	-3.385349	-1.131960	-1.848468
26	6	0	-1.711336	3.189113	-0.054083
27	6	0	-2.771788	3.951966	-0.855814
28	1	0	-3.248252	4.683053	-0.201247
29	1	0	-2.326189	4.484039	-1.695431
30	1	0	-3.547784	3.285255	-1.235325
31	6	0	-0.600896	4.142009	0.366276
32	1	0	-1.050921	5.018101	0.836024
33	1	0	0.077709	3.696227	1.088477
34	1	0	-0.031516	4.475483	-0.500392
35	6	0	-2.355135	2.469760	1.121068

36	1	0	-3.213598	1.883996	0.797266
37	1	0	-1.660737	1.804627	1.630776
38	1	0	-2.707259	3.213321	1.838024
39	35	0	-1.429826	-3.455952	-0.637949
40	6	0	0.983167	1.333264	2.305229
41	1	0	0.485830	2.263053	2.551968
42	1	0	2.048526	1.308633	2.483974
43	6	0	0.268312	0.187181	2.386681
44	6	0	-0.437656	-0.830451	2.181745
45	1	0	-0.866230	-1.529807	2.883450
46	9	0	1.261901	-1.607055	-0.634441
47	9	0	3.485492	2.382128	0.573837
48	9	0	5.821774	1.080428	0.499426
49	9	0	5.888362	-1.559976	-0.111597
50	9	0	3.582267	-2.871833	-0.671281

PRODUCT for *Si* attack in THF of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.720413	1.743188	-1.304029
2	7	0	-0.182982	0.714929	-0.152471
3	8	0	0.435712	2.388295	-2.010258
4	6	0	0.944751	1.131231	0.660147
5	1	0	1.095636	2.203008	0.587982
6	6	0	2.266729	0.527749	0.200630
7	6	0	2.434316	-0.791936	-0.179206
8	6	0	3.393718	1.331445	0.106823
9	6	0	3.634127	-1.296229	-0.644614

10	6	0	4.611914	0.862975	-0.351862
11	6	0	4.733025	-0.461026	-0.732114
12	12	0	-1.045999	-1.109298	-0.024861
13	8	0	-3.031979	-0.662445	0.272386
14	6	0	-3.990620	-0.627158	-0.812809
15	6	0	-5.307944	-0.271488	-0.152388
16	6	0	-5.177736	-0.953237	1.209468
17	6	0	-3.712158	-0.739240	1.548202
18	1	0	-6.158210	-0.628306	-0.727869
19	1	0	-3.276220	-1.555879	2.119113
20	1	0	-5.832647	-0.526861	1.965028
21	1	0	-5.394366	-2.017578	1.122584
22	1	0	-5.398035	0.808685	-0.034650
23	1	0	-3.638395	0.108335	-1.533810
24	1	0	-3.539758	0.202061	2.070071
25	1	0	-4.017005	-1.614137	-1.276322
26	6	0	-1.543215	3.186345	-0.422564
27	6	0	-2.224366	3.952630	-1.557725
28	1	0	-2.805167	4.778947	-1.143771
29	1	0	-1.487926	4.362726	-2.247748
30	1	0	-2.905397	3.310426	-2.119490
31	6	0	-0.535240	4.085661	0.282185
32	1	0	-0.996204	5.053144	0.491739
33	1	0	-0.211809	3.670534	1.236395
34	1	0	0.336489	4.253247	-0.350471
35	6	0	-2.579971	2.628662	0.540813
36	1	0	-3.304568	2.000134	0.022691
37	1	0	-2.114886	2.030250	1.323514
38	1	0	-3.123457	3.450940	1.010497
39	35	0	-1.298132	-3.536934	-0.499548

40	6	0	0.658869	0.841306	2.151312
41	1	0	-0.058964	1.580722	2.508988
42	1	0	1.564567	0.948136	2.749330
43	6	0	0.090526	-0.487220	2.369186
44	6	0	-0.383371	-1.578597	2.532784
45	1	0	-0.758467	-2.557979	2.719439
46	9	0	1.411095	-1.663484	-0.107426
47	9	0	3.325557	2.615533	0.465396
48	9	0	5.660603	1.672721	-0.429145
49	9	0	5.892567	-0.927634	-1.171342
50	9	0	3.737824	-2.570329	-0.999326

RC for *Re* attack in THF of 1a with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.587562	2.185817	-0.689907
2	7	0	-0.300648	1.100072	-0.159539
3	8	0	-0.944492	3.314874	-1.406107
4	6	0	0.853655	1.513225	-0.512054
5	1	0	0.931858	2.440484	-1.080774
6	6	0	2.105187	0.828234	-0.210463
7	6	0	3.211118	1.061568	-1.025662
8	6	0	2.281250	-0.030531	0.869826
9	6	0	4.426387	0.445552	-0.799848
10	6	0	3.485829	-0.650927	1.121900
11	6	0	4.560417	-0.414907	0.277474
12	12	0	-0.789307	-1.122237	0.183258
13	35	0	-1.768029	-1.961444	2.328130

14	8	0	-2.421677	-0.956797	-1.058505
15	6	0	-3.722878	-1.514116	-0.734991
16	6	0	-4.512772	-1.444497	-2.027802
17	6	0	-3.421433	-1.627600	-3.081344
18	6	0	-2.277908	-0.824268	-2.495561
19	1	0	-4.987182	-0.468618	-2.134603
20	1	0	-2.355997	0.235231	-2.742152
21	1	0	-3.135773	-2.676674	-3.158922
22	1	0	-3.709362	-1.266329	-4.065550
23	1	0	-5.282961	-2.210627	-2.069970
24	1	0	-3.574263	-2.540338	-0.400590
25	1	0	-1.295619	-1.201259	-2.769245
26	1	0	-4.141314	-0.928941	0.079578
27	6	0	0.732667	-2.189890	-0.909195
28	1	0	1.475983	-2.609218	-0.227008
29	1	0	1.255608	-1.564906	-1.637452
30	6	0	-2.067474	2.839352	0.990244
31	6	0	-3.074627	3.940961	0.654354
32	1	0	-3.457918	4.351375	1.588789
33	1	0	-2.610109	4.746086	0.088121
34	1	0	-3.922022	3.552950	0.086850
35	6	0	-0.848418	3.404007	1.701040
36	1	0	-1.181484	3.967653	2.573200
37	1	0	-0.180523	2.616304	2.045209
38	1	0	-0.297833	4.084699	1.051024
39	6	0	-2.737763	1.711929	1.761985
40	1	0	-3.536536	1.245938	1.182943
41	1	0	-2.033427	0.941749	2.068502
42	1	0	-3.184926	2.126743	2.666280
43	6	0	0.010556	-3.242064	-1.576214

44	6	0	-0.677488	-4.081346	-2.105582
45	1	0	-1.244904	-4.841182	-2.584487
46	9	0	3.620971	-1.469744	2.151352
47	9	0	1.272204	-0.264466	1.706479
48	9	0	3.102100	1.877270	-2.064971
49	9	0	5.713626	-1.010271	0.503035
50	9	0	5.455361	0.668645	-1.600814

TS for *Re* attack in THF of 1a with 2a

Imaginary frequency: -378.6744

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.489237	-1.891829	-0.393813
2	7	0	-0.291007	-0.692182	-0.087996
3	8	0	-1.018991	-3.193253	0.147660
4	6	0	0.824778	-1.181079	0.420311
5	1	0	0.909703	-2.260377	0.496512
6	6	0	2.109302	-0.467686	0.261411
7	6	0	3.292258	-1.166456	0.496598
8	6	0	2.249024	0.849327	-0.155775
9	6	0	4.539365	-0.595842	0.335904
10	6	0	3.484012	1.449301	-0.323798
11	6	0	4.635963	0.723795	-0.075407
12	12	0	-1.053158	1.210494	0.498427
13	35	0	-1.812811	2.942014	-1.018646
14	8	0	-2.910539	0.527756	1.188318
15	6	0	-4.153388	0.663349	0.461322
16	6	0	-5.204908	0.060840	1.373216

17	6	0	-4.423601	-1.057739	2.061296
18	6	0	-3.061360	-0.418817	2.270230
19	1	0	-6.069067	-0.297048	0.818079
20	1	0	-2.238607	-1.129471	2.226341
21	1	0	-4.868169	-1.383121	2.999021
22	1	0	-4.336034	-1.921867	1.402338
23	1	0	-5.544646	0.797825	2.101732
24	1	0	-4.287257	1.716119	0.232793
25	1	0	-2.999158	0.133649	3.207768
26	1	0	-4.063292	0.104016	-0.472122
27	6	0	0.833052	-1.143095	2.651623
28	1	0	1.886320	-1.326382	2.810475
29	1	0	0.171480	-1.968077	2.889337
30	6	0	-1.279794	-1.988601	-2.242373
31	6	0	-2.308494	-3.035194	-2.669295
32	1	0	-2.279660	-3.145056	-3.754171
33	1	0	-2.095738	-4.003368	-2.217676
34	1	0	-3.320970	-2.735453	-2.391724
35	6	0	0.133524	-2.440708	-2.571793
36	1	0	0.200900	-2.660857	-3.638420
37	1	0	0.863355	-1.664206	-2.345340
38	1	0	0.389231	-3.345355	-2.019649
39	6	0	-1.608069	-0.620223	-2.826378
40	1	0	-2.581701	-0.255736	-2.493016
41	1	0	-0.863105	0.127372	-2.561444
42	1	0	-1.642188	-0.694556	-3.914681
43	6	0	0.355856	0.120912	2.750000
44	6	0	-0.152764	1.247348	2.534406
45	1	0	-0.417349	2.042148	3.213315
46	9	0	3.236016	-2.432312	0.902707

47	9	0	5.636927	-1.297639	0.573067
48	9	0	5.821292	1.285637	-0.229474
49	9	0	1.180689	1.604609	-0.437364
50	9	0	3.567827	2.708074	-0.719806

PRODUCT for *Re* attack in THF of 1b with 2a

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-1.493695	-1.787799	-0.890716
2	7	0	-0.639590	-0.700378	-0.014670
3	8	0	-1.478148	-3.126434	-0.207258
4	6	0	0.553866	-1.154841	0.668070
5	1	0	0.664397	-2.231483	0.544631
6	6	0	1.840697	-0.511780	0.166614
7	6	0	3.009244	-1.260607	0.132304
8	6	0	1.950103	0.799083	-0.268200
9	6	0	4.211390	-0.759544	-0.331555
10	6	0	3.136337	1.333539	-0.739633
11	6	0	4.274560	0.549482	-0.773959
12	12	0	-1.604622	1.024482	0.362375
13	35	0	-2.247511	3.052248	-0.868504
14	8	0	-3.248015	0.434110	1.413391
15	6	0	-4.572755	1.018362	1.310797
16	6	0	-5.390643	0.317841	2.378965
17	6	0	-4.757122	-1.072394	2.412463
18	6	0	-3.282870	-0.761003	2.237889
19	1	0	-6.448773	0.300669	2.130339
20	1	0	-2.724321	-1.540179	1.724788

21	1	0	-4.949181	-1.608748	3.338330
22	1	0	-5.116878	-1.677126	1.580093
23	1	0	-5.267971	0.816824	3.340440
24	1	0	-4.474479	2.091100	1.452801
25	1	0	-2.798618	-0.522086	3.185369
26	1	0	-4.950949	0.818987	0.308277
27	6	0	0.405545	-0.934463	2.193119
28	1	0	1.338876	-1.158500	2.710951
29	1	0	-0.353501	-1.626037	2.559038
30	6	0	-0.542664	-2.076530	-2.475661
31	6	0	-1.511929	-2.877544	-3.346072
32	1	0	-1.064760	-3.049616	-4.326644
33	1	0	-1.733301	-3.845184	-2.896521
34	1	0	-2.450732	-2.340952	-3.494396
35	6	0	0.728509	-2.873443	-2.224576
36	1	0	1.119715	-3.243236	-3.174450
37	1	0	1.504403	-2.262072	-1.769386
38	1	0	0.524426	-3.729001	-1.581288
39	6	0	-0.259150	-0.714773	-3.095237
40	1	0	-1.173471	-0.128040	-3.206982
41	1	0	0.440076	-0.140508	-2.489524
42	1	0	0.174403	-0.847868	-4.088298
43	6	0	-0.007840	0.430989	2.505285
44	6	0	-0.364532	1.556588	2.723579
45	1	0	-0.644405	2.556173	2.963545
46	9	0	2.988462	-2.529655	0.547334
47	9	0	5.296717	-1.522064	-0.357518
48	9	0	5.416687	1.049989	-1.220035
49	9	0	0.895888	1.630116	-0.254745
50	9	0	3.187107	2.593327	-1.151500

RC for *Re* attack in DCM of 1a with 2b

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	1.807659	0.815041	1.294378
2	6	0	0.094691	0.763026	2.612256
3	6	0	-0.517636	-0.537733	2.693562
4	6	0	-0.989892	-1.650533	2.707015
5	6	0	-0.540527	-1.218928	-0.272330
6	7	0	0.653413	-0.761220	-0.324605
7	1	0	-0.633209	1.515930	2.298253
8	1	0	0.470615	1.063458	3.594621
9	1	0	-0.743106	-2.272684	-0.099631
10	16	0	1.888086	-1.869734	0.054840
11	8	0	2.730254	-0.996535	0.968568
12	6	0	-1.713538	-0.378793	-0.460473
13	6	0	-2.973532	-0.959594	-0.305610
14	6	0	-1.673730	0.984307	-0.760855
15	6	0	-4.138676	-0.231897	-0.423496
16	6	0	-2.830371	1.729930	-0.883129
17	6	0	-4.063313	1.121449	-0.712099
18	35	0	3.065710	2.776416	0.396106
19	6	0	2.771988	-1.914868	-1.566543
20	6	0	3.126063	-0.507350	-2.020372
21	1	0	3.728556	0.010941	-1.275888
22	1	0	3.709862	-0.580935	-2.938608
23	1	0	2.236968	0.085563	-2.225407

24	6	0	1.837922	-2.628237	-2.540104
25	1	0	1.507002	-3.593683	-2.153779
26	1	0	0.964851	-2.021909	-2.777557
27	1	0	2.381289	-2.811464	-3.467070
28	6	0	4.023227	-2.746578	-1.281732
29	1	0	3.772323	-3.750419	-0.936733
30	1	0	4.592914	-2.840547	-2.206190
31	1	0	4.657586	-2.264215	-0.539217
32	6	0	-1.616751	-2.969910	2.819084
33	1	0	-1.149942	-3.704005	2.159605
34	1	0	-1.538225	-3.349638	3.838803
35	1	0	-2.676412	-2.924457	2.566069
36	9	0	-2.767236	3.021641	-1.168104
37	9	0	-5.168232	1.831073	-0.829859
38	9	0	-5.318634	-0.812151	-0.264468
39	9	0	-3.073487	-2.254795	-0.028582
40	9	0	-0.525044	1.611326	-0.955467

TS for *Re* attack in DCM of 1a with 2b

Frequency -214.275

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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2	6	0	0.286690	-0.941042	2.833340
3	6	0	1.283999	0.007394	2.591112
4	6	0	2.068530	0.868136	2.215407
5	6	0	1.043296	1.057439	0.019568
6	7	0	-0.175394	0.593812	0.012236

7	1	0	0.661466	-1.961773	2.912485
8	1	0	-0.362582	-0.687118	3.672162
9	1	0	1.233967	2.111679	0.184229
10	16	0	-1.375651	1.669892	0.526791
11	8	0	-2.285647	0.692423	1.258696
12	6	0	2.138089	0.313709	-0.612599
13	6	0	3.202560	1.022211	-1.161726
14	6	0	2.185064	-1.072725	-0.714976
15	6	0	4.261855	0.393617	-1.788112
16	6	0	3.233762	-1.723584	-1.332742
17	6	0	4.276621	-0.987215	-1.872530
18	35	0	-2.328426	-2.983072	0.086442
19	6	0	-2.212781	2.013108	-1.087895
20	6	0	-2.598580	0.710626	-1.770563
21	1	0	-3.241033	0.103687	-1.134031
22	1	0	-3.151189	0.949223	-2.680096
23	1	0	-1.722848	0.125943	-2.045804
24	6	0	-1.227027	2.833184	-1.914748
25	1	0	-0.885687	3.721488	-1.380583
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27	1	0	-1.730141	3.165955	-2.822844
28	6	0	-3.443286	2.836198	-0.707218
29	1	0	-3.170116	3.758146	-0.192133
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34	1	0	3.705734	1.807286	3.189836
35	1	0	3.962301	1.461727	1.482517
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37	9	0	5.284189	-1.604338	-2.462851
38	9	0	5.254589	1.101993	-2.305611
39	9	0	1.225746	-1.825061	-0.183347
40	9	0	3.211612	2.352599	-1.102987

PRODUCT for *Re* attack in DCM of 1a with 2b

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	12	0	-1.962037	-0.328538	0.494381
2	6	0	-1.436526	-2.674506	1.868483
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4	6	0	0.971725	-1.681959	1.770249
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7	1	0	-1.795521	-3.339335	1.091681
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11	8	0	-1.926021	1.564987	1.251220
12	6	0	2.285379	-0.453161	0.034727
13	6	0	3.519991	0.161616	0.149201
14	6	0	2.039071	-1.147006	-1.140877
15	6	0	4.470996	0.109782	-0.855887
16	6	0	2.968128	-1.217177	-2.162184
17	6	0	4.191535	-0.583908	-2.018307
18	35	0	-3.747362	-1.403638	-0.801111
19	6	0	-0.174512	2.927300	-0.222369
20	6	0	-0.937309	2.441901	-1.443061

21	1	0	-2.008781	2.399283	-1.249967
22	1	0	-0.770982	3.138438	-2.266201
23	1	0	-0.588064	1.458980	-1.760408
24	6	0	1.326548	2.984735	-0.488947
25	1	0	1.894698	3.191778	0.420342
26	1	0	1.683044	2.049413	-0.918679
27	1	0	1.534432	3.784629	-1.200520
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30	1	0	-0.565183	5.022784	-0.496341
31	1	0	-1.765915	4.207942	0.512055
32	6	0	2.162350	-2.392832	2.355558
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36	9	0	3.822218	0.853736	1.251000
37	9	0	5.640619	0.721481	-0.711666
38	9	0	5.090080	-0.645905	-2.990378
39	9	0	2.699377	-1.889007	-3.275234
40	9	0	0.876679	-1.774066	-1.317745

X. References.

[1] Llobat, A.; Escorihuela, J.; Sedgwick, D. M.; Rodenes, M.; Román, R.; Soloshonok, V. A.; Han, J.; Medio-Simón, M.; Fustero, S. The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioen-riched Nitrogen-Containing Heterocycles. *Eur. J. Org. Chem*. **2020**, 4193−4207.

[2] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst*. **2009**, *42*, 339−341.

[3] Sheldrick, G.M. A short history of SHELX. *Acta Cryst.* **2008**, *A64*, 112−122.

[4] Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst*. **2015**, *C71*, 3−8.

[5] Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. Phys. Chem. Chem. Phys. 2008, 10, 6615−6620.

[6] Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Mont-gomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

[7] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

[8] a) Gonzalez, C.; Schlegel, H.B. An improved algorithm for reaction path following. J. Chem. Phys. 1989, 90, 2154; b) Gonzalez, C.; Schlegel, H.B. Reaction path following in mass-weighted internal coordinates. *J. Phys. Chem*. **1990**, *94*, 5523−5527.

[9] Weinhold, F. Natural bond orbital analysis: A critical overview of relationships to alternative bonding perspectives. *J. Comput. Chem*. **2012**, *33*, 2363−2379.

[10] Tao, J.; Perdew, J. P.; Staroverov, V. N.; Scuseria, G. E. Climbing the density functional ladder: Nonempirical meta-generalized gradi-ent approximation designed for molecules and solids. *Phys. Rev. Lett*. **2003**, *91*, 146401−146404.

[11] a) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. Phys. Chem. Chem. Phys. 2005, 7, 3297−3305; b) Weigend, F. Accurate Coulomb-fitting basis sets for H to Rn. *Phys. Chem. Chem. Phys*. **2006**, *8*, 1057−1065.

[12] CYLview20; Legault, C. Y., Université de Sherbrooke, 2020 (http://www.cylview.org).

Scientific Article 2:

The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles

The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles

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Supporting information for this article is given via a link at the end of the document.

Abstract: The tetrahydropyridine structure is present in a wide variety of natural and synthetic compounds with interesting pharmacological properties. Therefore, the search for new chemical routes capable of yielding this valuable nitrogen-containing heterocycle is of utmost interest. Herein, we report the use of the ruthenium-catalyzed ring-closing enyne metathesis (RCEYM) and cross enyne metathesis/ring-closing metathesis (CEYM/RCM) reactions of chiral nitrogen-containing 1,7-enynes as an efficient route to synthesize a variety of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes. The RCEYM presented wide functional group tolerance and took place in moderate to high yields, with no significant differences when carried out at gram scale. These 1,3-dienes were suitable for further transformations, such as the Diels-Alder reaction, effectively yielding more complex enantioenriched bicyclic structures.

Introduction

Nitrogen-containing heterocycles are important motifs present in a wide variety of natural products and biologically active molecules, i.e. pharmaceuticals and agrochemicals.[1] This is evident when looking at the alkaloid class of natural products, many of which have served as starting points in modern drug discovery processes.[2] Among this class of heterocycles, tetrahydropyridines and piperidines have emerged as promising targets with potential applications in the treatment of schizophrenic syndromes, sleep disorders and Parkinson's disease, among others (Figure 1).[3] However, the synthesis of such compounds can often be fairly laborious and require several synthetic steps to achieve the desired substitution patterns.[4] On the other hand, a key feature of many natural products and biologically active compounds is their optical purity; most exist as a single enantiomer due to their biosynthetic origins.[5] This is crucial in drug discovery, since opposing enantiomers may present very different biological activity.[6] For this reason, great efforts have been invested in the development of novel synthetic strategies for the construction of enantioenriched nitrogen-containing heterocycles throughout the past few decades.[7] However, the

emergence of alternative methodologies capable of easily constructing such target molecules remains scarce in medicinal and synthetic organic chemistry.[8]

In view of the need for alternative and more efficient strategies for the synthesis of these valuable olefin-containing building blocks, metathesis reactions offer easy access to worthwhile alkenes with high efficiency and atom economy. Since the seminal report by Grubbs in 1992,[9] metathesis reactions have become some of the most powerful for carbon-carbon bond formation in recent organic chemistry, especially the ring-closing metathesis (RCM) reaction between two olefins.[10] Another interesting variant is the ring-closing enyne

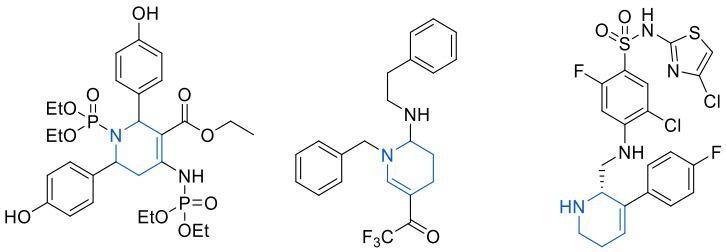


Figure 1. Interesting biological activities of tetrahydropyridine derivatives.

metathesis (RCEYM) reaction which, under mild conditions, generates conjugated cyclic 1,3-dienes with an exocyclic double bond.[11] RCEYM reactions have been widely applied to the synthesis of medium- and large-sized rings containing 1,3-dienes, which are interesting building blocks amenable to further synthetic transformations and are present in many drugs and natural products.[12] The RCEYM reaction is also compatible with nitrogen-based functional groups, and *N*-tethered enynes can also be used to afford desirable tetrahydropyridine-based 1,3-dienes.[13] Furthermore, the possibility of performing an *exo* cross enyne metathesis reaction between the triple bond of the enyne and a monoalkene would widen the structural diversity of the final products.[14] For this reason, as well as their wide functional-group tolerance, they have become a fundamental part of the modern synthetic chemist's toolkit.[15] These ruthenium-catalyzed transformations have also been

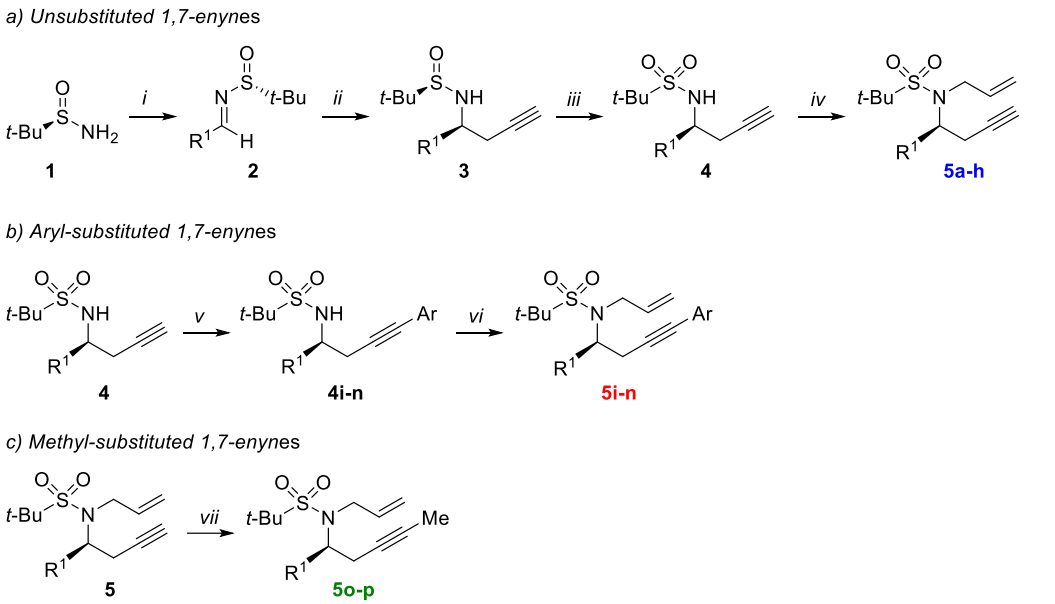
applied to various cascade reaction during the past decade,[16] often leading to the introduction of high molecular complexity in a single step, for example through coupling with Diels–Alder or other cyclization reactions to form polycyclic systems,[17] as well as in the synthesis of alkaloids and other natural products.[18]

In the quest for novel chemical routes capable of generating enantioenriched tetrahydropyridine derivatives, herein we report the use of chiral *N*-tethered 1,7-enynes in the ruthenium-catalyzed RCEYM reaction to form aza-cyclic conjugated 1,3-dienes. The chiral *N*-tethered 1,7-enynes were synthesized from Ellman's *tert*-butanesulfinyl imines in good yields following a simple four-step synthetic route. The building blocks obtained through the efficient RCEYM reaction could be used in subsequent Diels-Alder reactions to access piperidine-based bicyclic scaffolds.

Discussion

The synthesis of the chiral *N*-tethered 1,7-enyne building blocks was performed in good yields following a previously reported four-step synthetic sequence (Scheme 1).[19] The initial condensation reaction of *tert*-butanesulfinamide **1** with aldehydes in CH_2Cl_2 provided Ellman's *tert*-butanesulfinyl imines

2 in high yields.[20] Over the past decade, *N*-*tert*-butanesulfinyl imines have been widely used in synthetic applications, since they provide easy access to both enantiomers from commercially available *tert*-butanesulfinamide.[21] Following this, the diastereoselective propargylation of imines **2** using propargylmagnesium bromide in CH_2Cl_2 at –48 °C afforded the chiral homopropargyl sulfinamides **3**,[22] which were oxidized to the corresponding sulfonamides **4** using *m*-CPBA in CH_2Cl_2 at 0 °C in high yields. Finally, allylation with allyl bromide in the



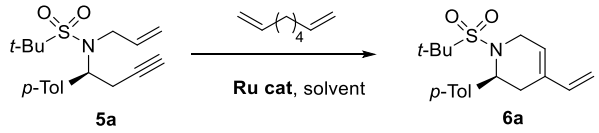
Scheme 1. Synthesis of chiral *N*-tethered 1,7-enynes.

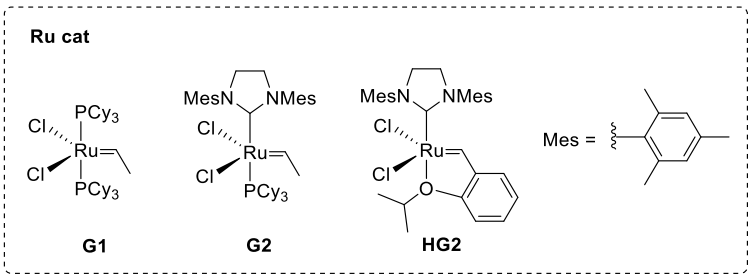
presence of NaH in DMF yielded the chiral *N*-tethered 1,7-enyne derivatives **5a-f** in good to high global yields (Scheme 1a). Additionally, enantioenriched *N*-tethered fluorinated enynes (R = CF_3 or C_3F_7) were also synthesized in good to high yields (**5g** and **5h**). Substitution at the triple bond with aryl groups via Sonogashira reaction with homopropargylic sulfonamides **4**, and subsequent allylation as previously mentioned, allowed the preparation of aryl-substituted 1,7-enynes (**5i-n**) (Scheme 1b). On the other hand, methyl-substituted enynes (**5o** and **5p**) were synthesized via direct methylation of the triple bond using HMDSLi and methyl iodide (Scheme 1c).

With these versatile substrates in hand, we began to explore the ring closing enyne metathesis reaction, using 1,7-octadiene as an in situ source of ethylene.[23] Under metathesis conditions, 1,7-octadiene undergoes a highly favorable ring-closing metathesis reaction without interfering with the substrate.

This process releases cyclohexene and ethylene into the reaction mixture, generating the reactive ruthenium carbene

Table 1. Optimization of the reaction conditions.[a)]





Entry	Solvent	[Ru cat]	cat loading (%)	Yield (%)[b)]
1	Toluene	**G1**	10	52
2	Toluene	**G2**	10	56
3	Toluene	**HG2**	10	83
4	MeCN	**HG2**	10	81
5	CH_2Cl_2	**HG2**	10	89
6	THF	**HG2**	10	65
7	CH_2Cl_2	**HG2**	5	87

8	CH_2Cl_2	**HG2**	3	85
9	CH_2Cl_2	**HG2**	1	57
10[c)]	CH_2Cl_2	**HG2**	3	0

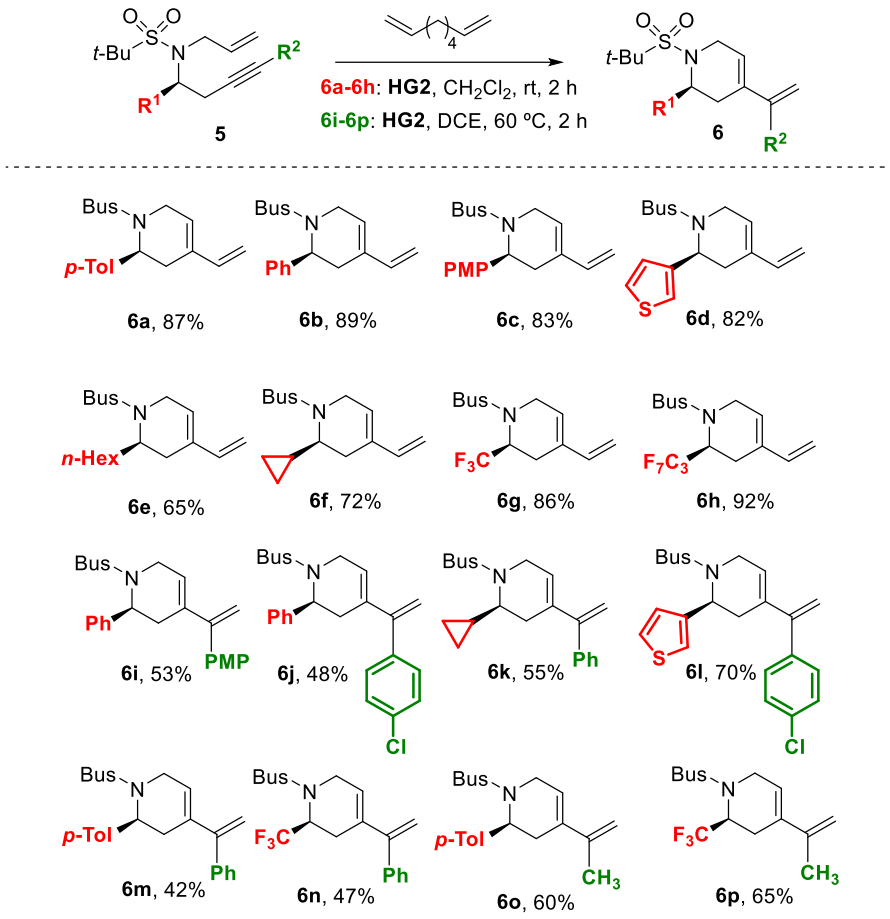
[a)] Reaction conditions: **5a** (0.1 mmol), 1,7-octadiene (0.4 mmol), r.t., 2 h. [b)] Yields of the isolated product **6a**. [c)] In the absence of 1,7-octadiene.

catalyst in the process, ready to enter the catalytic cycle that leads to the formation of the desired conjugated 1,3-diene. To our delight, enyne **5a** successfully took part in a ruthenium-catalyzed intramolecular RCEYM reaction yielding the corresponding enantioenriched tetrahydropyridine-based 1,3-diene **6a** (Table 1).

An initial screening of the reaction conditions was carried out using enyne **5a** (R^1 = *p*-Tol) as the model substrate for the ruthenium-catalyzed RCEYM (Table 1). First, a screening of the different Grubbs catalysts (10 mol%) was performed using toluene as solvent. Our model substrate was efficiently cyclized to give the cyclic 1,3-diene in all cases (entries 1-3, Table 1), but second-generation Hoveyda–Grubbs catalyst (**HG2**) proved the most efficient in terms of yield of **6a** (entry 3, Table 1). We then explored the use of different solvents using the **HG2** catalyst (10 mol%). Similar yields were observed when using other non-coordinating solvents such as acetonitrile or CH_2Cl_2 (entries 4 and 5, Table 1), although the yield was slightly higher in CH_2Cl_2. On the contrary, the use of THF, a coordinating solvent, remarkably decreased the formation of the cyclic 1,3-diene (entry 6, Table 1). The catalyst loading could be lowered to 3 mol% without a significant decrease in the reaction yield (entries 7 and 8, Table 1); however, the yield decreased under same reaction conditions (2 h) beyond this value (entry 9, Table 1). When the reaction was assayed in the absence of 1,7-octadiene (entry 10, Table 1), the formation of **6a** was not observed, but a triene resulting from a homo cross metathesis was formed in 48% yield. The formation of this from a cross metathesis of **6a** has also been recently reported by Foubelo and coworkers under high dilution conditions.[12a]

With the optimal reaction conditions in hand (CH_2Cl_2, **HG2** catalyst 3 mol%; (entry 8 Table 1), the formation of the corresponding tetrahydropyridine-based 1,3-dienes through

our ring-closing enyne metathesis (RCEYM) procedure was then evaluated (Scheme 2). For this purpose, a set of chiral 1,7-enynes with different substituents at the stereogenic carbon was submitted to our optimized RCEYM reaction conditions, usually resulting in complete conversion of the chiral 1,7-enyne after 2 h (determined by TLC analysis). The resulting 1,3-dienes could be isolated through simple flash column chromatography. As a general trend, substrates with aromatic substituents (R^1 = Ph, *p*-Tol, PMP) at the stereogenic center gave higher yields than those bearing aliphatic substituents such as *n*-hexyl or cyclopropyl (**6e** and **6f**, Scheme 2). Interestingly, 1,7-enynes containing fluorinated substituents ($R^1 = CF_3$ or C_3F_7) afforded the corresponding 1,3-diene compounds with high yields (**6g** and **6h**, Scheme 2). Fluorinated substitutions are of great importance in modern organic and medicinal chemistry, since the unique properties of the C-F bond allow the fine-tuning of the acidity/basicity, metabolic stability and lipophilicity of biologically active compounds as desired.[24] A gram-scale synthesis of diene **6b** was also successfully performed through the ruthenium catalyzed metathesis reaction with 1,7-octadiene in good global yield (70%, 4 steps, see Supporting Information for details).

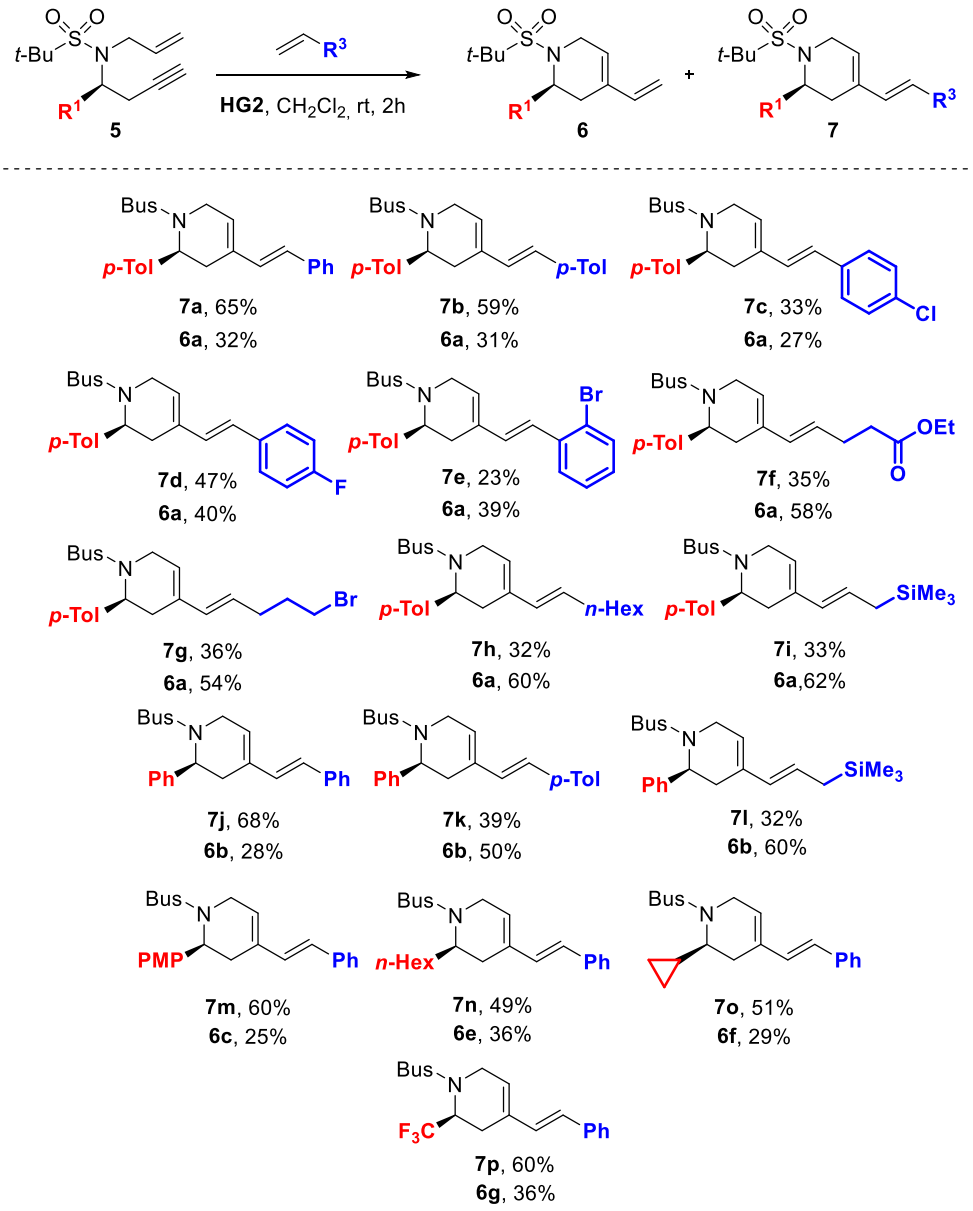


Scheme 2. Ruthenium-catalyzed RCEYM of chiral *N*-tethered 1,7-enynes.

The influence of the alkyne substitution was also evaluated in the RCEYM. To this end, alkyl and aryl substituents were introduced at the corresponding chiral propargyl sulfonamides **4** following a previously escribed synthetic route by our group.[19] The ruthenium-catalyzed RCEYM in the presence of 1,7-octadiene afforded the corresponding aryl- or alkyl-substituted 1,3-dienes (**6i-6p**, Scheme 2) in moderate yields after 2 h in DCE at 60 °C. In general, lower yields were obtained when compared to the unsubstituted analogues (Scheme 2). Our results indicate that enyne substituents have an important effect on the reactivity of the process, as observed in similar systems.[25]

Next, a ruthenium-catalyzed domino cross enyne metathesis/ring-closing metathesis (CEYM/RCM) of enyne **5a** and styrene was assayed.[26] In this case, we observed the formation of a mixture of products easily separable by flash chromatoraphy: **7**, presumably via a cross enyne metathesis (CEYM) followed by a ring closing metathesis (RCM) reaction; and **6**, through the simple RCEYM previously discussed. When performing the reaction of enyne **5a** (R^1 = *p*-Tol) with styrene in the presence of **HG2** catalyst (3 mol%), both **6a** and **7a** were isolated with yields of 32 and 65%, respectively. Under the aforementioned conditions, the formation of the CEYM product, i.e. conjugated (*E*)-diene **7a**, was favored over the RCEYM product **6a**. Slow addition of the catalyst was assayed with the aim of preserving catalytic activity, but this yielded **7a** in lower yields and slightly favored the formation of RCEYM product **6a**.[27] The use of other aromatic olefins afforded the corresponding compound **7** in similar yields to that observed for styrene. However, electron-withdrawing substituents in the ortho or para position of the styrene derivative had a dramatic effect and decreased the isolated yield of the CEYM product (**7c-e**, Scheme 3). A similar negative effect was observed in compounds **7f-i** when carrying out the metathesis reaction with aliphatic olefins which, in contrast, favored the formation of the RCEYM product over that of CEYM.

Next, we evaluated the effect of the substituent on the stereogenic center of 1,7-enyne. The presence of aromatic substituents (R^1 = Ph, *p*-Tol, PMP) on the stereogenic center resulted in higher yields of the corresponding CEYM/RCM product **7** with slight variations depending on the aromatic substituents (**7a**, **7j** and **7m**, Scheme 3). On the contrary, the aliphatic substituents (R^1 = *n*-Hex, *c*-Pr) on the chiral center lowered the formation of the CEYM/RCM product (**7n** and **7o**, Scheme 3), similar to the previously observed results with 1,7-octadiene. Finally, fluorine-containing 1,7-enyne (R^1 = CF_3) afforded the corresponding 1,3-diene derived from the CEYM/RCM with a 60% yield (**7p**).



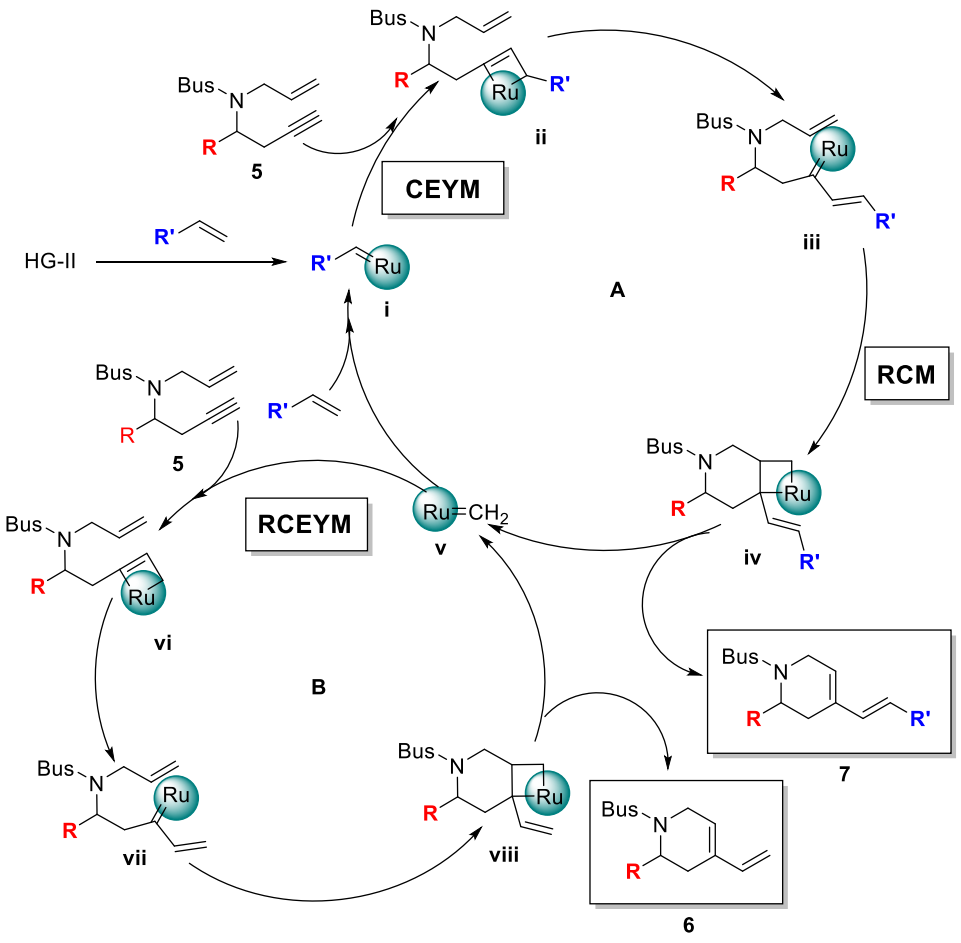
Scheme 3. Scope of the CEYM/RCM of *N*-tethered 1,7- enynes.

To account for the formation of 1,3-dienes **6** and **7** from the corresponding chiral *N*-tethered 1,7-enynes, a possible catalytic cycle is depicted in Scheme 4. Accordingly, diene **7** should be the result of a domino cross enyne metathesis/ring-closing metathesis

(CEYM/RCM) process. The initial formation of the intermediate ruthenium complex **i** would come from the reaction of second-generation Hoveyda–Grubbs catalyst (**HG2**) with the monoalkene. Next, a [2 +2] cycloaddition with 1,7-enyne **5** would take place to form ruthenacyclobutene **ii**. This intermediate would be then converted into the vinylcarbene complex **iii** via ring-opening, and followed by RCM with the alkene group of the 1,7-enyne yielding cyclic compound ruthenacyclobutane **iv**. Subsequent ring-opening of **iv** should give the cyclized 1,3-diene **7**, and a methylidene ruthenium complex **v**, which could then react with the monoalkene and restart the catalytic cycle.

On the other hand, should intermediate **v** react with enyne **5**, a second cycle could be formed leading to the formation of diene **6**. For this to take place, methylidene ruthenium complex **v** should undergo a [2 +2] cycloaddition with the 1,7-enyne **5**, giving ruthenacyclobutene **vi**, which is then converted into vinylcarbene complex **vii** via ring-opening. Subsequent reaction with the alkene group of the 1,7-enyne gives ruthenacyclobutane **viii**. Finally, ring opening of ruthenacyclobutane **viii** gives cyclized diene **6**, and the methylidene ruthenium complex **v** is regenerated. The whole process could also start with a RCEYM followed by a CM, especially if the RCEYM goes by the ene-first mechanism (not shown in Scheme 4), which would directly lead to the carbene needed for the subsequent cross-metathesis reaction. The one-pot reaction of **5a** with 1,7-octadiene in the presence of **HG2** catalyst (3 mol%), followed by the addition of styrene after complete conversion to **6a**, failed to give **7a**. However, the cross-metathesis reaction from isolated **6a** with styrene was partly successful in forming **7a**, although the reaction was much more sluggish and resulted in a low yield (45%). The hypothesized pathway was in agreement with the results reported by Park *et al*. in the tandem CM/RCM reaction of alkynyl silyloxy-tethered enynes.[28]

In order to achieve more complex chemical structures and form polycyclic heterocycles, the reactivity of several chiral 1,3-dienes was evaluated through Diels-Alder reaction with readily available carbo- and heterodienophiles, such as tetracyanoethylene (TCNE) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Notably, all reactions took place efficiently to give cycloadducts **8** in high diastereoselectivity (*dr* > 20:1) (Scheme 5).



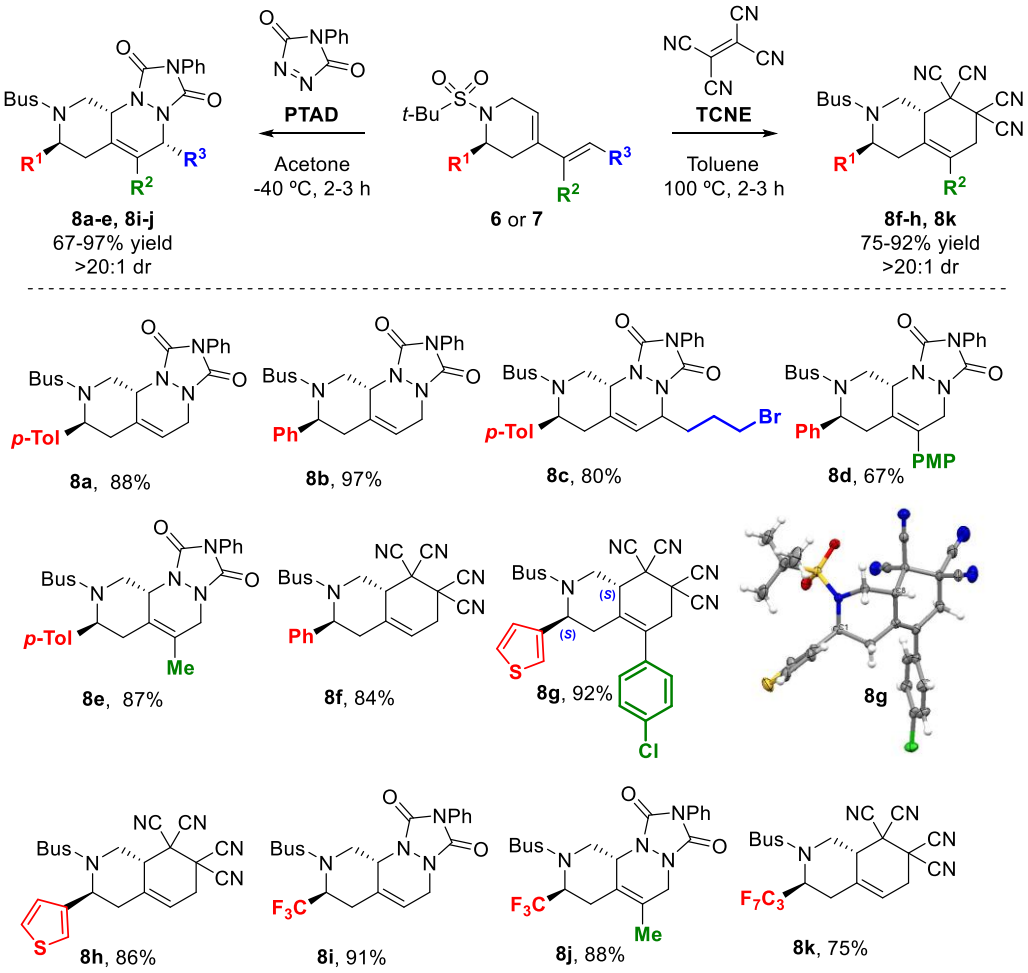
Scheme 4. Tentative catalytic cycle for the domino CEYM/RCM and RCEYM of chiral 1,7-*N*-tethered enynes.

Cycloaddition of **6a** and **6b**, both bearing an aromatic substituent on the stereogenic center, with PTAD yielded Diels-Alder adducts **8a** and **8b** in high yields of 88% and 97% respectively. The Diels-Alder reaction affording **8b** was also carried out at gram scale with no loss of yield. However, a decrease in yield was observed when performing the reaction with **6i** and **7g**, affording the corresponding cycloadducts **8c** and **8d**, respectively, in lower yields (80 and 67%). Similar yields were obtained when performing the reaction with TCNE for example,

6b afforded cycloadduct **8f** in 84% yield. The absolute stereochemistry of product **8g** was determined to be (*S*,*S*) according to X-ray crystallography analysis,[29] and was confirmed by a NOESY experiment using compound **8c**. This absolute stereochemistry was extrapolated to the rest of the Diels-Alder cycloadducts displayed in Scheme 5. Following our ongoing interest in the development of new fluorinated building blocks, we extended the scope of the Diels-Alder reaction to fluorinated derivatives. In this regard, these chiral fluorinated compounds were subjected to the cycloaddition conditions with PTAD and TCNE, again yielding the corresponding cycloadducts in high yields and diastereoselectivities (**8i-8k**, Scheme 5).

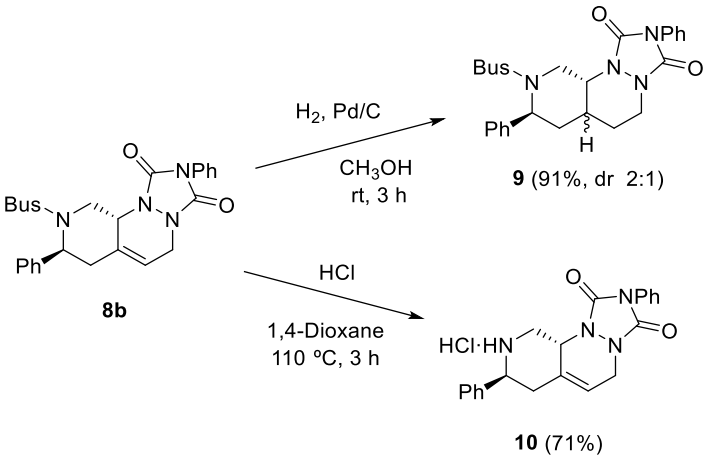
Further modifications to the final Diels_Alder adducts were also assayed. In this regard, the double bond in the resulting cycloadduct **8b** could be efficiently hydrogenated using palladium over activated charcoal under an atmosphere of hydrogen with high yield (91%) but low diastereoselectively (*dr* 2:1) (Scheme 6). The removal of the *tert*-butanesulfonyl group was also assayed. An initial attempt to remove it was performed in hydrochloric acid in methanol at room temperature, but no reaction took place. However, through treatment of **8b** with HCl in 1,4-dioxane at 110 ºC the *tert*-butylsulfonyl group could be cleanly removed and hydrochloride salt **10** was successfully isolated in a 71% yield, with no loss in optical purity (Scheme 6). The protecting group could also be removed with $AlCl_3$ in anisole, albeit in a lower yield (50%).

Considering the rapidly growing number of marketed fluorine-containing drugs, it is of utmost interest to access these drugs through short and easy synthetic routes. In this regard, our metathesis products could be efficiently used in the preparation of more complex heterocyclic systems containing fluorine atoms. In our case, the incorporation of a fluorine atom into the piperidine ring was possible through the electrophilic fluorodesilylation of the allylsilane-bearing metathesis product **7l**, as described by Thibaudeau and Gouverneur.[30] The aforementioned transformation was carried out in acetonitrile at room temperature in the presence of Selectfluor, yielding fluorinated compound **11** in 58% yield with high diastereoselectively (*dr* >20:1) (Scheme 7).



Scheme 5. Scope of the Diels–Alder reaction of 1,3-dienes derived from RCEYM of chiral *N*-tethered 1,7-enynes and ORTEP representation of compound **8g**

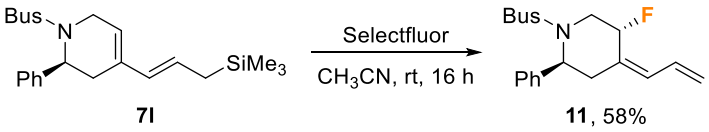
The stereochemistry of **11** was tentatively assigned by a series of 2D NMR experiments (see Supporting Information). It should be emphasized that the aforementioned method can be successfully applied to the preparation of derivatives featuring α-fluoroalkyl-amino moieties as a part of structurally complex heterocyclic systems.[31]



Scheme 6. Examples of further modifications to the final Diels–Alder adducts.

Conclusion

In conclusion, the effective use of RCEYM and domino CEYM/RCM reactions for the preparation of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes has been demonstrated using chiral nitrogen-containing 1,7-enynes as starting materials. Noteworthy, the obtained chiral 1,3-dienes were suitable substrates for Diels-Alder reactions with tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione, yielding more complex bicyclic scaffolds in high diastereoselectivity (*dr* > 20:1). These structures could potentially be used in medicinal or biological studies given the prevalence of the tetrahydropyridine moiety in pharmaceutical contexts. The RCEYM and Diels-Alder reaction was also carried out at gram scale with no loss of yield. Further synthetic applications of these chiral nitrogen-containing 1,7-enynes are under investigation.



7l **11**, 58%

Scheme 7. Fluorodesilylation of metathesis product **7l**.

Experimental Section

General methods. Reactions were carried out under nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: tetrahydrofuran (THF) and toluene were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). The reactions were monitored by thin layer chromatography (TLC) using 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate ($KMnO_4$) stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer (Bruker 300 MHz DPX). Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents ($CHCl_3$: δ 7.26 ppm for proton and δ 77.0 ppm for carbon). Coupling constants (*J*) are reported in Hertz (Hz). The notation s, d, dd, ddd, t, q, m, and bs in NMR signals stands for singlet, doublet, doublet of doublets, doublet of dd, triplet, quartet, multiplet and broad singlet, respectively. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points were measured on a Büchi B−540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P−1020 polarimeter at 25 °C.

I. General procedure for the propargylation reaction to sulfinamides 3. A 1 M solution of propargylmagnesium bromide in THF was prepared by stirring propargyl bromide (14 mmol) and activated Mg (28 mmol) in anhydrous THF (1 M, 14 mL) at 50 °C for 2 h. This freshly prepared solution was then added (1.5 equiv, 13.5 mmol) to a solution of corresponding imine (9.0 mmol) in CH_2Cl_2 (0.1 M, 90 mL) at −48 °C. After stirring during 18 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl

and extracted with CH_2Cl_2. The organic phase was washed with brine (3 × 10 mL), dried with anhydrous $MgSO_4$, and the solvent evaporated. The residue was purified by flash column chromatography to yield the corresponding sulfinamide **3**. Sulfinamides **3a-h** were prepared according to previously published procedures.[19]

II. General procedure for oxidation reaction to sulfonamides. To a solution of corresponding sulfinamide **3** (12.3 mmol) in CH_2Cl_2 (120 mL) at 0 °C, *m*-CPBA (14.8 mmol) was added and the mixture was stirred at room temperature for 2 h. After this time, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography affording sulfonamides **4**. Sulfonamides **4a-h**,[19a] were prepared according to previously published procedures.[19]

III. General procedure for Sonogashira reaction. CuI (8 mmol%) and $Pd(PPh_3)_2Cl_2$ (4 mmol%) were added to *i*-Pr_2NH (0.06 M) and the mixture was stirred at room temperature for 10 min. The solution was then heated to 50 °C, and a solution of sulfonamide **4** (0.3 mmol) in *i*-Pr_2NH (0.06 M) was added slowly for 1 h (slow addition pump), and the resulting mixture was stirred at 50 °C for a further 2 h. The reaction was quenched with a saturated solution of aqueous NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude mixture was purified by column chromatography (*n*-hexane:EtOAc). Compound **4n** was prepared according to previously published procedures.[19a]

(*S*)-*N*-(4-(4-Methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4i). According to general procedure III, **4i** was obtained as a white solid (68 mg, 49% yield). mp 102−104 ºC; $[\alpha]^{25}_D = -39.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 7H), 6.75–6.70 (m, 2H), 4.80–4.68 (m, 2H), 3.71 (s, 3H), 3.00–2.77 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 141.2, 133.1, 128.6, 127.8, 126.4, 115.2, 113.9, 84.2, 83.2, 60.1, 56.9, 55.3, 30.2, 24.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_3S$ $[M+NH_4^+]$: 389.1893; found: 389.1891.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4j). According to general procedure III, **4j** was obtained as a white solid 68 mg, (78% yield). mp 138–140 ºC; $[\alpha]^{25}_{D}$ = −37.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (m, 9H), 4.77–4.64 (m, 2H), 3.01−2.91 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 134.1, 132.9, 128.7, 128.6, 127.9, 126.3, 121.5, 85.9, 83.2, 60.1, 56.8, 30.3, 24.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{26}ClN_2O_2S$ [M+NH_4^+]: 393.1398; found: 393.1396.

(*S*)-*N*-(1-Cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4k). According to general procedure III, **4k** was obtained as a yellowish oil 49 mg, (62% yield). $[\alpha]^{25}_{D}$ = +33.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.34–7.27 (m, 3H), 3.06–2.94 (m, 1H), 2.89 (dd, *J* = 16.7, 5.2 Hz, 1H), 2.77 (dd, *J* = 16.7, 4.3 Hz, 1H), 1.42 (s, 1H), 1.27–1.13 (m, 1H), 0.70–0.55 (m, 3H), 0.44–0.33 (m, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 128.4, 128.2, 123.4, 85.7, 83.7, 60.0, 57.9, 27.6, 24.4, 17.0, 4.6, 4.5. HRMS (ESI): *m/z* calcd for $C_{20}H_{26}ClN_2O_2S$ [M+NH_4^+]: 323.1787; found: 323.1789.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4l). According to general procedure III, **4l** was obtained as a white solid (61 mg, 44% yield). mp 153–154 ºC; $[\alpha]^{25}_{D}$ = −32.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.16 (m, 6H), 7.06 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.84–4.77 (m, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 3.04−2.85 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 134.2, 132.9, 128.6, 126.6, 126.0, 121.8, 121.5, 86.0, 83.2, 60.2, 53.1, 29.4, 24.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{24}ClN_2O_2S_2$ [M+NH_4^+]: 399.0962; found: 399.0958.

(*S*)-2-Methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (4m). According to general procedure III, **4m** was obtained as a white solid (63 mg, 70% yield). mp 133–135 ºC; $[\alpha]^{25}_{D}$ = −47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.29–7.27 (m, 5H), 7.20–7.17 (m, 2H), 4.97-4.94 (m, 1H), 4.81–4.74 (m, 1H), 3.08-2.87 (m, 2H), 2.36 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.5, 1331.7, 129.3, 128.3, 128.1, 126.3, 123.2, 85.1, 84.1, 60.1, 56.8, 30.3, 24.2, 21.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_2S$ [M+NH_4^+]: 373.1944; found: 373.1951.

IV. General procedure for allylation reaction. To a suspension of NaH (60%, 6.8 mmol) in dry DMF (40 mL), the corresponding sulfonamide (4.5 mmol) was added dropwise at 0 °C.

After stirring at this temperature for 20 min, allyl bromide (9.1 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH_4Cl aq. and extracted with diethyl ether. The organic layer was then dried over anhydrous Na_2SO_4, concentrated under vacuum and the crude reaction mixture was then purified by flash column chromatography to yield **5**. Compounds **5g-h**[19a] and **5n**[19b] were prepared according to previously published procedures.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5a). According to general procedure IV, **5a** was obtained as a white solid (63 mg, 94% yield). mp 93–94 ºC. $[\alpha]^{25}_D$ = −28.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.92–5.73 (m, 1H), 5.15 (dd, *J* = 10.1, 5.3 Hz, 1H), 5.07 (bs, 1H), 5.03 (ddd, *J* = 7.5, 2.7, 1.3 Hz, 1H), 4.02–3.82 (m, 1H), 3.52 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.16 (ddd, *J* = 16.8, 10.2, 2.6 Hz, 1H), 2.97 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 2.36 (s, 3H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.2, 134.2, 129.3, 128.9, 117.4, 81.2, 71.4, 62.2, 61.4, 49.0, 25.2, 24.3, 21.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_2S$ $[M+NH_4^+]$: 337.1943; found: 337.1944.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-phenylbut-3-yn-1-yl) propane-2-sulfonamide (5b). According to general procedure IV, **5b** was obtained as a white solid (102 g, 91% yield). mp 134–136 ºC. $[\alpha]^{25}_D$ = −43.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.28 (m, 5H), 5.97–5.70 (m, 1H), 5.18 (dd, *J* = 10.0, 5.4 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.95 (ddd, *J* = 16.5, 3.1, 1.9 Hz, 1H), 3.54 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.18 (ddd, *J* = 16.8, 10.0, 2.6 Hz, 1H), 2.99 (ddd, *J* = 16.8, 5.4, 2.7 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 137.0, 128.9, 128.6, 128.3, 117.5, 81.0, 71.6, 62.2, 61.5, 49.1, 25.2, 24.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_2O_2S$ $[M+NH_4^+]$: 306.1549; found: 306.1522.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5c). According to general procedure IV, **5c** was obtained as a colorless oil (67 mg, 35% yield). $[\alpha]^{25}_D$ = −20.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.89–5.70 (m, 1H), 5.13 (dd, *J* = 10.2, 5.3 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.02–3.86 (m, 1H), 3.82 (s, 3H), 3.51 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.14 (ddd, *J* = 16.8, 10.3, 2.6

Hz, 1H), 2.96 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 137.2, 130.2, 129.2, 117.3, 113.9, 81.1, 71.4, 62.2, 61.0, 55.4, 48.9, 25.2, 24.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_3S$ [M+NH_4^+]: 353.1891; found: 353.1893.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(tiophen-2-yl)but-3-yn-1-yl)propane-2-sulfonamide (5d). According to general procedure IV, **5d** was obtained as a white solid (122 mg, 74% yield). mp 118–120 ºC. [α]$^{25}_D$ = −22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16–7.14 (dt, *J* = 3.6, 0.9 Hz, 1H), 7.00–6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.93–5.80 (m, 1H), 5.33–5.27 (dd, *J* = 9.3, 6.0 Hz, 1H), 5.08–5.05 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.02 (s, 1H), 3.99–3.92 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.63–3.55 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.18–2.97 (m, 2H), 2.05–2.03 (t, *J* = 2.7 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 137.0, 127.5, 126.6, 126.0, 117.4 , 80.6, 71.7, 62.3, 57.9, 48.7, 26.0, 24.9. HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O_2S_2$: 329.1350 [M+NH_4^+]; found: 329.1352.

(*R*)-*N*-Allyl-*N*-(dec-1-yn-4-yl)-2-methylpropane-2-sulfonamide (5e). According to general procedure IV, **5e** was obtained as a colorless oil (110 mg, 50% yield). [α]$^{25}_D$ = +4.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09–5.87 (m, 1H), 5.18 (ddd, *J* = 17.2, 2.7, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.1, 1.2 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 2H), 3.84–3.78 (m, 1H), 2.60–2.49 (m, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.82–1.63 (m, 2H), 1.41 (s, 9H), 1.28 (dd, *J* = 9.7, 6.5 Hz, 8H), 0.87 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 117.1, 81. 8, 71.2, 62.2, 59.2, 48.6, 31.8, 29.3, 27.2, 25.0, 22.7, 14.2. HRMS (ESI): *m/z* calcd for $C_{17}H_{36}N_2O_2S$ [M+NH_4^+]: 331.2414; found: 331.2414.

(*S*)-*N*-Allyl-*N*-(1-cyclopropylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5f). According to general procedure IV, **5f** was obtained as a white solid (97 mg, 84% yield). mp 62–63 ºC. [α]$^{25}_D$ = −2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11–5.95 (m, 1H), 5.21 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.11 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.16 (dt, *J* = 9.5, 7.1 Hz, 1H), 2.72 (dt, *J* = 5.3, 2.3 Hz, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.40 (s, 9H), 1.22–1.01 (m, 1H), 0.79 – 0.58 (m, 2H), 0.59–0.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137. 9, 117.0, 81.7, 71.1, 63. 6, 62.2, 49.5, 25.1, 15.9, 7.2, 4.2. HRMS (ESI): *m/z* calcd for $C_{14}H_{27}N_2O_2S$ [M+NH_4^+]: 287.1776; found: 287.1788.

(*S*)-*N*-Allyl-*N*-(4-(4-methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5i). According to general procedure IV, **5i** was obtained as a colorless oil (43

mg, 53% yield). $[\alpha]^{25}_D$ = −36.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.21 (m, 5H), 7.21–7.18 (m, 2H), 6.78–6.75 (m, 2H), 5.92–5.82 (m, 1H), 5.25 (dd, *J* = 9.0, 6.4 Hz, 1H), 5.10–5.07 (m, 1H), 5.04–5.03 (m, 1H), 4.03 (dd, *J* = 16.7, 5.2 Hz, 1H), 3.65 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.33 (dd, *J* = 16.9, 9.1 Hz, 1H), 3.19 (dd, *J* = 16.9, 6.3 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.9, 137.0, 132.9, 128.8, 128.4, 128.0, 117.2, 115.5, 113.8, 85.1, 83.4, 62.1, 61.6, 55.3, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ [M+H$^+$]: 412.1941; found: 412.1931.

(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5j). According to general procedure IV, **5j** was obtained as a colorless oil (44 mg, 48% yield). $[\alpha]^{25}_D$ = −38.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.30 (m, 5H), 7.22–7.14 (m, 4H), 5.95–5.81 (m, 1H), 5.26–5.10 (m, 1H), 5.18 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.10–5.04 (m, 2H), 4.05–3.98 (m, 1H), 3.62 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.4 Hz, 1H), 3.21 (dd, *J* = 16.9, 6.1 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.0, 133.8, 132.7, 128.8, 128.5, 128.1, 121.9, 117.3, 87.8, 82.5, 62.1, 61.6, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}ClN_2O_2S$ [M+NH_4^+]: 433.1711; found: 433.1706.

(*S*)-*N*-Allyl-*N*-(1-cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5k). According to general procedure IV, **5i** was obtained as a colourless oil (68 mg, 93% yield). $[\alpha]^{25}_D$ = −9.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.33–7.27 (m, 3H), 6.16–6.01 (m, 1H), 5.23 (dq, *J* = 17.3, 1.4 Hz, 1H), 5.12 (dq, *J* = 10.1, 1.3 Hz, 1H), 4.12 (t, *J* = 6.5 Hz, 2H), 3.25 (dt, *J* = 9.4, 7.2 Hz, 1H), 2.94 (dd, *J* = 7.2, 1.9 Hz, 2H), 1.41 (s, 9H), 1.24–1.10 (m, 1H), 0.81–0.66 (m, 2H), 0.59–0.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 131.5, 128.4, 128.0, 123.64 116.9, 87.4, 83.0, 63.8, 62.1, 49.5, 25.0, 16.2, 7.1, 4.4. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ [M+H$^+$]: 363.2110; found: 363.2101.

(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5l). According to general procedure IV, **5l** was obtained as a colorless oil (61 mg, 70% yield). $[\alpha]^{25}_D$ = −30.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.16 (m, 5H), 5.83–5.72 (m, 1H), 5.18 (dd, *J* = 8.4, 6.8 Hz, 1H), 5.01–4.98 (m, 1H), 4.95 (s, 1H), 3.94 (dd, *J* = 16.4, 5.5 Hz, 1H), 3.56 (dd, *J* = 16.4, 7.4 Hz, 1H), 3.32 (dd, *J* = 16.9, 8.7 Hz, 1H), 3.2 (dd, *J* = 16.9, 6.5 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 136.9,

134.0, 132.8, 128.6, 128.1, 125.8, 124.2, 121.8, 117.2, 87.7, 82.5, 62.1, 57.8, 49.0, 25.9, 25.0. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 439.1275; found: 439.1273.

(*S*)-*N*-Allyl-2-methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (5m). According to general procedure IV, **5m** was obtained as a colorless oil (147 mg, 99% yield). $[\alpha]^{25}_D$ = −21.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.30–7.19 (m, 7H), 5.98-5.84 (m, 1H), 5.25 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.11 (dd, *J* = 6.4, 1.2 Hz, 1H), 5.06 (s, 1H), 4.03 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.64 (dd, *J* = 16.5, 7.7 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.2 Hz, 1H), 3.22 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.37 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 137.2, 131.5, 129.1, 128.7, 128.2, 127.8, 123.5, 117.2, 86.9, 83.4, 62.1, 61.4, 48.9, 25.1, 22.7, 21.1. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 413.2259; found: 413.2257.

V. General procedure for the methylation reaction. The corresponding enyne (0.17 mmol) was dissolved in THF (0.4 mL) at −78 ºC under an argon atmosphere. HMDSLi (1 M in toluene, 0.34 mmol) was then added dropwise to the reaction mixture. After 1 h, MeI (0.84 mmol) was added to the reaction mixture and the temperature was increased to -40 ºC. After 12 h the solvent was then removed and the reaction mixture was purified by flash column chromatography in *n*-hexane:EtOAc (10:1).

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl)pent-3-yn-1-yl)propane-2-sulfonamide (5o). According to general procedure V, **5o** was obtained as a colorless oil (194 mg, 93% yield). $[\alpha]^{25}_D$ = −24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.87-5.73 (m, 1H), 5.09 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.02 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.98 (s, 1H), 3.93 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.55 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.09−2.84 (m, 2H), 2.34 (s, 3H), 1.67 (t, *J* = 2.5 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.2, 134.9, 129.0, 128.6, 116.9, 78.7, 76.0, 62.0, 61.4, 48.7, 25.0, 24.3, 21.1, 3.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{31}N_2O_2S$ [M+NH_4^+]: 351.2101; found: 351.2101.

((*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluorohex-4-yn-2-yl)propane-2-sulfonamide (5p). According to general procedure V, **5p** was obtained as a white solid (87 mg, 83% yield). mp 42−44 ºC; $[\alpha]^{25}_D$ = −26.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05−5.91 (m, 1H),

5.22−5.10 (m, 2H), 4.52−4.40 (m, 1H), 3.99 (qd, *J* = 16.7, 6.5 Hz, 1H), 2.78−2.66 (m, 2H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.44 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.64 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 124.7 (q, $^1J_{CF}$ = 285.8 Hz, C), 117.8, 80.1, 73.0, 63.0, 59.6 (q, $^2J_{CF}$ = 29.7 Hz, CH), 49.4, 24.7, 19.0, 3.5. HRMS (ESI): *m/z* calcd for $C_{13}H_{24}F_3N_2O_2S$ [M+NH_4^+]: 329.1505; found: 329.1504.

VI. General procedure for the RCEYM reaction to 6. The corresponding enyne (0.2 mmol) and 1,7-octadiene (0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane:Et_2O (5:1).

(*S*)-1-(*tert*-Butylsulfonyl)-4-vinyl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6a). According to general procedure VI, **6a** was obtained as a white solid (96 mg, 87% yield). mp 72–73 °C; $[\alpha]^{25}_D$ = +67.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.44 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.69 (s, 1H), 5.32–5.20 (m, 2H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.03 (dd, *J* = 19.3, 4.3 Hz, 1H), 3.50 (d, *J* = 19.2 Hz, 1H), 2.84 (bs, 2H), 2.31 (s, 3H), 1.42 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 137.4, 136.1, 133.9, 129.3, 127.6, 125.2, 112.3, 61.8, 54.1, 43.0, 27.2, 24.8, 21.1. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_2S$ [M+NH_4^+]: 337.1937; found: 337.1944.

(*S*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-vinyl-1,2,3,6-tetrahydropyridine (6b). According to general procedure VI, **6b** was obtained as a colorless oil (89 mg, 89% yield). $[\alpha]^{25}_D$ = +36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (bs, 1H), 5.36–5.22 (m, 2H), 5.12 (d, *J* = 10.7 Hz, 1H), 4.04 (dd, *J* = 19.5, 4.2 Hz, 1H), 3.50 (d, *J* = 19.3 Hz, 1H), 2.86 (bs, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.2, 133.8, 128.6, 127.7, 127.6, 125.2, 112.4, 61.8, 54.3, 43.0, 27.2, 24.8. HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_2O_2S$ [M+NH_4^+]: 323.1785; found: 323.1788.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6c). According to general procedure VI, **6c** as obtained as a colorless oil (79 mg, 83% yield).

$[\alpha]^{25}_D$ = +55.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.70 (bs, 1H), 5.37–5.18 (m, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 19.1, 4.5 Hz, 1H), 3.78 (s, 3H), 3.48 (dd, *J* = 19.2, 1.3 Hz, 1H), 2.82 (bs, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.2, 133.9, 131.2, 129.0, 125.2, 113.8, 112.4, 61.8, 55.4, 53.8, 42.9, 27.4, 24.8. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_3S$ $[M+NH_4^+]$: 353.1880; found: 353.1893.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(thiophen-3-yl)-4-vinyl-1,2,3,6-tetrahydropyridine (6d). According to general procedure VI, **6d** was obtained as a colorless oil (75 mg, 82% yield). $[\alpha]^{25}_D$ = +84.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.13 (m, 3H), 6.44 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (s, 1H), 5.29–5.23 (m, 2H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 19.1 Hz, 1H), 3.53 (d, *J* = 19.1 Hz, 1H), 2.81 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 138.1, 133.4, 127.9, 125.6, 124.9, 122.8, 112.2, 61.6, 51.1, 43.1, 28.3, 24.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{22}NO_2S_2$ $[M+H^+]$: 312.1086; found: 312.1083.

(*R*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-vinyl-1,2,3,6-tetrahydropyridine (6e). According to general procedure VI, **6e** was obtained as a colorless oil (66 mg, 65% yield). $[\alpha]^{25}_D$ = −17.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.65 (bs, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.08−3.87 (m, 2H), 3.73 (d, *J* = 19.0 Hz, 1H), 2.49 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.18 (d, *J* = 16.9 Hz, 1H), 1.60−1.40 (m, 3H), 1.31 (s, 9H), 1.25−1.23 (m, 7H), 0.83 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 132.9, 123.9, 111.7, 61.2, 52.3, 42.4, 31.9, 31.7, 29.2, 27.7, 26.7, 24.4, 22.6, 14.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{35}N_2O_2S$ $[M+NH_4^+]$: 331.2419; found: 331.2412.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-vinyl-1,2,3,6-tetrahydropyridine (6f). According to general procedure VI, **6f** was obtained as a colorless oil (72 mg, 72% yield). $[\alpha]^{25}_D$ = −13.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.75 (bs, *J* = 2.4 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.06 (bs, 2H), 3.28 (dd, *J* = 9.0, 6.2 Hz, 1H), 2.58 (ddd, *J* = 16.8, 6.1, 3.0 Hz, 1H), 2.37 (d, *J* = 16.8 Hz, 1H), 1.33 (s, 9H), 1.16–1.01 (m, 1H), 0.77–0.63 (m, 1H), 0.58–0.49 (m, 2H), 0.33–0.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd for $C_{14}H_{27}N_2O_2S$ $[M+NH_4^+]$: 287.1795; found: 287.1788.

***(S)*-1-(*tert*-Butylsulfonyl)-2-(trifluoromethyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6g).** According to general procedure VI, **6g** was obtained as a colorless oil (61 mg, 86% yield). $[\alpha]^{25}_{D}$ = −1.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.75 (s, 1H), 5.13 (dd, *J* = 23.4, 14.2 Hz, 2H), 4.67–4.57 (m, 1H), 4.27-4.21 (m, 1H), 3.91–3.84 (m, 1H), 2.71–2.50 (m, 2H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.08 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 131.3, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.5, 112.5, 62.4, 52.7 (q, *J* = 31.1 Hz, CH), 43.7, 24.4, 22.6. HRMS (ESI): *m/z* calcd for $C_{12}H_{22}F_3N_2O_2S$ [M+NH_4^+]: 315.1349; found: 315.1343.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(perfluoropropyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6h). According to general procedure VI, **6h** was obtained as a colorless oil (79 mg, 92% yield). $[\alpha]^{25}_{D}$ = +14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (s, 1H), 5.10 (dd, *J* = 22.0, 14.2 Hz, 2H), 4.80 (d, *J* = 22.8 Hz, 1H), 4.20 (d, *J* = 18.5 Hz, 1H), 3.88 (d, *J* = 18.5 Hz, 1H), 2.75–2.51 (m, 2H), 1.36 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -80.56 (t, *J* = 10.7 Hz, 3F), -114.37 – -115.52 (m, 1F), -119.15 – -120.15 (m, 1F), -124.81 – -127.66 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 131.7, 123.3, 120.1-104.9 (C_3F_7), 112.4, 62.4, 51.1 (dd, $^2J_{CF}$ = 23.2, 18.7 Hz, CH), 44.1, 24.3, 23.6. HRMS (ESI): *m/z* calcd for $C_{14}H_{22}F_7N_2O_2S$ [M+NH_4^+]: 415.1285; found: 415.1291.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-methoxyphenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6i). According to general procedure VI, **6i** was obtained as a colorless oil (41 mg, 53% yield). $[\alpha]^{25}_{D}$ = +22.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.30–7.19 (m, 3H), 7.10–7.07 (m, 2H), 6.80–6.77 (m, 2H), 5.52–5.50 (m, 1H), 5.23–5.21 (m, 2H), 5.07 (s, 1H), 3.97 (d, *J* = 18.5 Hz, 1H), 3.74 (s, 3H), 3.46 (d, *J* = 18.5 Hz, 1H), 3.01–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 149.4, 139.2, 135.1, 133.2, 129.8, 128.5, 127.5, 124.5, 113.5, 112.3, 61.7, 55.3, 54.6, 43.2, 29.8, 24.7. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ [M+NH_4^+]: 429.2206; found: 429.2208.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6j). According to general procedure VI, **6j** was obtained as a colorless oil (79 mg, 48% yield). $[\alpha]^{25}_{D}$ = +33.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.06 (m, 9H), 5.46–5.54 (m, 1H), 5.30–5.09 (m, 3H), 3.97 (d, *J* = 18.7 Hz, 1H), 3.45 (d, *J* = 18.7 Hz, 1H), 3.00–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 139.2, 139.1, 134.6, 133.5,

130.1, 128.6, 128.3, 127.6, 127.4, 125.0, 113.5, 61.8, 54.6, 43.2, 29.6, 24.7. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}ClN_2O_2S$ [M+NH_4^+]: 433.1711; found: 433.1708.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-(1-phenylvinyl)-1,2,3,6-tetrahydropyridine (6k). According to general procedure VI, **6k** was obtained as a colorless oil (38 mg, 55% yield). $[\alpha]^{25}_D$ = +2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5H), 5.64 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 4.04 (s, 2H), 3.30 (dd, *J* = 8.7, 6.2 Hz, 1H), 2.83–2.66 (m, 1H), 2.44 (d, *J* = 16.9 Hz, 1H), 1.35 (s, 9H), 1.24–1.12 (m, 1H), 0.77–0.65 (m, 1H), 0.63–0.53 (m, 2H), 0.37–0.26 (m, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 141.1, 134.9, 128.8, 128.2, 127.6, 123.9, 113.0, 61.4, 57.7, 43.6, 31.6, 24.7, 13.7, 5.0, 4.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{31}N_2O_2S$ [M+NH_4^+]: 363.2111; found: 363.2101.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-(thiophen-3-yl)-1,2,3,6-tetrahydropyridine (6l). According to general procedure VI, **6l** was obtained as a colorless oil (70 mg, 70% yield). $[\alpha]^{25}_D$ = +31.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3H), 7.20–7.14 (m, 4H), 5.54–5.51 (m, 1H), 5.35 (s, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 5.16 (s, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.55 (d, *J* = 18.6 Hz, 1H), 3.06–2.80 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 140.6, 139.2, 134.3, 130.1, 128.4, 127.7, 125.8, 124.9, 122.7, 113.5, 61.6, 51.6, 43.3, 30.7, 24.5. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 439.1275; found: 439.1278.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6m). According to general procedure VI, **6m** were obtained as a colorless oil (37 mg, 42% yield). $[\alpha]^{25}_D$ = +25.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 7.24–7.15 (m, 4H), 5.56–5.55 (m, 1H), 5.37 (s, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.19 (s, 1H), 4.03 (d, *J* = 19.0 Hz, 1H), 3.53 (d, *J* = 19.0 Hz, 1H), 3.08–2.88 (m, 2H), 2.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 140.9, 137.2, 136.1, 134.9, 129.2, 128.8, 128.1, 127.5, 127.4, 124.8, 113.0, 61.7, 54.4, 43.1, 29.6, 24.7, 21.1. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_2S$ [M+NH_4^+]: 391.1650; found: 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (6n). According to general procedure VI, **6n** was obtained as a colorless oil (44 mg, 47% yield). $[\alpha]^{25}_D$ = +33.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.30–7.16 (m, 5H), 5.58 (s, 1H), 5.14 (d, *J* = 29.0 Hz, 2H), 4.60–4.54 (m, 1H), 4.17-4.11 (m, 1H), 3.82–3.76 (m, 1H), 2.79–2.49 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.77 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 140.4, 132.8, 128.6, 128.2, 127.7, 125.4 (q, $^1J_{CF}$ = 285.2 Hz, C), 123.4, 113.3, 62.4, 52.9 (q, $^2J_{CF}$ = 31.1 Hz, CH), 43.9, 25.0, 24.5. HRMS (ESI): *m/z* calcd for $C_{18}H_{26}F_3N_2O_2S$ [M+NH_4^+]: 391.1650; found: 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6o). According to general procedure VI, **6o** was obtained as a colorless oil (150 mg, 60% yield) $[\alpha]^{25}_D$ = +33.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.77 (s, 1H), 5.24–5.22 (m, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 4.06 (d, *J* = 19.4 Hz, 1H), 3.54 (d, *J* = 19.4 Hz, 1H), 2.32 (s, 3H), 1.95 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 137.1, 136.2, 134.5, 129.1, 127.5, 120.8, 111.6, 61.6, 54.2, 43.0, 28.5, 24.7, 21.0, 20.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{31}N_2O_2S$ [M+NH_4^+]: 351.2101; found: 351.2093.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (6p). According to general procedure VI, **6p** was obtained as a colorless oil (73 mg, 65% yield). $[\alpha]^{25}_D$ = +12.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.00–4.99 (m, 2H), 4.62–4.57 (m, 1H), 4.26 (d, *J* = 18.6 Hz, 1H), 3.89 (d, *J* = 18.6 Hz, 1H), 2.80–2.56 (m, 2H), 1.91 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 132.1, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 119.5, 111.8, 62.3 (q, $^2J_{CF}$ = 30.6 Hz, CH), 43.9, 24.4, 23.9, 20.2. HRMS (ESI): *m/z* calcd for $C_{13}H_{24}F_3N_2O_2S$ [M+NH_4^+]: 329.1505; found: 329.1511.

VII. General procedure for the CEYM/RCM reaction to 7. The enyne (0.2 mmol) and the corresponding olefin (0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in hexane:ether (5:1).

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7a). According to general procedure VII, **7a** was obtained as a colorless oil (40 mg, 65% yield). $[\alpha]^{25}_D$ =

+116.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 7H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 5.71 (bs, 1H), 5.19 (bs, 1H), 3.99 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.47 (dd, *J* = 19.4, 1.6 Hz, 1H), 2.89 (bs, 2H), 2.22 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 137.6, 136.5, 134.1, 130.7, 129.7, 129.3, 128.1 (d, *J* = 13.7 Hz), 127.5, 127.0, 126.1, 62.2, 54.6, 43.6, 28.4, 25.2, 21.6, 1.6. HRMS (ESI): *m/z* calcd for $C_{24}H_{35}N_2O_2S$ $[M+NH_4^+]$: 415.2250; found: 415.2257.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7b). According to general procedure VII, **7b** was obtained as a colorless oil (32 mg, 59% yield). $[\alpha]^{25}_D$ = +128.9. (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.1, 1.7 Hz, 4H), 7.14 (dd, *J* = 11.1, 8.0 Hz, 4H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.61 (d, *J* = 16.3 Hz, 1H), 5.78 (bs, 1H), 5.29 (bs, 1H), 4.08 (dd, *J* = 19.4, 4.4 Hz, 1H), 3.56 (dd, *J* = 19.6, 2.3 Hz, 1H), 2.98 (bs, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 137.4, 136.1, 134.3, 133.8, 129.6, 129.4, 129.3, 127.6, 127.0, 126.4, 125.0, 61.8, 54.2, 43.2, 28.0, 24.8, 21.4, 21.2. HRMS (ESI): *m/z* calcd for $C_{25}H_{37}N_2O_2S$ $[M+NH_4^+]$: 429.2418; found: 429.2414.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-chlorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7c). According to general procedure VII, **7c** was obtained as a white solid (22 mg, 33% yield). mp 139–140 °C; $[\alpha]^{25}_D$ = +102.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m,6), 7.12 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.1, 4.4 Hz, 1H), 3.56 (d, *J* = 19.5 Hz, 1H), 2.96 (bs, 2H), 2.31 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.9, 135.6, 133.4, 133.2, 130.8, 129.2, 128.9, 127.6, 127.4, 126.2, 125.7, 61.7, 54.0, 43.1, 27.8, 24.7, 21.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}ClN_2O_2S$ $[M+NH_4^+]$: 449.1863; found: 449.1868.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-fluorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7d). According to general procedure VII, **7d** was obtained as a white solid (30 mg, 47% yield).mp 110–111 °C; $[\alpha]^{25}_D$ = +110.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 16.2 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 5.80 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.56 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.96 (bs, 2H), 2.32 (s, 3H), 1.43 (s, 9H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247.3 Hz), 137.4, 136.0, 133.6, 133.4 (d, *J* = 3.4 Hz), 130.1 (d, *J* = 2.2 Hz), 129.3, 128.1 (s, *J* = 7.9 Hz), 128.0, 127.6, 125.8 (d, *J* = 11.4 Hz), 115.8 (d, *J* = 21.7 Hz), 61.8, 54.1, 43.2, 28.0, 24.8, 21.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –14.14 (t, *J* = 9.0 Hz). HRMS (ESI): *m/z* calcd for $C_{24}H_{34}FN_2O_2S$ $[M+NH_4^+]$: 433.2172; found: 433.2163.

(*S,E*)-4-(2-Bromostyryl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7e). According to general procedure VII, **7e** was obtained as a white solid (17 mg, 23% yield). mp 226–228°C; $[\alpha]^{25}_D$ = +105.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.9, 1.3 Hz, 2H), 7.39–7.28 (m, 3H), 7.16–7.07 (m, 3H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 5.87 (bs, 1H), 5.30 (bs, 1H), 4.10 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.58 (dd, *J* = 19.6, 1.9 Hz, 1H), 3.03 (bs, 2H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 136.9, 136.0, 133.9, 133.3, 132.9, 129.4, 129.0, 127.7, 127.6, 126.8, 126.6, 125.8, 124.3, 61.9, 54.2, 43.3, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}BrN_2O_2S$ $[M+NH_4^+]$: 493.1354; found: 493.1362.

Ethyl (*S,E*)-5-(1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)pent-4-enoate (7f). According to general procedure VII, **7f** was obtained as a white solid (23 mg, 35% yield). mp 74–75 °C; $[\alpha]^{25}_D$ = +66.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.16 (d, *J* = 15.7 Hz, 1H), 5.80–5.67 (m, 1H), 5.57 (bs, 1H), 5.21 (bs, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.00 (dd, *J* = 19.0, 4.3 Hz, 1H), 3.48 (d, *J* = 19.6 Hz, 1H), 2.79 (bs, 2H), 2.53–2.39 (m, 4H), 2.31 (s, 3H), 1.41 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 137.3, 136.2, 133.3, 132.7, 129.2, 127.6, 126.8, 123.4, 61.7, 60.5, 54.1, 42.9, 34.2, 28.2, 28.0, 24.8, 21.2, 14.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{39}N_2O_4S$ $[M+NH_4^+]$: 439.2480; found: 439.2469

(*S,E*)-4-(5-Bromopent-1-en-1-yl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7g). According to general procedure VII, **7g** was obtained as a colorless oil (25 mg, 36% yield). $[\alpha]^{25}_D$ = +77.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 15.8 Hz, 1H), 5.76–5.62 (m, 1H), 5.58 (br, 1H), 5.22 (br, 1H), 4.01 (dd, *J* = 19.1, 4.3 Hz, 1H), 3.54–3.41 (m, 3H), 2.80 (br, 2H), 2.37–2.27 (m, 5H), 2.00 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 136.2, 133.3, 133.0, 129.3, 127.6, 126.8, 123.3, 61.8, 54.2, 42.9, 33.3, 32.4, 31.2, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{34}BrN_2O_4S$ $[M+NH_4^+]$: 457.1526; found: 457.1519.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-4-(oct-1-en-1-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7h). According to general procedure VII, **7h** was obtained as a colorless oil (20 mg, 32% yield). $[\alpha]^{25}_{D}$ = +77.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.12 (d, *J* = 15.7 Hz, 1H), 5.83–5.66 (m, 1H), 5.55 (bs, 1H), 5.21 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.9, 4.3 Hz, 1H), 3.48 (d, *J* = 18.6 Hz, 1H), 2.81 (bs, 2H), 2.31 (s, 3H), 2.22–2.08 (m, 2H), 1.41 (s, *J* = 9.1 Hz, 9H), 1.40–1.24 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.3, 133.6, 131.5, 129.5, 129.2, 127.6, 122.2, 61.7, 54.2, 42.9, 33.0, 31.9, 29.5, 29.1, 28.0, 24.8, 22.8, 21.2, 14.2. HRMS (ESI): *m/z* calcd for $C_{24}H_{41}N_2O_2S$ $[M+NH_4^+]$: 421.2883; found: 421.2883.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-2-(*p*-tolyl)-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7i). According to general procedure VII, **7i** was obtained as a colorless oil (45 mg, 33% yield); $[\alpha]^{25}_{D}$ = +53.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.82-5.71 (m, 1H), 5.45 (s, 1H), 5.20 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.8, 4.2 Hz, 1H), 3.48 (d, *J* = 18.8 Hz, 1H), 2.79 (s, 2H), 2.31 (s, 3H),, 1.60 (d, *J* = 8.1 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.1, 135.4, 132.0, 130.9, 129.4, 129.3, 127.7, 122.4, 63.5, 55.9, 44.7, 29.8, 26.5, 25.5, 22.9, 0.00. HRMS (ESI): *m/z* calcd for $C_{22}H_{39}N_2O_2SSi$ $[M+NH_4^+]$: 423.2158; found: 423.2163.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-styryl-1,2,3,6-tetrahydropyridine (7j). According to general procedure VII, **7j** was obtained as a white solid (43 mg, 68% yield). mp 129–131 °C; $[\alpha]^{25}_{D}$ = +134.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.25 (m, 10H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.65 (d, *J* = 16.3 Hz, 1H), 5.82 (bs, 1H), 5.33 (bs, 1H), 4.10 (dd, *J* = 19.5, 4.4 Hz, 1H), 3.57 (dd, *J* = 19.5, 2.2 Hz, 1H), 3.01 (bs, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.1, 133.6, 130.2, 128.8, 128.6, 127.8, 127.7, 127.7, 127.1, 126.5, 125.6, 61.8, 54.3, 43.3, 27.8, 24.8. HRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_2O_2S$ $[M+NH_4^+]$: 401.2098; found: 401.2101.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-phenyl-1,2,3,6-tetrahydropyridine (7k). According to general procedure VII, **7k** was obtained as a white solid (20 mg, 39% yield). mp 66–67 °C; $[\alpha]^{25}_{D}$ = +134.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.31–7.17 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 16.3 Hz, 1H), 6.54 (d, *J* = 16.3

Hz, 1H), 5.71 (bs, 1H), 5.24 (bs, 1H), 4.01 (dd, *J* = 19.3, 4.5 Hz, 1H), 3.48 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.92 (bs, 2H), 2.28 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.7, 134.3, 133.7, 129.6, 129.3, 128.6, 127.7, 127.1, 126.5, 125.0, 61.8, 54.4, 43.3, 27.8, 24.8, 21.4. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_2S$ [M+NH_4^+]: 413.2263; 413.2267.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7l). According to general procedure VII, **7l** was obtained as a white solid (40 mg, 32% yield). $[\alpha]^{25}_D$ = +57.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.33–7.28 (m, 3H), 6.00 (d, *J* = 15.7 Hz, 1H), 5.83–5.72 (m, 1H), 5.47 (d, *J* = 2.7 Hz, 1H), 5.24 (t, *J* = 3.7 Hz, 1H), 4.00 (dd, *J* = 18.9, 4.3 Hz, 1H), 3.48 (d, *J* = 18.9Hz, 1H), 2.82 (s, 2H), 1.60 (d, *J* = 8.2 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 135.4, 131.9, 130.3, 129.4, 129.3, 127.8, 122.4, 63.5, 56.1, 44.8, 29.7, 26.5, 25.5, 0.0. HRMS (ESI): *m/z* calcd for $C_{21}H_{37}N_2O_2SSi$ [M+NH_4^+]: 409.2340; found: 409.2357.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-styryl-1,2,3,6-tetrahydropyridine (7m). According to general procedure VII, **7m** was obtained as a colorless oil (24 mg, 60% yield). $[\alpha]^{25}_D$ = +116.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.27 (m, 7H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 16.2 Hz, 1H), 5.83 (bs, 1H), 5.28 (bs, 1H), 4.07 (dd, *J* = 19.5, 4.6 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, *J* = 19.4, 2.0 Hz, 1H), 2.97 (bs, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}NO_3S$ [M+H^+]: 428.2206; found: 428.2206.

(*R,E*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-styryl-1,2,3,6-tetrahydropyridine (7n). According to general procedure VII, **7n** was obtained as a colorless oil (20 mg, 49% yield). $[\alpha]^{25}_D$ = −3.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H), 6.81 (d, *J* = 16.2 Hz, 1H), 6.50 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 4.18–3.97 (m, 2H), 3.84 (d, *J* = 19.4 Hz, 1H), 2.67 (dd, *J* = 16.7, 3.0 Hz, 1H), 2.36 (d, *J* = 16.5 Hz, 1H), 1.68–1.51 (m, 3H), 1.37 (s, 9H), 1.28 (bs, 7H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 132.9, 130.9, 128.8, 127.6, 126.7, 126.5, 124.6, 61.4, 52.5, 42.8, 32.2, 31.9, 29.4, 28.6, 26.9, 24.6, 22.8, 14.2. HRMS (ESI): *m/z* calcd for $C_{23}H_{38}NO_2S$ [M+H^+]: 392.2544; found: 392.2461.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-styryl-1,2,3,6-tetrahydropyridine (7o). According to general procedure VII, **7o** was obtained as a yellowish oil (32 mg, 51% yield).

$[\alpha]^{25}_D$ = +4.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.18 (m, 5H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 5.88 (bs, 1H), 4.12 (bs, 2H), 3.33 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.73 (ddd, *J* = 16.5, 5.8, 2.7 Hz, 1H), 2.52 (d, *J* = 16.7 Hz, 1H), 1.35 (s, 9H), 1.22–1.03 (m, 1H), 0.78–0.65 (m, 1H), 0.64 – 0.49 (m, 2H), 0.40 – 0.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 133.4, 130.8, 128.8, 127.7, 127.0, 126.5, 124.7, 61.4, 57.5, 43.7, 29.9, 24.6, 13.7, 5.1, 4.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{33}N_2O_2S$ $[M+NH_4^+]$: 365.2104; found: 365.2101.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (7p). According to general procedure VII, **7p** were obtained as a colorless oil (23 mg, 60% yield). $[\alpha]^{25}_D$ = +35.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H), 6.72 (d, *J* = 16.3 Hz, 1H), 6.44 (d, *J* = 16.3 Hz, 1H), 5.81 (s, 1H), 4.62–4.57 (m, 1H), 4.26–4.19 (m, 1H), 3.90–3.84 (m, 1H), 2.79–2.58 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 131.1, 129.5, 128.7, 127.8, 127.3, 126.4, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.8, 62.4, 52.7 (q, $^2J_{CF}$ = 31.2 Hz, CH), 43.9, 24.4, 23.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{26}F_3N_2O_2S$ $[M+NH_4^+]$: 391.1662; found: 391.1658.

VIII. Standard procedure for the Diels–Alder reaction with PTAD. The corresponding diene (0.10 mmol) was dissolved in acetone (0.1 M) and cooled down to −40 ºC. PTAD (0.13 mmol) was then added and the mixture was stirred at the same temperature until the reaction was complete (followed by TLC analysis, typically 2−3 h). Next, the crude mixture was concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane:EtOAc).

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8a). According to general procedure VIII, **8a** was obtained from **6a** as a white solid (45 mg, 88% yield). mp 86–87 °C; $[\alpha]^{25}_D$ = +10.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.37 (m, 5H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.95 (bs, 1H), 5.13 (t, *J* = 8.2 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.48 (bs, 1H), 4.32 (ddd, *J* = 16.5, 6.5, 2.7 Hz, 1H), 4.24–4.08 (m, 2H), 3.02 (dd, *J* = 14.1, 7.9 Hz, 1H), 2.57–2.45 (m, 1H), 2.38 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 151.3, 138.6, 137.7, 131.3, 130.3, 129.7, 129.2, 128.2, 126.5, 125.7, 118.0, 62.0,

60.3, 56.0, 48.9, 42.4, 37.8, 24.6, 21.2. HRMS (ESI): *m/z* calcd for $C_{26}H_{34}N_5O_4S$ [M+NH_4^+]: 512.2331; found: 512.2326.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8b). According to general procedure VIII, **8b** was obtained from **6b** as a white solid (1.529 g, 97% yield). mp 97−99 ºC; $[\alpha]^{25}_D$ = +9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 10H), 5.95 (s, 1H), 5.16 (t, *J* =8.4 Hz, 1H), 4.68 (d, *J* = 15.1 Hz, 1H), 4.49–4.47 (m, 1H), 4.36–4.13 (m, 3H), 3.03 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.54–2.47 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 151.2, 141.6, 131.2, 130.1, 129.1, 128.9, 128.1, 127.8, 126.4, 125.9, 118.0, 61.6, 60.4, 55.9, 48.7, 42.2, 37.6, 24.4. HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_4O_4S$ [M+NH_4^+]: 498.2170; found: 498.2163.

(8*S*,10a*R*)-5-(3-Bromopropyl)-9-(*tert*-butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8c). According to general procedure VIII, **8c** was obtained from **7g** as a white solid (28 mg, 80% yield). mp 85−87 ºC; $[\alpha]^{25}_D$ = −67.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.34 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.95 (bs, 1H), 5.14 (t, *J* = 8.7 Hz, 1H), 4.82 (d, *J* = 15.4 Hz, 1H), 4.61 (bs, 1H), 4.36 (bs, 1H), 4.19 (dd, *J* = 15.5, 6.1 Hz, 1H), 3.53–3.41 (m, 2H), 2.95 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.43 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H), 2.22–1.97 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 150.1, 139.1, 137.7, 131.2, 130.2, 129.8, 129.2, 128.2, 126.4, 125.6, 122.4, 61.5, 60.2, 57.2, 51.7, 49.20, 37.9, 33.3, 31.6, 28.7, 24.6, 21.2. HRMS (ESI): *m/z* calcd for $C_{29}H_{39}BrN_5O_4S$ [M+NH_4^+]: 632.1899; found: 632.1901.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-(4-methoxyphenyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8d). According to general procedure VIII, **8d** was obtained from **6i** as a white solid (20 mg, 67% yield). mp 88–90 ºC; $[\alpha]^{25}_D$ = –8.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.44 (m, 4H), 7.40–7.27 (m, 8H), 7.00–6.98 (m, 2H), 5.20 (t, *J* = 8.6 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.57–4.55 (m, 1H), 4.39 (m, 2H), 4.13 (dd, *J* = 15.3, 6.4 Hz, 1H), 3.86 (s, 3H), 3.08 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.19–2.12 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 153.2, 151.1, 141.8, 131.2, 130.7, 129.6, 129.1, 129.0, 128.9, 128.1, 127.6, 125.9, 125.6, 124.5, 114.4, 61.5,

59.8, 56.3, 55.3, 48.4, 46.6, 34.5, 29.7, 24.4. HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_4O_5S$ [M+NH_4^+]: 604.2588; found: 604.2585.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8e). According to general procedure VIII, **8e** was obtained from **6o** as a white solid (48 mg, 87% yield). mp 112–114 ºC; $[\alpha]^{25}_D$ = –16.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9, 125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd for $C_{27}H_{32}N_4O_4S$ [M+NH_4^+]: 526.2483; found: 526.2479.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8i). According to general procedure VIII, **8i** was obtained from **6g** as a white solid (43 mg, 91% yield). mp 145–147 ºC; $[\alpha]^{25}_D$ = –7.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.33 (m, 5H), 4.87–4.73 (m, 1H), 4.42 (d, *J* =12.0 Hz, 2H), 4.11 (dd, *J* = 16.2, 7.5 Hz, 2H), 3.91 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.15 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.08 (dd, *J* = 14.5, 8.2 Hz, 1H), 1.89 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.26 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 150.7, 131.2, 129.1, 128.1, 127.3, 125.5, 125.3 (q, $^1J_{CF}$ = 282.7 Hz, C), 118.5, 62.9, 55.4 (q, $^2J_{CF}$ = 31.4 Hz, CH), 54.8, 49.2, 45.9, 24.6, 24.3, 15.9. HRMS (ESI): *m/z* calcd for $C_{21}H_{25}F_3N_4O_4S$ [M+NH_4^+]: 490.1730; found: 490.1728.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8j). According to general procedure VIII, **8j** was obtained from **6p** as a white solid (36 mg, 88% yield). mp 145−147 ºC; $[\alpha]^{25}_D$ = –16.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9,

125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd for $C_{27}H_{32}N_4O_4S$ [M+NH_4^+]: 504.1887; found: 504.1891.

IX. Standard procedure for the Diels–Alder reaction with tetracyanoethylene. The corresponding diene (0.10 mmol) and tetracyanoethylene (0.20 mmol) were added to a Schlenk tube, dissolved in toluene (0.1 M), and heated at 100 ºC until the reaction was complete (TLC analysis, typically 2–3 h). The crude mixture was then concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane:EtOAc).

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-phenyl-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8f). According to general procedure IX, **8f** was obtained from **6b** as a white solid (38 mg, 84% yield). mp 186–188 ºC; $[\alpha]^{25}_D$ = +31.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.69 (s, 1H), 4.86 (s, 1H), 4.27 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.76 (t, *J* = 10.9 Hz, 1H), 3.62 (s, 1H), 3.25–3.14 (m, 3H), 2.93 (d, *J* = 13.6 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 131.2, 128.6, 128.4, 128.1, 127.3, 117.2, 110.9, 110.2, 110.1, 108.5, 62.7, 48.4, 41.6, 40.8, 38.8, 37.2, 32.7, 24.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{23}N_5O_2S$ [M+NH_4^+]: 451.1576; found: 451.1569.

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-5-(4-chlorophenyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8g). According to general procedure IX, **8g** was obtained from **6l** as a colorwhite solid (31 mg, 92% yield). mp 137–139 ºC; $[\alpha]^{25}_D$ = +20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.19–7.18 (m, 1H), 7.10–7.05 (m, 2H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.02 (s, 1H), 4.26 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.85–3.78 (m, 1H), 3.70-3.67 (m, 1H), 3.40–3.20 (m, 2H), 2.87 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 135.4, 134.8, 129.9, 129.2, 128.9, 127.3, 126.6, 126.2, 123.4, 110.4, 110.0, 109.9, 108.3, 62.9, 54.9, 46.5, 41.5, 40.7, 38.8, 38.3, 34.4, 24.6. HRMS (ESI): *m/z* calcd for $C_{27}H_{24}ClN_5O_2S_2$ [M+NH_4^+]: 567.1060; found: 567.1056.

(3*S*,10a*R*)-2-(*tert*-Butylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8h). According to general procedure IX, **8h** was obtained from

6d as a colorless oil (46 mg, 86% yield); $[\alpha]^{25}_D$ = +32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2H), 7.14–7.12 (m, 1H), 5.72 (s, 1H), 4.89 (s, 1H), 4.22 (d, *J* = 7.4 Hz, 1H), 3.69-3.57 (m, 2H), 3.25–3.16 (m, 3H), 2.92 (d, *J* = 15.7 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 131.2, 127.4, 126.4, 124.8, 117.2, 110.9, 110.1, 110.0, 108.4, 62.7, 56.8, 41.6, 40.5, 38.6, 37.2, 32.6, 29.7, 24.3. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_5O_2S_2$ $[M+NH_4^+]$: 457.1475; found: 457.1475.

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoropropyl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8k). According to general procedure IX, **8k** was obtained from **6h** as a white solid (41 mg, 75% yield). mp 172–174 ºC; $[\alpha]^{25}_D$ = +40.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73–5.71 (m, 1H), 4.87 (d, *J* = 24.6 Hz, 1H), 3.91–3.76 (m, 2H), 3.52–3.50 (m, 1H), 3.17–3.13 (m, 2H), 3.02 (d, *J* = 18.3 Hz, 1H), 2.76 (d, *J* = 18.3 Hz, 1H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -80.70 (t, *J* = 10.7 Hz, 3F), -110.24 (d, *J* = 275.8 Hz, 1F), -119.07 (d, *J* = 275.8 Hz, 1F), -125.15 – -127.59 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.0, 119.4–108.9 (C_3F_7), 118.3, 110.8, 110.2, 110.1, 108.2, 64.1, 51.9, 44.6, 42.2, 39.6, 38.7, 32.7, 29.7, 24.7. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}F_7N_5O_2S$ $[M+NH_4^+]$: 543.1408; found: 543.1407.

X. General procedure for the hydrogenation reaction. Synthesis of (8*S*,10a*R*)-9-(*tert*-butylsulfonyl)-2,8-diphenyloctahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (9). A round-bottom flask was charged with Diels-Alder adduct **8b** (200 mg, 0.42 mmol), Pd (10% on activated carbon) (42 mg, 0.042 mmol), and a stirrer bar, and the mixture was suspended in anhydrous methanol (10 mL). The vessel was purged three times with hydrogen gas and fitted with a gas bag containing hydrogen. The mixture was stirred for 3 h before filtering through a short pad of Celite. The filtrate was then concentrated to dryness under reduced pressure. No further purification was necessary and compound **9** was isolated as a white solid (183 mg, 91% yield) (2:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (m), 5.25–5.20 (m), 4.95 (d, *J* = 18.1 Hz, 1H, *minor*), 4.20–4.09 (m, 1H, *minor*), 3.98 (dt, *J* = 12.6, 4.3 Hz, 1H, *major*), 3.89–3.83 (m, 1H, *minor*), 3.79–3.72 (m), 3.66–3.55 (m), 3.08–3.01 (m, 1H, *minor*), 2.65–2.39 (m), 2.21 (dt, *J* = 13.9, 3.7 Hz, 1H, *major*), 2.12–2.05 (m, 1H, *major*), 1.94–1.83 (m), 1.46 (s,

9H, *minor*), 1.42 (s, 9H, *major*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 149.9, 145.9, 138.5, 129.1, 129.0, 128.3, 127.2, 126.7, 125.7, 108.8, 62.2, 62.0, 54.6, 54.4, 43.6, 40.7, 38.1, 31.1, 30.5, 27.4, 26.9, 26.7, 24.6. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_4O_2$ [M+H$^+$]: 483.2061; found 483.2054.

XI. General procedure for the deprotection of *tert*-butylsulfonyl. Synthesis of (8*S*,10a*R*)-1,3-dioxo-2,8-diphenyl-2,3,5,7,8,9,10,10a-octahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazin-9-ium chloride (10). Diels-Alder adduct **8b** (100 mg, 0.21 mmol) was dissolved in anhydrous 1,4-dioxane (1.8 mL), and concentrated hydrochloric acid (12 M, 0.2 mL) was added. The reaction mixture was then stirred at 110 ºC for 3 h. After this time, the crude mixture was concentrated to dryness under reduced pressure, and the resulting solid was precipitated and washed with methanol and diethyl ether. No further purification was needed, affording **10** as an off-white solid (59 mg, 71% yield). mp 296−298 ºC; $[\alpha]^{25}_D$ = +40.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 10.14 (s, 1H), 7.74–7.72 (m, 2H), 7.56–7.40 (m, 8H), 6.05 (s, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.38 (s, 1H), 4.27–4.06 (m, 3H), 3.21–3.15 (m, 1H), 2.99–2.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 152.1, 136.7, 131.7, 129.6, 129.4, 129.3, 128.7, 128.3, 126.8, 117.9, 60.5, 50.9, 46.6, 42.9, 39.2, 36.8. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_4O_2$ [M+NH_4^+]: 361.1659; found: 361.1659.

XII. General procedure for the preparation of (2*S*,5*R*,*Z*)-4-allylidene-1-(*tert*-butylsulfonyl)-5-fluoro-2-phenylpiperidine (11). Metathesis product **7l** (39 mg, 0.1 mmol) was dissolved in acetonitrile (0.1 M) and Selectfluor (46 mg, 0.13 mmol) was added, and the reaction mixture was then stirred for 16 h at room temperature. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography using mixtures of *n*-hexane:EtOAc as the eluent, affording a colorless oil (20 mg, 58% yield). $[\alpha]^{25}_D$ = +78.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 6.65–6.53 (m, 1H), 6.15 (dd, *J* = 10.9, 5.4 Hz, 1H), 5.36–5.17 (m, 3H), 4.76 (d, *J* = 48.5 Hz, 1H), 4.13–4.03 (m, 1H), 3.45–3.26 (m, 2H), 3.06–2.98 (m, 1H), 1.52 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -167.32 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 130.6, 130.0, 128.6, 127.2,

121.9, 92.4, 90.1, 62.4, 57.7, 48.0, 28.1, 24.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{28}FN_2O_2S$ $[M+NH_4^+]$: 355.1850; found: 355.1848.

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[1] a) E. C. Taylor, J. E. Saxton, *The Chemistry of Heterocyclic Compounds*, vol. 47, Wiley-Interscience, New York, **1994**; b) T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles*, Wiley-VCH Verlag GmbH & Co, Weinheim, 2nd ed, **2003**; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem*. **2014**, *57*, 10257–10274.

[2] a) J. A. Joule, *Adv. Heterocyc. Chem*. **2016**, *119*, 81–106; b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem*. **2014**, *57*, 5845–5859; c) T. J. Ritchie, S. J. F. Macdonald, S. Peace, S. D. Pickett, C. N. Luscombe, *Med. Chem. Commun*. **2012**, *3*, 1062–1069; d) P. Cheng, N. Huang, Z.-Y. Jiang, Q. Zhang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang, Y.-B. Ma, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 2475–4278; e) C. de Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131–155.

[3] a) M. M. Nebe, T. Opatz, *Adv. Heterocycl. Chem*. **2017**, *122*, 191–244; b) *Pyridine and its Derivatives in Heterocycles in Natural Product Synthesis*, (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH: Weinheim, **2011**; c) K. M. K. Reddy, K. Peddanna, M. Varalakshmi, N. B. Reddy, G. Sravya, G. V. Zyryanov, C S. Reddy, *Phosphorus, Sulfur Relat. Elem*. **2019**, *194*, 812–819; d) L. Silva, L. L. Carrion, A. von Groll, S. S. Costa, E. Junqueira, D. F. Ramos, J. Cantos, V. R. Seus, I. Couto, L. D. Fernandes, H. G. Bonacorso, M. A. Martins, N.; Zanatta, M. Viveiros, K.S. Machado, P. E. A. da Silva, *Int J. Antimicrob. Agents* **2017**, *49*, 308–314; e) W. Wu, Z. Li, G. Yang, M. Teng, J. Qin, Z. Hu, L. Hou, L.

Shen, H. Dong, Y. Zhang, J. Li, S. Chen, J. Tian, J. Zhang, L. Ye, *Bioorg. Med. Chem. Lett*. **2017**, *27*, 2210–2215.

[4] a) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem*. **2019**, *17*, 3670–3708; b) E. Marcantoni, M. Petrini, *Adv. Synth. Catal*. **2016**, *358*, 3657–3682.

[5] B. Waldeck, *Chirality* **1993**, *5*, 350–355.

[6] a) A. Calcaterra, I. D'Acquaric, *J. Pharm. Biomed. Anal.* **2018**, *147*, 323–340; b) W. H. Brooks, W. C. Guida, K. G. Daniel, *Curr. Top. Med. Chem*. **2011**, *11*, 760–770; c) H. Caner, E. Groner, L. Levy, I. Agranat, *Drug Discov. Today* **2004**, *9*, 105–110.

[7] a) N. Kandepedu, I. Abrunhosa-Thomas, Y. Troin, *Org. Chem. Front*. **2017**, *4*, 1655–1704; b) B. V. S. Reddy, P. N. Nair, A. Anthony, C. Lally, R. Grée, *Eur. J. Org. Chem*. **2017**, 1805–1819; c) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res*. **2011**, *44*, 1156–1171; d) J. Cho, Y. M. Lee, D. Kim, S. Kim, *J. Org. Chem*. **2009**, *74*, 3900–3904.

[8] J. J. Michael, *Nat. Prod. Rep*. **2008**, *25*, 139–165.

[9] S.-B. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc*. **1992**, *114*, 3974–3975.

[10] a) O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev*. **2018**, *47*, 4510–4544; b) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251; c) T. M. Trunk, R. H. Grubbs, *Acc. Chem. Res*. **2001**, *34*, 18–29; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed*. **2000**, *39*, 3012–3043.

[11] a) G. C. Lloyd-Jones, R. G. Margue, J. G de Vries, *Angew. Chem.* **2005**, *117*, 7608–7613; *Angew. Chem. Int. Ed*. **2005**, *44*, 7442–7447; b) C.-J. Wu, R. J. Madhushaw, R.-S. Liu, *J. Org. Chem*. **2003**, *68*, 7889–7892; c) K. Tonogaki, M. Mori, *Tetrahedron Lett*. **2002**, *43*, 2235–2238; d) A. Kinoshita, N. Sakakibara, M. Mori, *J. Am. Chem. Soc*. **1997**, *119*, 12388–12389.

[12] a) A. Sirvent, M. J. García-Muñoz, M. Yus, F. Foubelo, *Eur. J. Org. Chem*. **2020**, 113–126; b) M. Mori, *Adv. Synth. Catal*. **2007**, *349*, 121–135; c) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev*. **2007**, *36*, 55–66; d) M. D. McReynolds, J. M. Dougherty, P. R. Hanson, *Chem. Rev*. **2004**, *104*, 2239–2258.

[13] N. Kaur, *Catal. Lett*. **2019**, *149*, 1513–1559.

[14] a) D. N. Prada Gori, C. Permingeat Squizatto, P. G. Cornier, C. M. L. Delpiccolo, *J. Org. Chem*. **2018**, *83*, 12798−12805; b) S. Arimitsu, G. B. Hammond, *Beilstein J. Org. Chem*. **2010**, *6*, doi:10.3762/bjoc.6.48; c) J. M. Kim, K. Y. Lee, S. Lee, J. N. Kim, *Tetrahedron Lett*. **2004**, *45*, 2805–2808; d) F. Royer, C. Vilain, L. Elkaïm, L. Grimaud, *Org. Lett*. **2003**, *5*, 2007–2009.

[15] a) M. R. Becker, R. B. Watson, C. S. Schindler, *Chem. Soc. Rev*. **2018**, *47*, 7867–7881; b) S. Fustero, A. Simón-Fuentes, P. Barrio, G. Haufe, *Chem. Rev*. **2015**, *115*, 871–930; c) S. T. Diver, J. R. Griffiths in *Olefin Metathesis: Theory And Practice*, (Ed.: K. Grela), John Willey & Sons, Inc., Hoboken, NJ, **2014**, pp; 153–185; d) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev*. **2010**, *110*, 1746–1787; e) A. Deiters, S. F. Martin, *Chem. Rev*. **2004**, *104*, 2199–2238; f) S. T. Diver, A. J. Giessert, *Chem. Rev*. **2004**, *104*, 1317–1382.

[16] a) A. Letort, D.-L. Long, J. Prunet, *J. Org. Chem*. **2016**, *81*, 1231–1233; b) C. Ma, A. Letort, R. Aouzal, A. Wilkes, G. Maiti, L. J. Farrugia, J. Ricard, J. Prunet, *Chem. Eur. J*. **2016**, *22*, 6891–6899; c) J. Miró, M. Sánchez-Roselló, A. Sanz, F. Rabasa, C. del Pozo, S. Fustero, *Beilstein J. Org. Chem*. **2015**, *11*, 1486–1493; d) S. Mukherjee, D. Lee, *Org. Lett*. **2009**, *11*, 2916–2919.

[17] a) S. Kotha, M. Meshram, A. Tiwari, *Chem. Soc. Rev*. **2009**, *38*, 2065–2092; b) K. C. Shital, B. Titas, N. Kaushik, *Chem. Lett*. **2006**, *35*, 376–377; c) Y.-K. Yang, J.-H. Choi, J. Tae, *J. Org. Chem*. **2005**, *70*, 6995–6998; d) B. G. Kim, M. L. Snapper, *J. Am. Chem. Soc*. **2006**, *128*, 52–53; e) M. Eckert, F. Monnier, G. T. Shchetnikov, I. D. Titanyuk, S. N. Osipov, L. Toupet, S. Dérien, P. H. Dixneuf, *Org. Lett.* **2005**, *7*, 3741–3743.

[18] a) R. A. Bauer, C. M. DiBlasi, D. S. Tan, *Org. Lett*. **2010**, *12*, 2084–2087; b) K. P. Kaliappan, *Lett. Org. Chem*. **2005**, *2*, 678–686.

[19] a) A. Llobat, D. M. Sedgwick, A. Cabré, A.; R. Román, N. Mateu, J. Escorihuela, M. Medio-Simón, V. A. Soloshonok, J. Han, A. Riera, S. Fustero, *Adv. Synth. Catal*. **2020**, *362*, 1378–1384; b) A. Llobat, R. Román, N. Mateu, D. M. Sedgwick, P. Barrio, M. Medio-Simón, S. Fustero, *Org. Lett*. **2019**, *21*, 7294−7297.

[20] a) F. Ferreira, C. Botuha, F. Chemla, A. Pérez-Luna, *Chem. Soc. Rev*. **2009**, *38*, 1162–1186; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res*. **2002**, *35*, 984–995; c) D.

A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc*. **1998**, *120*, 8011–8019.

[21] For reviews, see: a) H. Meia, J. Han, S. Fustero, R. Román, R. Ruzziconi, V. A. Soloshonok, *J. Fluorine Chem*. **2018**, *216*, 57–70; b) M. A. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev*. **2010**, *110*, 3600–3740; c) F. Ferreira, C. Botuha, F. Chemla, A. Pérez-Luna, *Chem. Soc. Rev*. **2009**, *38*, 1162–1186; d) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, X.-W. Sun, *Acc. Chem. Res*. **2008**, *41*, 831–840; e) H. Mei, C. Xie, J. Han, V. A. Soloshonok *Eur. J. Org. Chem*. **2016**, 5917–5932; f) C. Xie, L. Wu, H. Mei, V. A. Soloshonok, J. Han, Y. Pan, *Org. Biomol. Chem*. **2014**, *12*, 7836–7843; g) C. Xie, H. Mei, L. Wu, V. A. Soloshonok, J. Han, Y. Pan, *RSC Adv*. **2014**, *4*, 4763–4768; h) H. Mei, C. Xie, L. Wu, V. A. Soloshonok, J. Han, Y. Pan, *Org. Biomol. Chem*. **2013**, *11*, 8018–8021.

[22] L. Cui, C. Li, L. Zhang, *Angew. Chem.* **2010**, *122*, 9364–9367; *Angew. Chem. Int. Ed*. **2010**. *49*, 9178–9181.

[23] S. Fustero, P. Bello, J. Miró, A. Simón, C. del Pozo, *Chem. Eur. J*. **2012**, *18*, 10991–10997.

[24] a) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M.Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J*. **2019**, *25*, 11797–11819; b) Y. Zhou, J.Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev*. **2016**, *116*, 422–518; c) J. Dinges, C. Lamberth in *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, Wiley-VCH, Weinheim, **2012**.

[25] a) F. Núñez-Zarur, X. Solans-Monfort, L. Rodríguez-Santiago, M. Sodupe, *ACS Catal.* **2013**, *3*, 206−218; b) T. Kitamura, Y. Sato, M. Mori, *Adv. Synth. Catal*. **2002**, *344*, 678–693.

[26] G. K. Zieliński, K. Grela, *Chem. Eur. J.* **2016**, *22*, 9440–9454.

[27] M. Serra, E. G. Peviani, E. Bernardi, C. Lino, *J. Org. Chem*. **2017**, *82*, 11091–11101.

[28] S. Park, M. Kim, D. Lee, *J. Am. Chem. Soc*. **2005**, *127*, 9410−9415.

[29] CCDC 1972570 (for **8g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[30] a) S. Thibaudeau, V. Gouverneur, *Org. Lett*. **2003**, *5*, 4891−4893; b) S. Gille, A. Ferry, T. Billard, B. R. Langlois, *J. Org. Chem*. **2003**, *68*, 8932−8935.

[31] H. Mei, J. Han, K. D. Klika, K. Izawa, T. Sato, N. A. Meanwell, V. A. Soloshonok, *Eur. J. Med. Chem*. **2020**, *186*, 111826.

Supporting Information

The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles

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I. General methods. Reactions were carried out under nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: tetrahydrofuran (THF) and toluene were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). The reactions were monitored by thin layer chromatography (TLC) using 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate ($KMnO_4$) stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer (Bruker 300 MHz DPX). Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents ($CHCl_3$: δ 7.26 ppm for proton and δ 77.0 ppm for carbon). Coupling constants (*J*) are reported in Hertz (Hz). The notation s, d, dd, ddd, t, q, m, and bs in NMR signals stands for singlet, doublet, doublet of doublets, doublet of dd, triplet, quartet, multiplet and broad singlet, respectively. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points were measured on a Büchi B−540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P−1020 polarimeter at 25 °C.

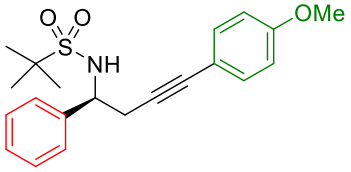
II. General procedure for the propargylation reaction to sulfinamides 3. A 1 M solution of propargylmagnesium bromide in THF was prepared by stirring propargyl bromide (14 mmol) and activated Mg (28 mmol) in anhydrous THF (1 M, 14 mL) at 50 °C for 2 h. This freshly prepared solution was then added (1.5 equiv, 13.5 mmol) to a solution of corresponding imine (9.0 mmol) in CH_2Cl_2 (0.1 M, 90 mL) at −48 °C. After stirring during 18 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine (3 × 10 mL), dried with anhydrous $MgSO_4$, and the solvent evaporated. The residue was purified by flash column chromatography to yield the corresponding sulfinamide **3**. Sulfinamides **3a-f**[1] and **3g-h**[2] were prepared according to previously published procedures.

III. General procedure for oxidation reaction to sulfonamides. To a solution of corresponding sulfinamide **3** (12.3 mmol) in CH_2Cl_2 (120 mL) at 0 °C, *m*-CPBA (14.8 mmol) was added and the mixture was stirred at room temperature for 2 h. After this time, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The

combined organic layers were washed with brine (3×10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography affording sulfonamides **4**. Sulfonamides **4a-f**[1] and **4g-h**[2] were prepared according to previously published procedures.

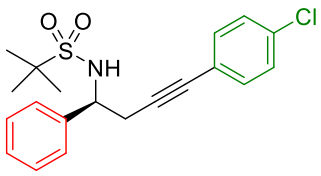
IV. General procedure for Sonogashira reaction. CuI (8 mmol%) and $Pd(PPh_3)_2Cl_2$ (4 mmol%) were added to *i*-Pr_2NH (0.06 M) and the mixture was stirred at room temperature for 10 min. The solution was then heated to 50 °C, and a solution of sulfonamide **4** (0.3 mmol) in *i*-Pr_2NH (0.06 M) was added slowly for 1 h (slow addition pump), and the resulting mixture was stirred at 50 °C for a further 2 h. The reaction was quenched with a saturated solution of aqueous NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude mixture was purified by column chromatography (*n*-hexane:EtOAc). Compound **4n** was prepared according to previously published procedures.[2]

(*S*)-*N*-(4-(4-Methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4i).



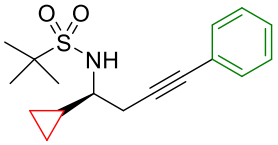
According to general procedure IV, **4i** was obtained as a white solid (68 mg, 49% yield). mp 102−104 ºC; $[\alpha]^{25}_D$ = −39.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 7H), 6.75–6.70 (m, 2H), 4.80–4.68 (m, 2H), 3.71 (s, 3H), 3.00–2.77 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 141.2, 133.1, 128.6, 127.8, 126.4, 115.2, 113.9, 84.2, 83.2, 60.1, 56.9, 55.3, 30.2, 24.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_3S$ $[M+NH_4^+]$: 389.1893; found: 389.1891.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4j).



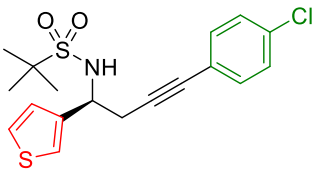
According to general procedure IV, **4j** was obtained as a white solid 68 mg, (78% yield). mp 138–140 ºC; $[\alpha]^{25}_{D}$ = −37.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (m, 9H), 4.77–4.64 (m, 2H), 3.01−2.91 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 134.1, 132.9, 128.7, 128.6, 127.9, 126.3, 121.5, 85.9, 83.2, 60.1, 56.8, 30.3, 24.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{26}ClN_2O_2S$ $[M+NH_4^+]$: 393.1398; found: 393.1396.

(*S*)-*N*-(1-Cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4k).



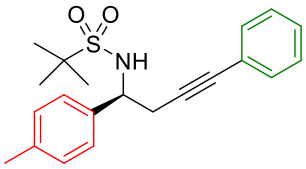
According to general procedure IV, **4k** was obtained as a yellowish oil 49 mg, (62% yield). $[\alpha]^{25}_{D}$ = +33.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.34–7.27 (m, 3H), 3.06–2.94 (m, 1H), 2.89 (dd, *J* = 16.7, 5.2 Hz, 1H), 2.77 (dd, *J* = 16.7, 4.3 Hz, 1H), 1.42 (s, 1H), 1.27–1.13 (m, 1H), 0.70–0.55 (m, 3H), 0.44–0.33 (m, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 128.4, 128.2, 123.4, 85.7, 83.7, 60.0, 57.9, 27.6, 24.4, 17.0, 4.6, 4.5. HRMS (ESI): *m/z* calcd for $C_{20}H_{26}ClN_2O_2S$ $[M+NH_4^+]$: 323.1787; found: 323.1789.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4l).



According to general procedure IV, **4l** was obtained as a white solid (61 mg, 44% yield). mp 153–154 ºC; $[\alpha]^{25}_{D}$ = −32.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.16 (m, 6H), 7.06 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.84–4.77 (m, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 3.04−2.85 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 134.2, 132.9, 128.6, 126.6, 126.0, 121.8, 121.5, 86.0, 83.2, 60.2, 53.1, 29.4, 24.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{24}ClN_2O_2S_2$ $[M+NH_4^+]$: 399.0962; found: 399.0958.

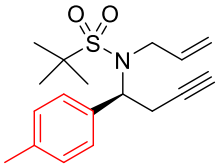
(*S*)-2-Methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (4m).



According to general procedure IV, **4m** was obtained as a white solid (63 mg, 70% yield). mp 133–135 ºC; $[\alpha]^{25}_{D}$ = −47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.29–7.27 (m, 5H), 7.20–7.17 (m, 2H), 4.97-4.94 (m, 1H), 4.81–4.74 (m, 1H), 3.08-2.87 (m, 2H), 2.36 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.5, 1331.7, 129.3, 128.3, 128.1, 126.3, 123.2, 85.1, 84.1, 60.1, 56.8, 30.3, 24.2, 21.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_2S$ [M+NH_4^+]: 373.1944; found: 373.1951.

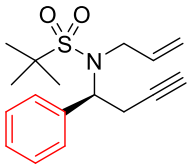
V. General procedure for allylation reaction. To a suspension of NaH (60%, 6.8 mmol) in dry DMF (40 mL), the corresponding sulfonamide (4.5 mmol) was added dropwise at 0 °C. After stirring at this temperature for 20 min, allyl bromide (1.1 g, 9.1 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH_4Cl aq. and extracted with diethyl ether. The organic layer was then dried over anhydrous Na_2SO_4, concentrated under vacuum and the crude reaction mixture was then purified by flash column chromatography to yield **5**. Compounds **5g-h**[1] and **5n**[2] were prepared according to previously published procedures.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5a).



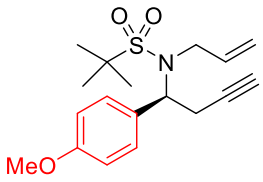
According to general procedure V, **5a** was obtained as a white solid (63 mg, 94% yield). mp 93–94 ºC. $[\alpha]^{25}_{D}$ = −28.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.92–5.73 (m, 1H), 5.15 (dd, *J* = 10.1, 5.3 Hz, 1H), 5.07 (bs, 1H), 5.03 (ddd, *J* = 7.5, 2.7, 1.3 Hz, 1H), 4.02–3.82 (m, 1H), 3.52 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.16 (ddd, *J* = 16.8, 10.2, 2.6 Hz, 1H), 2.97 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 2.36 (s, 3H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.2, 134.2, 129.3, 128.9, 117.4, 81.2, 71.4, 62.2, 61.4, 49.0, 25.2, 24.3, 21.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_2S$ [M+NH_4^+]: 337.1943; found: 337.1944.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-phenylbut-3-yn-1-yl) propane-2-sulfonamide (5b). According



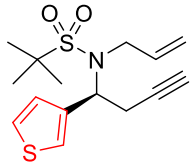
to general procedure V, **5b** was obtained as a white solid (102 g, 91% yield). mp 134–136 ºC. $[\alpha]^{25}_{D}$ = –43.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.28 (m, 5H), 5.97–5.70 (m, 1H), 5.18 (dd, *J* = 10.0, 5.4 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.95 (ddd, *J* = 16.5, 3.1, 1.9 Hz, 1H), 3.54 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.18 (ddd, *J* = 16.8, 10.0, 2.6 Hz, 1H), 2.99 (ddd, *J* = 16.8, 5.4, 2.7 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 137.0, 128.9, 128.6, 128.3, 117.5, 81.0, 71.6, 62.2, 61.5, 49.1, 25.2, 24.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_2O_2S$ $[M+NH_4^+]$: 306.1549; found: 306.1522.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5c). According



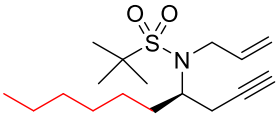
to general procedure V, **5c** was obtained as a colorless oil (67 mg, 35% yield). $[\alpha]^{25}_{D}$ = –20.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.89–5.70 (m, 1H), 5.13 (dd, *J* = 10.2, 5.3 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.02–3.86 (m, 1H), 3.82 (s, 3H), 3.51 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.14 (ddd, *J* = 16.8, 10.3, 2.6 Hz, 1H), 2.96 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 137.2, 130.2, 129.2, 117.3, 113.9, 81.1, 71.4, 62.2, 61.0, 55.4, 48.9, 25.2, 24.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_3S$ $[M+NH_4^+]$: 353.1891; found: 353.1893.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(tiophen-2-yl)but-3-yn-1-yl)propane-2-sulfonamide (5d).

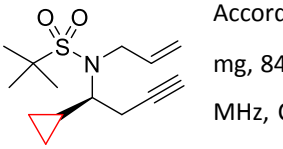


According to general procedure V, **5d** was obtained as a white solid (122 mg, 74% yield). mp 118–120 ºC. $[\alpha]^{25}_{D}$ = –22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16–7.14 (dt, *J* = 3.6, 0.9 Hz, 1H), 7.00–6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.93–5.80 (m, 1H), 5.33–5.27 (dd, *J* = 9.3, 6.0 Hz, 1H), 5.08–5.05 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.02 (s, 1H), 3.99–3.92 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.63–3.55 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.18–2.97 (m, 2H), 2.05–2.03 (t, *J* = 2.7 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 137.0, 127.5, 126.6, 126.0, 117.4 , 80.6, 71.7, 62.3, 57.9, 48.7, 26.0, 24.9. HRMS (ESI): *m/z* calcd for $C_{15}H_{25}N_2O_2S_2$: 329.1350 $[M+NH_4^+]$; found: 329.1352.

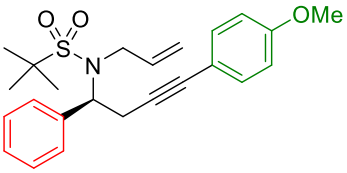
(*R*)-*N*-Allyl-*N*-(dec-1-yn-4-yl)-2-methylpropane-2-sulfonamide (5e). According to general procedure V, **5e** was obtained as a colorless oil (110 mg, 50% yield). $[\alpha]^{25}_{D}$ = +4.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09–5.87 (m, 1H), 5.18 (ddd, *J* = 17.2, 2.7, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.1, 1.2 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 2H), 3.84–3.78 (m, 1H), 2.60–2.49 (m, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.82–1.63 (m, 2H), 1.41 (s, 9H), 1.28 (dd, *J* = 9.7, 6.5 Hz, 8H), 0.87 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 117.1, 81. 8, 71.2, 62.2, 59.2, 48.6, 31.8, 29.3, 27.2, 25.0, 22.7, 14.2. HRMS (ESI): *m/z* calcd for $C_{17}H_{36}N_2O_2S$ [M+NH_4^+]: 331.2414; found: 331.2414.

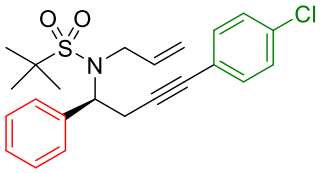


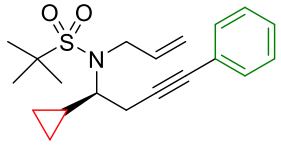
(*S*)-*N*-Allyl-*N*-(1-cyclopropylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5f). According to general procedure V, **5f** was obtained as a white solid (97 mg, 84% yield). mp 62–63 ºC. $[\alpha]^{25}_{D}$ = –2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11–5.95 (m, 1H), 5.21 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.11 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.16 (dt, *J* = 9.5, 7.1 Hz, 1H), 2.72 (dt, *J* = 5.3, 2.3 Hz, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.40 (s, 9H), 1.22–1.01 (m, 1H), 0.79 – 0.58 (m, 2H), 0.59–0.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137. 9, 117.0, 81.7, 71.1, 63. 6, 62.2, 49.5, 25.1, 15.9, 7.2, 4.2. HRMS (ESI): *m/z* calcd for $C_{14}H_{27}N_2O_2S$ [M+NH_4^+]: 287.1776; found: 287.1788.

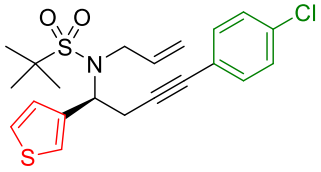


(*S*)-*N*-Allyl-*N*-(4-(4-methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5i). According to general procedure V, **5i** was obtained as a colorless oil (43 mg, 53% yield). $[\alpha]^{25}_{D}$ = –36.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.21 (m, 5H), 7.21–7.18 (m, 2H), 6.78–6.75 (m, 2H), 5.92–5.82 (m, 1H), 5.25 (dd, *J* = 9.0, 6.4 Hz, 1H), 5.10–5.07 (m, 1H), 5.04–5.03 (m, 1H), 4.03 (dd, *J* = 16.7, 5.2 Hz, 1H), 3.65 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.33 (dd, *J* = 16.9, 9.1 Hz, 1H), 3.19 (dd, *J* = 16.9, 6.3 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.9, 137.0, 132.9, 128.8, 128.4, 128.0, 117.2, 115.5, 113.8, 85.1, 83.4, 62.1, 61.6, 55.3, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ [M+H^+]: 412.1941; found: 412.1931.



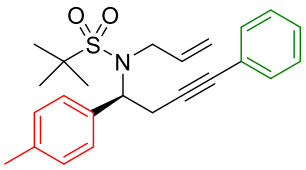
(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5j).  According to general procedure V, **5j** was obtained as a colorless oil (44 mg, 48% yield). $[\alpha]^{25}_{D}$ = −38.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.30 (m, 5H), 7.22–7.14 (m, 4H), 5.95–5.81 (m, 1H), 5.26–5.10 (m, 1H), 5.18 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.10–5.04 (m, 2H), 4.05–3.98 (m, 1H), 3.62 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.4 Hz, 1H), 3.21 (dd, *J* = 16.9, 6.1 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.0, 133.8, 132.7, 128.8, 128.5, 128.1, 121.9, 117.3, 87.8, 82.5, 62.1, 61.6, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}ClN_2O_2S$ [M+NH_4^+]: 433.1711; found: 433.1706.

(*S*)-*N*-Allyl-*N*-(1-cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5k).  According to general procedure V, **5i** was obtained as a colourless oil (68 mg, 93% yield). $[\alpha]^{25}_{D}$ = −9.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.33–7.27 (m, 3H), 6.16–6.01 (m, 1H), 5.23 (dq, *J* = 17.3, 1.4 Hz, 1H), 5.12 (dq, *J* = 10.1, 1.3 Hz, 1H), 4.12 (t, *J* = 6.5 Hz, 2H), 3.25 (dt, *J* = 9.4, 7.2 Hz, 1H), 2.94 (dd, *J* = 7.2, 1.9 Hz, 2H), 1.41 (s, 9H), 1.24–1.10 (m, 1H), 0.81–0.66 (m, 2H), 0.59–0.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 131.5, 128.4, 128.0, 123.64 116.9, 87.4, 83.0, 63.8, 62.1, 49.5, 25.0, 16.2, 7.1, 4.4. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ [M+H^+]: 363.2110; found: 363.2101.

(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5l).  According to general procedure V, **5l** was obtained as a colorless oil (61 mg, 70% yield). $[\alpha]^{25}_{D}$ = −30.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.16 (m, 5H), 5.83–5.72 (m, 1H), 5.18 (dd, *J* = 8.4, 6.8 Hz, 1H), 5.01–4.98 (m, 1H), 4.95 (s, 1H), 3.94 (dd, *J* = 16.4, 5.5 Hz, 1H), 3.56 (dd, *J* = 16.4, 7.4 Hz, 1H), 3.32 (dd, *J* = 16.9, 8.7 Hz, 1H), 3.2 (dd, *J* = 16.9, 6.5 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 136.9, 134.0, 132.8, 128.6, 128.1, 125.8, 124.2, 121.8,

117.2, 87.7, 82.5, 62.1, 57.8, 49.0, 25.9, 25.0. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 439.1275; found: 439.1273.

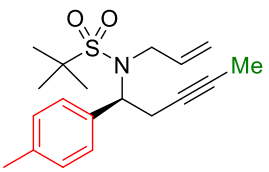
(*S*)-*N*-Allyl-2-methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (5m).



According to general procedure V, **5m** was obtained as a colorless oil (147 mg, 99% yield). $[\alpha]^{25}_D$ = –21.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.30–7.19 (m, 7H), 5.98-5.84 (m, 1H), 5.25 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.11 (dd, *J* = 6.4, 1.2 Hz, 1H), 5.06 (s, 1H), 4.03 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.64 (dd, *J* = 16.5, 7.7 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.2 Hz, 1H), 3.22 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.37 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 137.2, 131.5, 129.1, 128.7, 128.2, 127.8, 123.5, 117.2, 86.9, 83.4, 62.1, 61.4, 48.9, 25.1, 22.7, 21.1. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 413.2259; found: 413.2257.

VI. General procedure for the methylation reaction. The corresponding enyne (0.17 mmol) was dissolved in THF (0.4 mL) at –78 ºC under an argon atmosphere. HMDSLi (1 M in toluene, 0.34 mmol) was then added dropwise to the reaction mixture. After 1 h, MeI (0.84 mmol) was added to the reaction mixture and the temperature was increased to –40 ºC. After 12 h the solvent was then removed and the reaction mixture was purified by flash column chromatography in *n*-hexane:EtOAc (10:1).

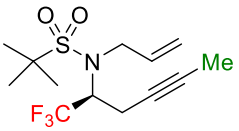
(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl)pent-3-yn-1-yl)propane-2-sulfonamide (5o). According



to general procedure VI, **5o** was obtained as a colorless oil (194 mg, 93% yield). $[\alpha]^{25}_D$ = –24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.87-5.73 (m, 1H), 5.09 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.02 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.98 (s, 1H), 3.93 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.55 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.09–2.84 (m, 2H), 2.34 (s, 3H), 1.67 (t, *J* = 2.5 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 137.5, 137.2, 134.9, 129.0, 128.6, 116.9, 78.7, 76.0, 62.0, 61.4, 48.7, 25.0, 24.3, 21.1, 3.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{31}N_2O_2S$ [M+NH_4^+]: 351.2101; found: 351.2101.

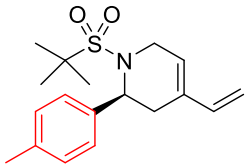
((*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluorohex-4-yn-2-yl)propane-2-sulfonamide (5p).



According to general procedure VI, **5p** was obtained as a white solid (87 mg, 83% yield). mp 42–44 ºC; $[\alpha]^{25}_D$ = –26.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05–5.91 (m, 1H), 5.22–5.10 (m, 2H), 4.52–4.40 (m, 1H), 3.99 (qd, *J* = 16.7, 6.5 Hz, 1H), 2.78–2.66 (m, 2H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.44 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –68.64 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 124.7 (q, $^1J_{CF}$ = 285.8 Hz, C), 117.8, 80.1, 73.0, 63.0, 59.6 (q, $^2J_{CF}$ = 29.7 Hz, CH), 49.4, 24.7, 19.0, 3.5. HRMS (ESI): *m/z* calcd for $C_{13}H_{24}F_3N_2O_2S$ [M+NH_4^+]: 329.1505; found: 329.1504.

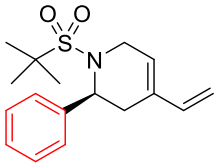
VII. General procedure for the RCEYM reaction to 6. The corresponding enyne (0.2 mmol) and 1,7-octadiene (88 mg, 0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane:Et_2O (5:1).

(*S*)-1-(*tert*-Butylsulfonyl)-4-vinyl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6a). According to general procedure VII, **6a** was obtained as a white solid (96 mg, 87% yield). mp 72–73 °C; $[\alpha]^{25}_D$ = +67.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.44 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.69 (s, 1H), 5.32–5.20 (m, 2H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.03 (dd, *J* = 19.3, 4.3 Hz, 1H), 3.50 (d, *J* = 19.2 Hz, 1H), 2.84 (bs, 2H), 2.31 (s, 3H), 1.42 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 137.4, 136.1, 133.9,

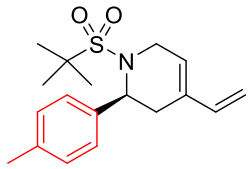


129.3, 127.6, 125.2, 112.3, 61.8, 54.1, 43.0, 27.2, 24.8, 21.1. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_2S$ [M+NH_4^+]: 337.1937; found: 337.1944.

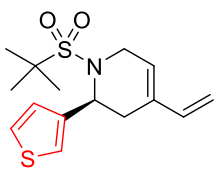
(*S*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-vinyl-1,2,3,6-tetrahydropyridine (6b). According to general procedure VII, **6b** was obtained as a colorless oil (89 mg, 89% yield). $[\alpha]^{25}_D$ = +36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (bs, 1H), 5.36–5.22 (m, 2H), 5.12 (d, *J* = 10.7 Hz, 1H), 4.04 (dd, *J* = 19.5, 4.2 Hz, 1H), 3.50 (d, *J* = 19.3 Hz, 1H), 2.86 (bs, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.2, 133.8, 128.6, 127.7, 127.6, 125.2, 112.4, 61.8, 54.3, 43.0, 27.2, 24.8. HRMS (ESI): *m/z* calcd for $C_{17}H_{27}N_2O_2S$ [M+NH_4^+]: 323.1785; found: 323.1788.



(*S*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6c). According to general procedure VII, **6c** as obtained as a colorless oil (79 mg, 83% yield). $[\alpha]^{25}_D$ = +55.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.70 (bs, 1H), 5.37–5.18 (m, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 19.1, 4.5 Hz, 1H), 3.78 (s, 3H), 3.48 (dd, *J* = 19.2, 1.3 Hz, 1H), 2.82 (bs, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.2, 133.9, 131.2, 129.0, 125.2, 113.8, 112.4, 61.8, 55.4, 53.8, 42.9, 27.4, 24.8. HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_3S$ [M+NH_4^+]: 353.1880; found: 353.1893.



(*S*)-1-(*tert*-Butylsulfonyl)-2-(thiophen-3-yl)-4-vinyl-1,2,3,6-tetrahydropyridine (6d). According to general procedure VII, **6d** was obtained as a colorless oil (75 mg, 82% yield). $[\alpha]^{25}_D$ = +84.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.13 (m, 3H), 6.44 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (s, 1H), 5.29–5.23 (m, 2H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 19.1 Hz, 1H), 3.53 (d, *J* = 19.1 Hz, 1H), 2.81 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 138.1, 133.4, 127.9, 125.6, 124.9, 122.8, 112.2, 61.6, 51.1, 43.1, 28.3, 24.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{22}NO_2S_2$ [M+H^+]: 312.1086; found: 312.1083.

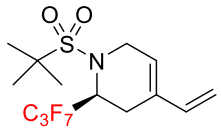


(*R*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-vinyl-1,2,3,6-tetrahydropyridine (6e). According to general procedure VII, **6e** was obtained as a colorless oil (66 mg, 65% yield). $[\alpha]^{25}_{D}$ = –17.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.65 (bs, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.08–3.87 (m, 2H), 3.73 (d, *J* = 19.0 Hz, 1H), 2.49 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.18 (d, *J* = 16.9 Hz, 1H), 1.60–1.40 (m, 3H), 1.31 (s, 9H), 1.25–1.23 (m, 7H), 0.83 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 132.9, 123.9, 111.7, 61.2, 52.3, 42.4, 31.9, 31.7, 29.2, 27.7, 26.7, 24.4, 22.6, 14.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{35}N_2O_2S$ $[M+NH_4^+]$: 331.2419; found: 331.2412.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-vinyl-1,2,3,6-tetrahydropyridine (6f). According to general procedure VII, **6f** was obtained as a colorless oil (72 mg, 72% yield). $[\alpha]^{25}_{D}$ = –13.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.75 (bs, *J* = 2.4 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.06 (bs, 2H), 3.28 (dd, *J* = 9.0, 6.2 Hz, 1H), 2.58 (ddd, *J* = 16.8, 6.1, 3.0 Hz, 1H), 2.37 (d, *J* = 16.8 Hz, 1H), 1.33 (s, 9H), 1.16–1.01 (m, 1H), 0.77–0.63 (m, 1H), 0.58–0.49 (m, 2H), 0.33–0.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd for $C_{14}H_{27}N_2O_2S$ $[M+NH_4^+]$: 287.1795; found: 287.1788.

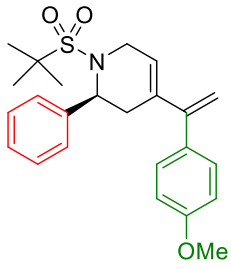
***(S)*-1-(*tert*-Butylsulfonyl)-2-(trifluoromethyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6g).** According to general procedure VII, **6g** was obtained as a colorless oil (61 mg, 86% yield). $[\alpha]^{25}_{D}$ = –1.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.75 (s, 1H), 5.13 (dd, *J* = 23.4, 14.2 Hz, 2H), 4.67–4.57 (m, 1H), 4.27-4.21 (m, 1H), 3.91–3.84 (m, 1H), 2.71–2.50 (m, 2H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.08 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 131.3, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.5, 112.5, 62.4, 52.7 (q, *J* = 31.1 Hz, CH), 43.7, 24.4, 22.6. HRMS (ESI): *m/z* calcd for $C_{12}H_{22}F_3N_2O_2S$ $[M+NH_4^+]$: 315.1349; found: 315.1343.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(perfluoropropyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6h).



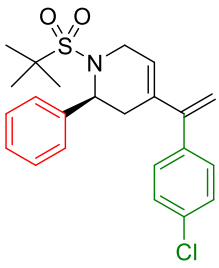
According to general procedure VII, **6h** was obtained as a colorless oil (79 mg, 92% yield). $[\alpha]^{25}_{D}$ = +14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (s, 1H), 5.10 (dd, *J* = 22.0, 14.2 Hz, 2H), 4.80 (d, *J* = 22.8 Hz, 1H), 4.20 (d, *J* = 18.5 Hz, 1H), 3.88 (d, *J* = 18.5 Hz, 1H), 2.75–2.51 (m, 2H), 1.36 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -80.56 (t, *J* = 10.7 Hz, 3F), -114.37 – -115.52 (m, 1F), -119.15 – -120.15 (m, 1F), -124.81 – -127.66 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 131.7, 123.3, 120.1-104.9 (C_3F_7), 112.4, 62.4, 51.1 (dd, $^2J_{CF}$ = 23.2, 18.7 Hz, CH), 44.1, 24.3, 23.6. HRMS (ESI): *m/z* calcd for $C_{14}H_{22}F_7N_2O_2S$ $[M+NH_4^+]$: 415.1285; found: 415.1291.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-methoxyphenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6i).



According to general procedure VII, **6i** was obtained as a colorless oil (41 mg, 53% yield). $[\alpha]^{25}_{D}$ = +22.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.30–7.19 (m, 3H), 7.10–7.07 (m, 2H), 6.80–6.77 (m, 2H), 5.52–5.50 (m, 1H), 5.23–5.21 (m, 2H), 5.07 (s, 1H), 3.97 (d, *J* = 18.5 Hz, 1H), 3.74 (s, 3H), 3.46 (d, *J* = 18.5 Hz, 1H), 3.01–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 149.4, 139.2, 135.1, 133.2, 129.8, 128.5, 127.5, 124.5, 113.5, 112.3, 61.7, 55.3, 54.6, 43.2, 29.8, 24.7. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_3S$ $[M+NH_4^+]$: 429.2206; found: 429.2208.

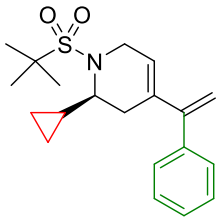
(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6j).



According to general procedure VII, **6j** was obtained as a colorless oil (79 mg, 48% yield). $[\alpha]^{25}_{D}$ = +33.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.06 (m, 9H), 5.46–5.54 (m, 1H), 5.30–5.09 (m, 3H), 3.97 (d, *J* = 18.7 Hz, 1H), 3.45 (d, *J* = 18.7 Hz, 1H), 3.00–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 139.2, 139.1, 134.6, 133.5, 130.1, 128.6, 128.3, 127.6, 127.4, 125.0, 113.5,

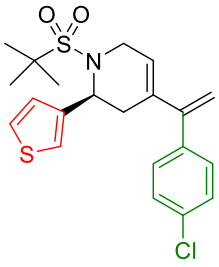
61.8, 54.6, 43.2, 29.6, 24.7. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}ClN_2O_2S$ [M+NH_4^+]: 433.1711; found: 433.1708.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-(1-phenylvinyl)-1,2,3,6-tetrahydropyridine (6k).



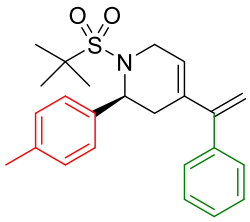
According to general procedure VII, **6k** was obtained as a colorless oil (38 mg, 55% yield). $[\alpha]^{25}_D$ = +2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5H), 5.64 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 4.04 (s, 2H), 3.30 (dd, *J* = 8.7, 6.2 Hz, 1H), 2.83–2.66 (m, 1H), 2.44 (d, *J* = 16.9 Hz, 1H), 1.35 (s, 9H), 1.24–1.12 (m, 1H), 0.77–0.65 (m, 1H), 0.63–0.53 (m, 2H), 0.37–0.26 (m, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 141.1, 134.9, 128.8, 128.2, 127.6, 123.9, 113.0, 61.4, 57.7, 43.6, 31.6, 24.7, 13.7, 5.0, 4.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{31}N_2O_2S$ [M+NH_4^+]: 363.2111; found: 363.2101.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-(thiophen-3-yl)-1,2,3,6-



tetrahydropyridine (6l). According to general procedure VII, **6l** was obtained as a colorless oil (70 mg, 70% yield). $[\alpha]^{25}_D$ = +31.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3H), 7.20–7.14 (m, 4H), 5.54–5.51 (m, 1H), 5.35 (s, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 5.16 (s, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.55 (d, *J* = 18.6 Hz, 1H), 3.06–2.80 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 140.6, 139.2, 134.3, 130.1, 128.4, 127.7, 125.8, 124.9, 122.7, 113.5, 61.6, 51.6, 43.3, 30.7, 24.5. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}ClN_2O_2S_2$ [M+NH_4^+]: 439.1275; found: 439.1278.

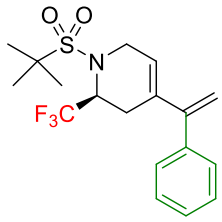
(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6m).



According to general procedure VII, **6m** were obtained as a colorless oil (37 mg, 42% yield). $[\alpha]^{25}_D$ = +25.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 7.24–7.15 (m, 4H), 5.56–5.55 (m, 1H), 5.37 (s, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.19 (s, 1H), 4.03 (d, *J* = 19.0 Hz, 1H), 3.53 (d, *J* = 19.0 Hz, 1H), 3.08–2.88 (m, 2H), 2.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 140.9, 137.2, 136.1,

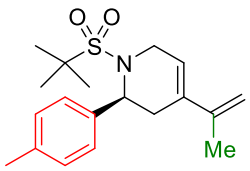
134.9, 129.2, 128.8, 128.1, 127.5, 127.4, 124.8, 113.0, 61.7, 54.4, 43.1, 29.6, 24.7, 21.1. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_2S$ [M+NH_4^+]: 391.1650; found: 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(trifluoromethyl)-1,2,3,6-



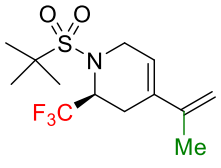
tetrahydropyridine (6n). According to general procedure VII, **6n** was obtained as a colorless oil (44 mg, 47% yield). $[\alpha]^{25}_D$ = +33.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 5.58 (s, 1H), 5.14 (d, *J* = 29.0 Hz, 2H), 4.60–4.54 (m, 1H), 4.17-4.11 (m, 1H), 3.82–3.76 (m, 1H), 2.79–2.49 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.77 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 140.4, 132.8, 128.6, 128.2, 127.7, 125.4 (q, $^1J_{CF}$ = 285.2 Hz, C), 123.4, 113.3, 62.4, 52.9 (q, $^2J_{CF}$ = 31.1 Hz, CH), 43.9, 25.0, 24.5. HRMS (ESI): *m/z* calcd for $C_{18}H_{26}F_3N_2O_2S$ [M+NH_4^+]: 391.1650; found: 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6o).



According to general procedure VII, **6o** was obtained as a colorless oil (150 mg, 60% yield) $[\alpha]^{25}_D$ = +33.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.77 (s, 1H), 5.24–5.22 (m, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 4.06 (d, *J* = 19.4 Hz, 1H), 3.54 (d, *J* = 19.4 Hz, 1H), 2.32 (s, 3H), 1.95 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 137.1, 136.2, 134.5, 129.1, 127.5, 120.8, 111.6, 61.6, 54.2, 43.0, 28.5, 24.7, 21.0, 20.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{31}N_2O_2S$ [M+NH_4^+]: 351.2101; found: 351.2093.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(trifluoromethyl)-1,2,3,6-

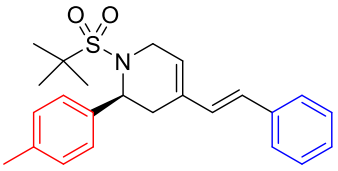


tetrahydropyridine (6p). According to general procedure VII, **6p** was obtained as a colorless oil (73 mg, 65% yield). $[\alpha]^{25}_D$ = +12.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.00–4.99 (m, 2H), 4.62–4.57 (m, 1H), 4.26 (d, *J* = 18.6 Hz, 1H), 3.89 (d, *J* = 18.6 Hz, 1H), 2.80–2.56 (m, 2H), 1.91 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 132.1, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 119.5, 111.8,

62.3 (q, $^{2}J_{CF}$ = 30.6 Hz, CH), 43.9, 24.4, 23.9, 20.2. HRMS (ESI): *m/z* calcd for $C_{13}H_{24}F_3N_2O_2S$ [M+NH_4^+]: 329.1505; found: 329.1511.

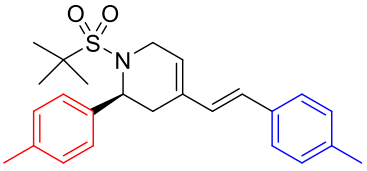
VIII. General procedure for the CEYM/RCM reaction to 7. The enyne (0.2 mmol) and the corresponding olefin (0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in hexane:ether (5:1).

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7a). According



to general procedure VIII, **7a** was obtained as a colorless oil (40 mg, 65% yield). $[\alpha]^{25}_D$ = +116.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 7H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 5.71 (bs, 1H), 5.19 (bs, 1H), 3.99 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.47 (dd, *J* = 19.4, 1.6 Hz, 1H), 2.89 (bs, 2H), 2.22 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 137.6, 136.5, 134.1, 130.7, 129.7, 129.3, 128.1 (d, *J* = 13.7 Hz), 127.5, 127.0, 126.1, 62.2, 54.6, 43.6, 28.4, 25.2, 21.6, 1.6. HRMS (ESI): *m/z* calcd for $C_{24}H_{35}N_2O_2S$ [M+NH_4^+]: 415.2250; found: 415.2257.

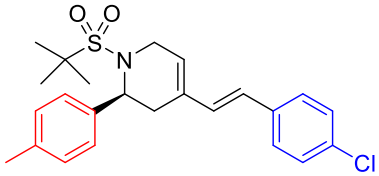
(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7b).



According to general procedure VIII, **7b** was obtained as a colorless oil (32 mg, 59% yield). $[\alpha]^{25}_D$ = +128.9. (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.1, 1.7 Hz, 4H), 7.14 (dd, *J* = 11.1, 8.0 Hz, 4H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.61 (d, *J* = 16.3 Hz, 1H), 5.78 (bs, 1H), 5.29 (bs, 1H), 4.08 (dd, *J* = 19.4, 4.4 Hz, 1H), 3.56 (dd, *J* = 19.6, 2.3 Hz, 1H), 2.98 (bs, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.44 (s, 9H);

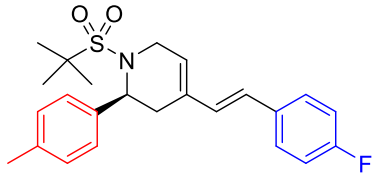
^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 137.4, 136.1, 134.3, 133.8, 129.6, 129.4, 129.3, 127.6, 127.0, 126.4, 125.0, 61.8, 54.2, 43.2, 28.0, 24.8, 21.4, 21.2. HRMS (ESI): *m/z* calcd for $C_{25}H_{37}N_2O_2S$ [M+NH_4^+]: 429.2418; found: 429.2414.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-chlorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7c).



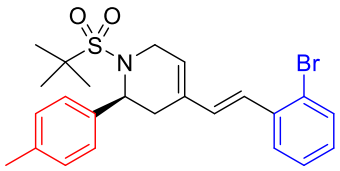
According to general procedure VIII, **7c** was obtained as a white solid (22 mg, 33% yield). mp 139–140 °C; $[\alpha]^{25}_D$ = +102.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m,6), 7.12 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.1, 4.4 Hz, 1H), 3.56 (d, *J* = 19.5 Hz, 1H), 2.96 (bs, 2H), 2.31 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.9, 135.6, 133.4, 133.2, 130.8, 129.2, 128.9, 127.6, 127.4, 126.2, 125.7, 61.7, 54.0, 43.1, 27.8, 24.7, 21.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}ClN_2O_2S$ [M+NH_4^+]: 449.1863; found: 449.1868.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-fluorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7d).



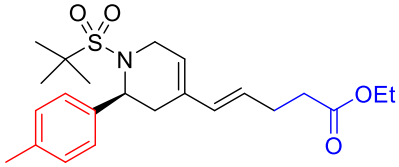
According to general procedure VIII, **7d** was obtained as a white solid (30 mg, 47% yield).mp 110–111 °C; $[\alpha]^{25}_D$ = +110.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 16.2 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 5.80 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.56 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.96 (bs, 2H), 2.32 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247.3 Hz), 137.4, 136.0, 133.6, 133.4 (d, *J* = 3.4 Hz), 130.1 (d, *J* = 2.2 Hz), 129.3, 128.1 (s, *J* = 7.9 Hz), 128.0, 127.6, 125.8 (d, *J* = 11.4 Hz), 115.8 (d, *J* = 21.7 Hz), 61.8, 54.1, 43.2, 28.0, 24.8, 21.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –14.14 (t, *J* = 9.0 Hz). HRMS (ESI): *m/z* calcd for $C_{24}H_{34}FN_2O_2S$ [M+NH_4^+]: 433.2172; found: 433.2163.

(*S,E*)-4-(2-Bromostyryl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7e).



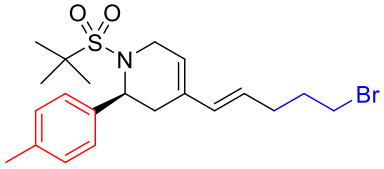
According to general procedure VIII, **7e** was obtained as a white solid (17 mg, 23% yield). mp 226–228°C; $[\alpha]^{25}_{D}$ = +105.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.9, 1.3 Hz, 2H), 7.39–7.28 (m, 3H), 7.16–7.07 (m, 3H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 5.87 (bs, 1H), 5.30 (bs, 1H), 4.10 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.58 (dd, *J* = 19.6, 1.9 Hz, 1H), 3.03 (bs, 2H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 136.9, 136.0, 133.9, 133.3, 132.9, 129.4, 129.0, 127.7, 127.6, 126.8, 126.6, 125.8, 124.3, 61.9, 54.2, 43.3, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}BrN_2O_2S$ [M+NH_4^+]: 493.1354; found: 493.1362.

Ethyl-(*S,E*)-5-(1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)pent-4-enoate (7f).



According to general procedure VIII, **7f** was obtained as a white solid (23 mg, 35% yield). mp 74–75 °C; $[\alpha]^{25}_{D}$ = +66.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.16 (d, *J* = 15.7 Hz, 1H), 5.80–5.67 (m, 1H), 5.57 (bs, 1H), 5.21 (bs, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.00 (dd, *J* = 19.0, 4.3 Hz, 1H), 3.48 (d, *J* = 19.6 Hz, 1H), 2.79 (bs, 2H), 2.53–2.39 (m, 4H), 2.31 (s, 3H), 1.41 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 137.3, 136.2, 133.3, 132.7, 129.2, 127.6, 126.8, 123.4, 61.7, 60.5, 54.1, 42.9, 34.2, 28.2, 28.0, 24.8, 21.2, 14.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{39}N_2O_4S$ [M+NH_4^+]: 439.2480; found: 439.2469.

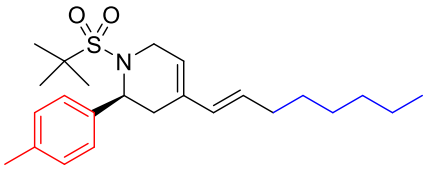
(*S,E*)-4-(5-Bromopent-1-en-1-yl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7g).



According to general procedure VIII, **7g** was obtained as a colorless oil (25 mg, 36% yield). $[\alpha]^{25}_{D}$ = +77.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 15.8 Hz, 1H), 5.76–5.62 (m, 1H), 5.58 (br, 1H), 5.22 (br, 1H), 4.01 (dd, *J* = 19.1, 4.3 Hz, 1H), 3.54–3.41 (m, 3H), 2.80 (br, 2H), 2.37–2.27 (m, 5H), 2.00 (m, 2H),

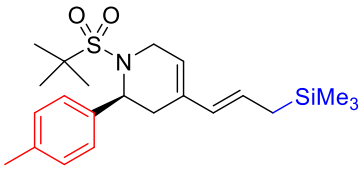
1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 136.2, 133.3, 133.0, 129.3, 127.6, 126.8, 123.3, 61.8, 54.2, 42.9, 33.3, 32.4, 31.2, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{34}BrN_2O_4S$ [M+NH_4^+]: 457.1526; found: 457.1519.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-4-(oct-1-en-1-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7h).



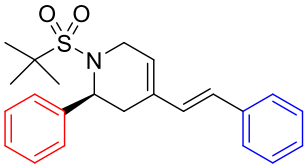
According to general procedure VIII, **7h** was obtained as a colorless oil (20 mg, 32% yield). $[\alpha]^{25}_D$ = +77.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.12 (d, *J* = 15.7 Hz, 1H), 5.83–5.66 (m, 1H), 5.55 (bs, 1H), 5.21 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.9, 4.3 Hz, 1H), 3.48 (d, *J* = 18.6 Hz, 1H), 2.81 (bs, 2H), 2.31 (s, 3H), 2.22–2.08 (m, 2H), 1.41 (s, *J* = 9.1 Hz, 9H), 1.40–1.24 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.3, 133.6, 131.5, 129.5, 129.2, 127.6, 122.2, 61.7, 54.2, 42.9, 33.0, 31.9, 29.5, 29.1, 28.0, 24.8, 22.8, 21.2, 14.2. HRMS (ESI): *m/z* calcd for $C_{24}H_{41}N_2O_2S$ [M+NH_4^+]: 421.2883; found: 421.2883.

(*S*,*E*)-1-(*tert*-Butylsulfonyl)-2-(*p*-tolyl)-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7i).



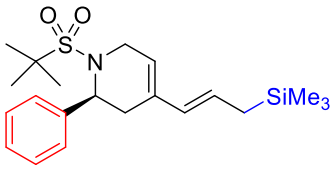
According to general procedure VIII, **7i** was obtained as a colorless oil (45 mg, 33% yield); $[\alpha]^{25}_D$ = +53.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.82-5.71 (m, 1H), 5.45 (s, 1H), 5.20 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.8, 4.2 Hz, 1H), 3.48 (d, *J* = 18.8 Hz, 1H), 2.79 (s, 2H), 2.31 (s, 3H),, 1.60 (d, *J* = 8.1 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.1, 135.4, 132.0, 130.9, 129.4, 129.3, 127.7, 122.4, 63.5, 55.9, 44.7, 29.8, 26.5, 25.5, 22.9, 0.00. HRMS (ESI): *m/z* calcd for $C_{22}H_{39}N_2O_2SSi$ [M+NH_4^+]: 423.2158; found: 423.2163.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-styryl-1,2,3,6-tetrahydropyridine (7j). According to general procedure VIII, **7j** was obtained as a white solid (43 mg, 68% yield). mp 129–131 °C; $[\alpha]^{25}_{D}$ = +134.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.25 (m, 10H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.65 (d, *J* = 16.3 Hz, 1H), 5.82 (bs, 1H), 5.33 (bs, 1H), 4.10 (dd, *J* = 19.5, 4.4 Hz, 1H), 3.57 (dd, *J* = 19.5, 2.2 Hz, 1H), 3.01 (bs, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.1, 133.6, 130.2, 128.8, 128.6, 127.8, 127.7, 127.7, 127.1, 126.5, 125.6, 61.8, 54.3, 43.3, 27.8, 24.8. HRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_2O_2S$ $[M+NH_4^+]$: 401.2098; found: 401.2101.



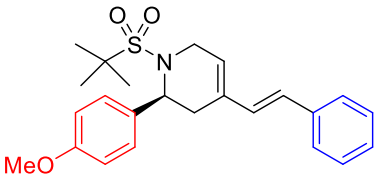
(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-phenyl-1,2,3,6-tetrahydropyridine (7k). According to general procedure VIII, **7k** was obtained as a white solid (20 mg, 39% yield). mp 66–67 °C; $[\alpha]^{25}_{D}$ = +134.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.31–7.17 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 16.3 Hz, 1H), 6.54 (d, *J* = 16.3 Hz, 1H), 5.71 (bs, 1H), 5.24 (bs, 1H), 4.01 (dd, *J* = 19.3, 4.5 Hz, 1H), 3.48 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.92 (bs, 2H), 2.28 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.7, 134.3, 133.7, 129.6, 129.3, 128.6, 127.7, 127.1, 126.5, 125.0, 61.8, 54.4, 43.3, 27.8, 24.8, 21.4. HRMS (ESI): *m/z* calcd for $C_{24}H_{33}N_2O_2S$ $[M+NH_4^+]$: 413.2263; 413.2267.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7l). According to general procedure VIII, **7l** was obtained as a white solid (40 mg, 32% yield). $[\alpha]^{25}_{D}$ = +57.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.33–7.28 (m, 3H), 6.00 (d, *J* = 15.7 Hz, 1H), 5.83–5.72 (m, 1H), 5.47 (d, *J* = 2.7 Hz, 1H), 5.24 (t, *J* = 3.7 Hz, 1H), 4.00 (dd, *J* = 18.9,



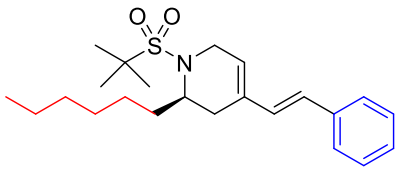
4.3 Hz, 1H), 3.48 (d, *J* = 18.9Hz, 1H), 2.82 (s, 2H), 1.60 (d, *J* = 8.2 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 135.4, 131.9, 130.3, 129.4, 129.3, 127.8, 122.4, 63.5, 56.1, 44.8, 29.7, 26.5, 25.5, 0.0. HRMS (ESI): *m/z* calcd for $C_{21}H_{37}N_2O_2SSi$ [M+NH_4^+]: 409.2340; found: 409.2357.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-styryl-1,2,3,6-tetrahydropyridine

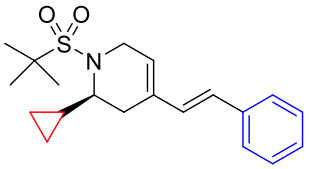


(7m). According to general procedure VIII, **7m** was obtained as a colorless oil (24 mg, 60% yield). $[\alpha]^{25}_D$ = +116.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.27 (m, 7H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 16.2 Hz, 1H), 5.83 (bs, 1H), 5.28 (bs, 1H), 4.07 (dd, *J* = 19.5, 4.6 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, *J* = 19.4, 2.0 Hz, 1H), 2.97 (bs, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd for $C_{24}H_{34}NO_3S$ [M+H^+]: 428.2206; found: 428.2206.

(*R,E*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-styryl-1,2,3,6-tetrahydropyridine (7n). According to general procedure VIII, **7n** was obtained as a colorless oil (20 mg, 49% yield). $[\alpha]^{25}_D$ = –3.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H), 6.81 (d, *J* = 16.2 Hz, 1H), 6.50 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 4.18–3.97 (m, 2H), 3.84 (d, *J* = 19.4 Hz, 1H), 2.67 (dd, *J* = 16.7, 3.0 Hz, 1H), 2.36 (d, *J* = 16.5 Hz, 1H), 1.68–1.51 (m, 3H), 1.37 (s, 9H), 1.28 (bs, 7H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 132.9, 130.9, 128.8, 127.6, 126.7, 126.5, 124.6, 61.4, 52.5, 42.8, 32.2, 31.9, 29.4, 28.6, 26.9, 24.6, 22.8, 14.2. HRMS (ESI): *m/z* calcd for $C_{23}H_{38}NO_2S$ [M+H^+]: 392.2544; found: 392.2461.

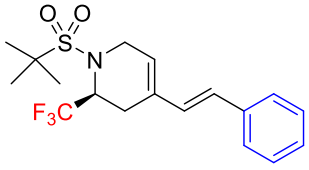


(*S*,*E*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-styryl-1,2,3,6-tetrahydropyridine (7o).



According to general procedure VIII, **7o** was obtained as a yellowish oil (32 mg, 51% yield). $[\alpha]^{25}_{D}$ = +4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.18 (m, 5H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 5.88 (bs, 1H), 4.12 (bs, 2H), 3.33 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.73 (ddd, *J* = 16.5, 5.8, 2.7 Hz, 1H), 2.52 (d, *J* = 16.7 Hz, 1H), 1.35 (s, 9H), 1.22–1.03 (m, 1H), 0.78–0.65 (m, 1H), 0.64 – 0.49 (m, 2H), 0.40 – 0.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 133.4, 130.8, 128.8, 127.7, 127.0, 126.5, 124.7, 61.4, 57.5, 43.7, 29.9, 24.6, 13.7, 5.1, 4.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{33}N_2O_2S$ [M+NH_4^+]: 365.2104; found: 365.2101.

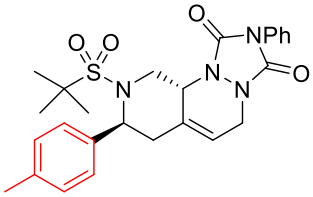
(*S*,*E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (7p).



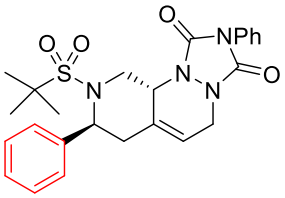
According to general procedure VIII, **7p** were obtained as a colorless oil (23 mg, 60% yield). $[\alpha]^{25}_{D}$ = +35.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H), 6.72 (d, *J* = 16.3 Hz, 1H), 6.44 (d, *J* = 16.3 Hz, 1H), 5.81 (s, 1H), 4.62–4.57 (m, 1H), 4.26–4.19 (m, 1H), 3.90–3.84 (m, 1H), 2.79–2.58 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 131.1, 129.5, 128.7, 127.8, 127.3, 126.4, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.8, 62.4, 52.7 (q, $^2J_{CF}$ = 31.2 Hz, CH), 43.9, 24.4, 23.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{26}F_3N_2O_2S$ [M+NH_4^+]: 391.1662; found: 391.1658.

IX. Standard procedure for the Diels–Alder reaction with PTAD. The corresponding diene (0.10 mmol) was dissolved in acetone (0.1 M) and cooled down to −40 ºC. PTAD (0.13 mmol) was then added and the mixture was stirred at the same temperature until the reaction was complete (followed by TLC analysis, typically 2−3 h). Next, the crude mixture was concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane:EtOAc).

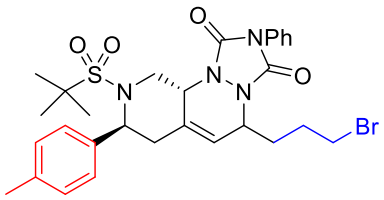
(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8a). According to general procedure IX, **8a** was obtained from **6a** as a white solid (45 mg, 88% yield). mp 86–87 °C; $[\alpha]^{25}_{D}$ = +10.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.37 (m, 5H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.95 (bs, 1H), 5.13 (t, *J* = 8.2 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.48 (bs, 1H), 4.32 (ddd, *J* = 16.5, 6.5, 2.7 Hz, 1H), 4.24–4.08 (m, 2H), 3.02 (dd, *J* = 14.1, 7.9 Hz, 1H), 2.57–2.45 (m, 1H), 2.38 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 151.3, 138.6, 137.7, 131.3, 130.3, 129.7, 129.2, 128.2, 126.5, 125.7, 118.0, 62.0, 60.3, 56.0, 48.9, 42.4, 37.8, 24.6, 21.2. HRMS (ESI): *m/z* calcd for $C_{26}H_{34}N_5O_4S$ [M+NH_4^+]: 512.2331; found: 512.2326.



(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8b). According to general procedure IX, **8b** was obtained from **6b** as a white solid (1.529 g, 97% yield). mp 97–99 ºC; $[\alpha]^{25}_{D}$ = +9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 10H), 5.95 (s, 1H), 5.16 (t, *J* =8.4 Hz, 1H), 4.68 (d, *J* = 15.1 Hz, 1H), 4.49–4.47 (m, 1H), 4.36–4.13 (m, 3H), 3.03 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.54–2.47 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 151.2, 141.6, 131.2, 130.1, 129.1, 128.9, 128.1, 127.8, 126.4, 125.9, 118.0, 61.6, 60.4, 55.9, 48.7, 42.2, 37.6, 24.4. HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_4O_4S$ [M+NH_4^+]: 498.2170; found: 498.2163.

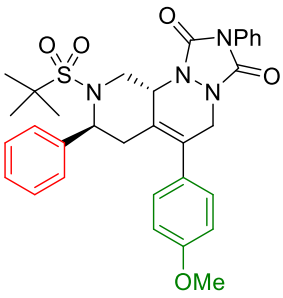


(8*S*,10a*R*)-5-(3-Bromopropyl)-9-(*tert*-butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8c). According



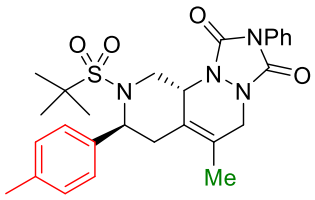
to general procedure IX, **8c** was obtained from **7g** as a white solid (28 mg, 80% yield). mp 85–87 ºC; $[\alpha]^{25}_{D}$ = –67.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.34 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.95 (bs, 1H), 5.14 (t, *J* = 8.7 Hz, 1H), 4.82 (d, *J* = 15.4 Hz, 1H), 4.61 (bs, 1H), 4.36 (bs, 1H), 4.19 (dd, *J* = 15.5, 6.1 Hz, 1H), 3.53–3.41 (m, 2H), 2.95 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.43 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H), 2.22–1.97 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 150.1, 139.1, 137.7, 131.2, 130.2, 129.8, 129.2, 128.2, 126.4, 125.6, 122.4, 61.5, 60.2, 57.2, 51.7, 49.20, 37.9, 33.3, 31.6, 28.7, 24.6, 21.2. HRMS (ESI): *m/z* calcd for $C_{29}H_{39}BrN_5O_4S$ [M+NH_4^+]: 632.1899; found: 632.1901.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-(4-methoxyphenyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8d). According

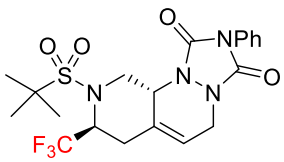


to general procedure IX, **8d** was obtained from **6i** as a white solid (20 mg, 67% yield). mp 88–90 ºC; $[\alpha]^{25}_{D}$ = –8.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.44 (m, 4H), 7.40–7.27 (m, 8H), 7.00–6.98 (m, 2H), 5.20 (t, *J* = 8.6 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.57–4.55 (m, 1H), 4.39 (m, 2H), 4.13 (dd, *J* = 15.3, 6.4 Hz, 1H), 3.86 (s, 3H), 3.08 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.19–2.12 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 153.2, 151.1, 141.8, 131.2, 130.7, 129.6, 129.1, 129.0, 128.9, 128.1, 127.6, 125.9, 125.6, 124.5, 114.4, 61.5, 59.8, 56.3, 55.3, 48.4, 46.6, 34.5, 29.7, 24.4. HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_4O_5S$ [M+NH_4^+]: 604.2588; found: 604.2585.

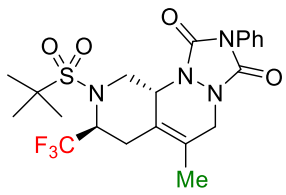
(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8e). According to general procedure IX, **8e** was obtained from **6o** as a white solid (48 mg, 87% yield). mp 112–114 ºC; $[\alpha]^{25}_{D}$ = –16.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9, 125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd for $C_{27}H_{32}N_4O_4S$ [M+NH_4^+]: 526.2483; found: 526.2479.



(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8i). According to general procedure IX, **8i** was obtained from **6g** as a white solid (43 mg, 91% yield). mp 145–147 ºC; $[\alpha]^{25}_{D}$ = –7.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.33 (m, 5H), 4.87–4.73 (m, 1H), 4.42 (d, *J* =12.0 Hz, 2H), 4.11 (dd, *J* = 16.2, 7.5 Hz, 2H), 3.91 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.15 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.08 (dd, *J* = 14.5, 8.2 Hz, 1H), 1.89 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.26 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 150.7, 131.2, 129.1, 128.1, 127.3, 125.5, 125.3 (q, $^1J_{CF}$ = 282.7 Hz, C), 118.5, 62.9, 55.4 (q, $^2J_{CF}$ = 31.4 Hz, CH), 54.8, 49.2, 45.9, 24.6, 24.3, 15.9. HRMS (ESI): *m/z* calcd for $C_{21}H_{25}F_3N_4O_4S$ [M+NH_4^+]: 490.1730; found: 490.1728.

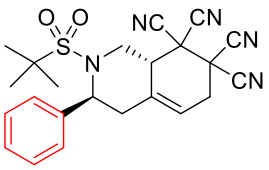


(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8j). According to general procedure IX, **8j** was obtained from **6p** as a white solid (36 mg, 88% yield). mp 145–147 ºC; $[\alpha]^{25}_{D}$ = –16.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–



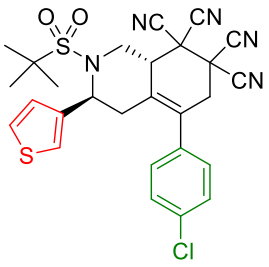
3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9, 125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd for $C_{27}H_{32}N_4O_4S$ [M+NH_4^+]: 504.1887; found: 504.1891.

X. Standard procedure for the Diels–Alder reaction with tetracyanoethylene. The corresponding diene (0.10 mmol) and tetracyanoethylene (0.20 mmol) were added to a Schlenk tube, dissolved in toluene (0.1 M), and heated at 100 ºC until the reaction was complete (TLC analysis, typically 2–3 h). The crude mixture was then concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane:EtOAc).

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-phenyl-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8f). 

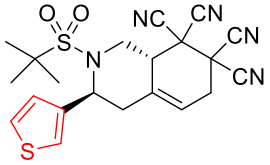
According to general procedure X, **8f** was obtained from **6b** as a white solid (38 mg, 84% yield). mp 186–188 ºC; $[\alpha]^{25}_D$ = +31.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.69 (s, 1H), 4.86 (s, 1H), 4.27 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.76 (t, *J* = 10.9 Hz, 1H), 3.62 (s, 1H), 3.25–3.14 (m, 3H), 2.93 (d, *J* = 13.6 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 131.2, 128.6, 128.4, 128.1, 127.3, 117.2, 110.9, 110.2, 110.1, 108.5, 62.7, 48.4, 41.6, 40.8, 38.8, 37.2, 32.7, 24.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{23}N_5O_2S$ [M+NH_4^+]: 451.1576; found: 451.1569.

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-5-(4-chlorophenyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8g). According to general procedure X,



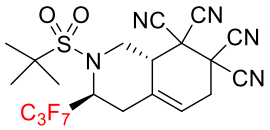
8g was obtained from **6l** as a white solid (31 mg, 92% yield). mp 137–139 ºC; $[\alpha]^{25}_{D}$ = +20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.19–7.18 (m, 1H), 7.10–7.05 (m, 2H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.02 (s, 1H), 4.26 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.85–3.78 (m, 1H), 3.70-3.67 (m, 1H), 3.40–3.20 (m, 2H), 2.87 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 135.4, 134.8, 129.9, 129.2, 128.9, 127.3, 126.6, 126.2, 123.4, 110.4, 110.0, 109.9, 108.3, 62.9, 54.9, 46.5, 41.5, 40.7, 38.8, 38.3, 34.4, 24.6. HRMS (ESI): *m/z* calcd for $C_{27}H_{24}ClN_5O_2S_2$ [M+NH_4^+]: 567.1060; found: 567.1056.

(3*S*,10a*R*)-2-(*tert*-Butylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8h). According to general procedure X, **8h** was obtained from **6d**



as a colorless oil (46 mg, 86% yield); $[\alpha]^{25}_{D}$ = +32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2H), 7.14–7.12 (m, 1H), 5.72 (s, 1H), 4.89 (s, 1H), 4.22 (d, *J* = 7.4 Hz, 1H), 3.69-3.57 (m, 2H), 3.25–3.16 (m, 3H), 2.92 (d, *J* = 15.7 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 131.2, 127.4, 126.4, 124.8, 117.2, 110.9, 110.1, 110.0, 108.4, 62.7, 56.8, 41.6, 40.5, 38.6, 37.2, 32.6, 29.7, 24.3. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_5O_2S_2$ [M+NH_4^+]: 457.1475; found: 457.1475.

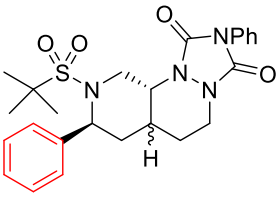
(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoropropyl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8k). According to general procedure X, **8k** was obtained from **6h**



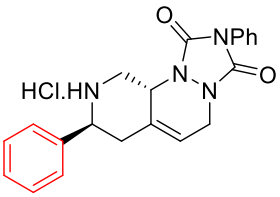
as a white solid (41 mg, 75% yield). mp 172–174 ºC; $[\alpha]^{25}_{D}$ = +40.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73–5.71 (m, 1H), 4.87 (d, *J* = 24.6 Hz, 1H), 3.91–3.76 (m, 2H), 3.52–3.50 (m, 1H), 3.17–3.13 (m, 2H), 3.02 (d, *J* = 18.3 Hz, 1H), 2.76 (d, *J* = 18.3 Hz, 1H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -80.70 (t, *J* = 10.7 Hz, 3F), -110.24 (d, *J* = 275.8 Hz, 1F), -119.07 (d, *J* = 275.8 Hz, 1F), -125.15 – -127.59 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.0, 119.4–108.9

(C_3F_7), 118.3, 110.8, 110.2, 110.1, 108.2, 64.1, 51.9, 44.6, 42.2, 39.6, 38.7, 32.7, 29.7, 24.7. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}F_7N_5O_2S$ [M+NH_4^+]: 543.1408; found: 543.1407.

XI. General procedure for the hydrogenation reaction. Synthesis of (8*S*,10a*R*)-9-(*tert*-butylsulfonyl)-2,8-diphenyloctahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (9). A round-bottom flask was charged with Diels-Alder adduct **8b** (200 mg, 0.42 mmol), Pd (10% on activated carbon) (42 mg, 0.042 mmol), and a stirrer bar, and the mixture was suspended in anhydrous methanol (10 mL). The vessel was purged three times with hydrogen gas and fitted with a gas bag containing hydrogen. The mixture was stirred for 3 h before filtering through a short pad of Celite. The filtrate was then concentrated to dryness under reduced pressure. No further purification was necessary and compound **9** was isolated as a white solid (183 mg, 91% yield) (2:1 mixture of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (m), 5.25–5.20 (m), 4.95 (d, *J* = 18.1 Hz, 1H, *minor*), 4.20–4.09 (m, 1H, *minor*), 3.98 (dt, *J* = 12.6, 4.3 Hz, 1H, *major*), 3.89–3.83 (m, 1H, *minor*), 3.79–3.72 (m), 3.66–3.55 (m), 3.08–3.01 (m, 1H, *minor*), 2.65–2.39 (m), 2.21 (dt, *J* = 13.9, 3.7 Hz, 1H, *major*), 2.12–2.05 (m, 1H, *major*), 1.94–1.83 (m), 1.46 (s, 9H, *minor*), 1.42 (s, 9H, *major*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 149.9, 145.9, 138.5, 129.1, 129.0, 128.3, 127.2, 126.7, 125.7, 108.8, 62.2, 62.0, 54.6, 54.4, 43.6, 40.7, 38.1, 31.1, 30.5, 27.4, 26.9, 26.7, 24.6. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_4O_2$ [M+H^+]: 483.2061; found 483.2054.

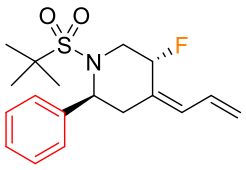


XII. General procedure for the deprotection of *tert*-butylsulfonyl. Synthesis of (8*S*,10a*R*)-1,3-dioxo-2,8-diphenyl-2,3,5,7,8,9,10,10a-octahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazin-9-ium chloride (10). Diels-Alder adduct **8b** (100 mg, 0.21 mmol) was dissolved in anhydrous 1,4-dioxane (1.8 mL), and concentrated hydrochloric acid (12 M, 0.2 mL) was added. The reaction mixture was then stirred at 110 ºC for 3 h. After this time, the crude mixture was concentrated to dryness under reduced pressure, and the resulting solid was precipitated and washed with methanol and diethyl



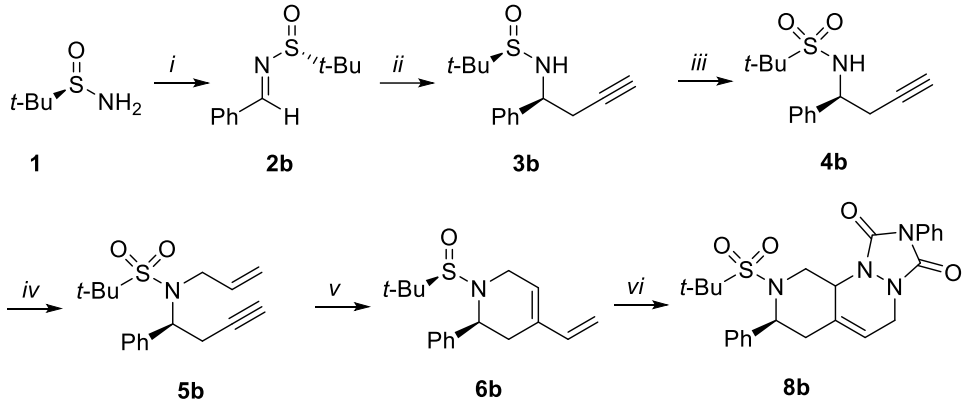
ether. No further purification was needed, affording **10** as an off-white solid (59 mg, 71% yield). mp 296–298 ºC; $[\alpha]^{25}_{D}$ = +40.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 10.14 (s, 1H), 7.74–7.72 (m, 2H), 7.56–7.40 (m, 8H), 6.05 (s, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.38 (s, 1H), 4.27–4.06 (m, 3H), 3.21–3.15 (m, 1H), 2.99–2.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 152.1, 136.7, 131.7, 129.6, 129.4, 129.3, 128.7, 128.3, 126.8, 117.9, 60.5, 50.9, 46.6, 42.9, 39.2, 36.8. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_4O_2$ [M+NH_4^+]: 361.1659; found: 361.1659.

XIII. General procedure for the preparation of (2*S*,5*R*,*Z*)-4-allylidene-1-(*tert*-butylsulfonyl)-5-fluoro-2-phenylpiperidine (11).



Metathesis product **7l** (39 mg, 0.1 mmol) was dissolved in acetonitrile (0.1 M) and Selectfluor (46 mg, 0.13 mmol) was added, and the reaction mixture was then stirred for 16 h at room temperature. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography using mixtures of *n*-hexane:EtOAc as the eluent, affording a colorless oil (20 mg, 58% yield). $[\alpha]^{25}_{D}$ = +78.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 6.65–6.53 (m, 1H), 6.15 (dd, *J* = 10.9, 5.4 Hz, 1H), 5.36–5.17 (m, 3H), 4.76 (d, *J* = 48.5 Hz, 1H), 4.13–4.03 (m, 1H), 3.45–3.26 (m, 2H), 3.06–2.98 (m, 1H), 1.52 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -167.32 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 130.6, 130.0, 128.6, 127.2, 121.9, 92.4, 90.1, 62.4, 57.7, 48.0, 28.1, 24.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{28}FN_2O_2S$ [M+NH_4^+]: 355.1850; found: 355.1848.

XIV. Gram-scale procedure for 5b.



Reaction conditions: *i*. PhCHO, $Ti(OEt)_4$, CH_2Cl_2, r.t., 16 h.
ii. Propargyl magnesium bromide, CH_2Cl_2, -48 ºC, 16 h.
iii. *m*-CPBA, CH_2Cl_2, r.t. 2 h.
iv. Allyl bromide, NaH, DMF, 0 ºC - r.t. 3 h.
v. HGII (3 mol%), CH_2Cl_2,1,7-octadiene, 2 h.
vi. PTAD, acetone, -40 ºC, 2-3 h.

A solution of benzaldehyde (690 mg, 6.5 mmol) and $Ti(OEt)_4$ (20 mmol) in CH_2Cl_2 (0.1 M, 100 mL) was stirred for 5 min at room temperature. To the resulting solution, (*R*)-N-(*tert*-butanesulfinyl)amine **1** was added (1 g, 8.3 mmol) and the mixture was stirred at room temperature for 12 h. After this time, saturated aqueous $NaHCO_3$ was added until white titanium salts precipitated. The suspension was filtered through a short pad of Celite washing with small portions of dichloromethane. The filtrate was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (n-hexane/EtOAc, 5:1) to afford imine **2b** (1.75 g, 7.8 mmol, 94%).

A freshly prepared 1 M solution of propargylmagnesium bromide in THF (1.5 equiv, 11.7 mmol) was added to a solution of the imine **2b** (7.8 mmol) in CH_2Cl_2 (0.1 M, 100 mL) at −48 °C. After stirring for 18 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 and purified by flash column chromatography (n-hexane/EtOAc, 3:1). Sulfinamide **3b** was obtained with 89% of chemical yield (1.83 g, 6.90 mmol).

m-CPBA (8.3 mmol) was added to a solution of this sulfinamide **3b** (1.83 g, 6.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to afford sulfonamide **4b** (1.92 g, 6.8 mmol) with 99% of yield.

To a suspension of NaH (60%, 10.2 mmol) in dry DMF (100 mL) at 0 °C, sulfonamide **4b** (1.92 g, 6.8 mmol) was added dropwise. After stirring at this temperature for 20 minutes, allyl bromide (9.12 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with NH_4Cl aq., extracted with diethyl ether, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (n-hexane/EtOAc, 10:1) to afford 2.02 g (6.3 mmol) of enyne **5b** (92%).

1.00 g of enyne **5b** (3.1 mmol) and 1,7-octadiene (1.8 mL, 12.5 mmol) were dissolved in CH_2Cl_2 (100 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (10 mol%, 194 mg, 0.3 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane:Et_2O (5:1) to yield 0.859 g (2.7 mmol) of 1,3-diene **6b** (86%).

1.00 g of 1,3-diene **6b** (3,28 mmol) was dissolved in acetone (0.1 M) and cooled down to −40 ºC. Then, 0.705 g of PTAD (4.03 mmol) was then added and the mixture was stirred at the same temperature until the reaction was complete (followed by TLC analysis, typically 2−3 h). Next, the crude mixture was concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane:EtOAc) to afford 1.53 g (2.7 mmol) of compound **8b** (97%).

XV. References.

[1] A. Llobat, R. Román, N. Mateu, D. M. Sedgwick, P. Barrio, M. Medio-Simón, S. Fustero*, Org. Lett*. **2019**, *21*, 7294−7297.

[2] A. Llobat, D. M. Sedgwick, A. Cabré, A.; R. Román, N. Mateu, J. Escorihuela, M. Medio-Simón, V. A. Soloshonok, J. Han, A. Riera, S. Fustero, *Adv. Synth. Catal*. **2020**, *362*, 1378–1384

XVI. Single crystal X-ray diffraction studies of compound 8g.

The single crystal was obtained through volatilize in CH_2Cl_2 and hexane. The X-ray single crystal data for compound **8g** were collected on a SuperNova diffractometer equipped with copper micro-focus X-ray sources (λ = 1.5406 Å) at 150 K. The crystal structures were resolved by direct methods and all calculations were performed on the SHELXTL-2016 program package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added in the riding model and refined with isotropic thermal parameters.

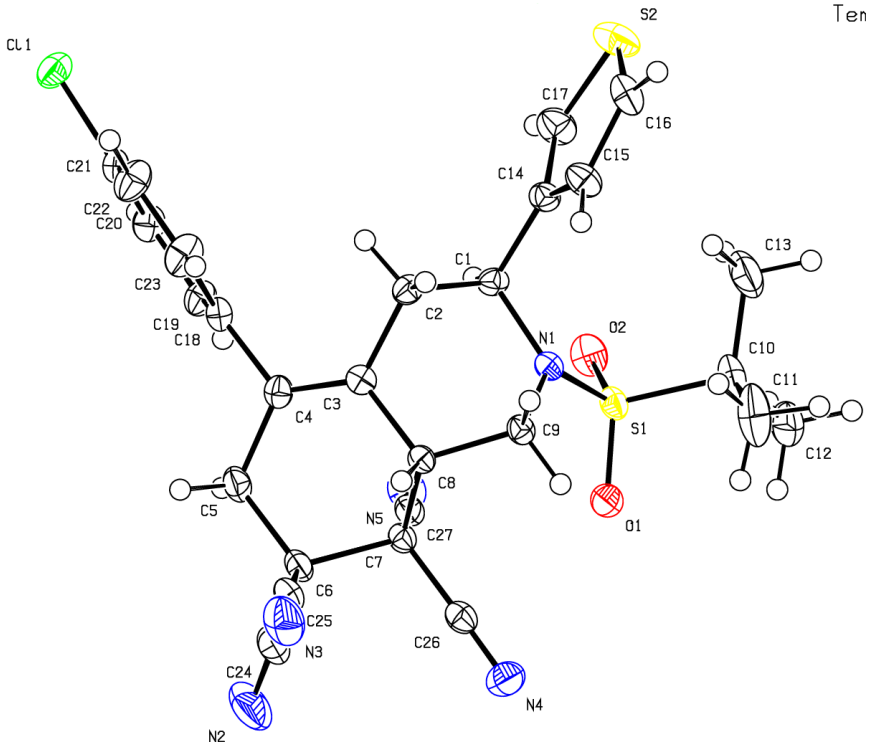


Figure S1. X-ray derived ORTEP of **8g** with thermal ellipsoids shown at the 50% probability level.

Table S1. Crystal data and structure refinement for **8g**.

Empirical formula	C27 H24 Cl N5 O2 S2
Formula weight	550.08
Temperature	150.00 (10) K
Wavelength	1.54184 Å
Crystal system	Orthorombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.78134(7) Å □ = 90°
	b = 18.88398(18) Å □ = 90°
	c = 21.0361(2) Å □ = 90°
Volume	2693.85(4)
Z	4
Density (calculated)	1.356 Mg/m^3
Absorption coefficient	2.985
F(000)	1144
Crystal size	$0.402 \times 0.100 \times 0.041$ mm^3
Crystal description	Plate
Crystal color	Yellow
Theta range for data collection	6.29 to 137.828
Index ranges	$-8 \le h \le 7$, $-20 \le k \le 22$, $-21 \le l \le 25$
Reflections collected	48629
Independent reflections	5005 [R_{int} = 0.0706, R_{sigma} = 0.0359]
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4455 / 0 / 300
Goodness-of-fit on F2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0886
R indices (all data)	R1 = 0.0386, wR2 = 0.0912
Bijvoet país coverage	100%
Flack parameter	-0.013(7)

Scientific Article 3:

Asymmetric synthesis of fluorinated monoterpenic alkaloid derivatives from chiral fluoroalkyl aldimines via the Pauson-Khand reaction

Asymmetric synthesis of fluorinated monoterpenic alkaloid derivatives from chiral fluoroalkyl aldimines via the Pauson-Khand reaction

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Enantioenriched fluorinated monoterpenic alkaloid analogues were synthesised, employing a strategy based on the previously undescribed diastereoselective propargylation of fluorinated *tert*-butanesulfinyl imines, and subsequent Pauson-Khand reaction of resulting enyne derivatives, carried out both stoichiometrically and catalytically. The Pauson-Khand reaction tolerated both substituted alkenes and alkynes, and took place in good yields and diastereoselectivities, even when applied to a gram-scale synthesis.

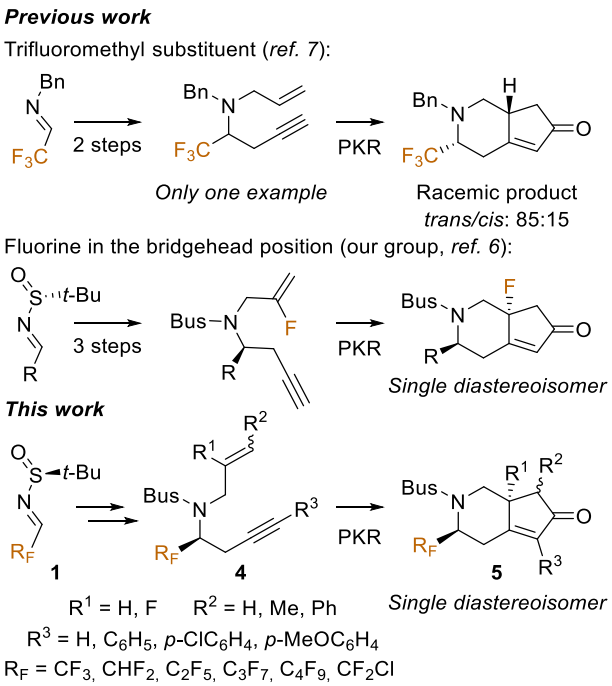
Keywords: *N*-*tert*-butanesulfinyl imine; propargylation; Pauson-Khand; organofluorine chemistry; asymmetric synthesis

Monoterpenic alkaloids possessing a piperidine heterocycle fused with a five-membered carbocyclic ring are of utmost interest since they present important biological activities.[1] Tecomanine and incarvilline, exhibiting hypoglucemic and analgesic activity respectively, are representative examples of this group of alkaloids. The intramolecular Pauson-Khand reaction (PKR) has been widely applied to the synthesis of natural products, both stoichiometrically and catalytically,[2] and has also proved to be a feasible method for the preparation of the cyclopentane[*c*]piperidine core present in this class of monoterpenic alkaloids.[3] Recent reports from several groups illustrate the preparation, in some cases stereocontrolled, of similar structures such as the marine alkaloid nakadomarin A,[3a] or those belonging to the kinabalurine, incarvilline and skytanthine families.[3c] In contrast, access to the tecomanine skeleton through the Pauson-Khand cycloaddition of chiral *N*-tethered 1,7-enynes has been more scarcely explored.[4,5]

In terms of fluorinated derivatives, our group recently reported the synthesis of similar bicyclic structures via fluoro-Pauson-Khand reaction, resulting in a stereogenic bridgehead C—F bond (Scheme 1).[6] In addition, Bonnet-Delpon and co-workers briefly explored the synthesis of racemic trifluoromethylated derivatives of the same heterobicylic skeleton

(Scheme 1).[7] This, incidentally, is the only documented example of the propargylation of fluorinated imines, to the best of our knowledge. The introduction of fluorine into organic molecules has become a common strategy to fine-tune their biological and pharmacological activities.[8] In this way, the potentially positive effects derived from the introduction of fluoroalkyl groups in heterocyclic structures, in particular nitrogen containing heterocycles, has been extensively demonstrated.[9]

Currently, there are several generalised methods for the introduction of fluorine in organic molecules, one of which is the use of fluorinated building blocks.[10] Imines bearing fluorinated groupings represent an interesting class of building blocks, given that they can be used as electrophiles in many transformations, giving rise to amines bearing proximal fluorinated groups that have the potential to modify the basicity of the amine as necessary.



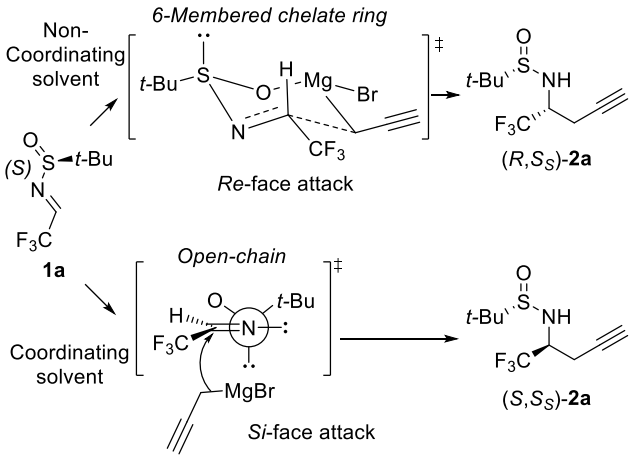
Scheme 1. Previous work relevant to this report.

Specifically, fluorinated *tert*-butane sulfinyl imines can be used to produce optically pure fluorinated amines that could be valuable to medicinal and pharmaceutical research,[11] although their full potential in organic synthesis is only recently coming to light.[12]

Therefore, continuing our interest in this class of fluorinated molecules, in this update we describe the asymmetric synthesis of tecomanine analogues through Pauson-Khand cyclisation of *N*-tethered 1,7-enynes **4** bearing a series of fluorinated substituents in a different position to those disclosed previously, originating from chiral fluorinated imines **1** (Scheme 1). Herein, we also report a wider reaction scope of the Pauson-Khand reaction, including an efficient catalytic version, and new substrates bearing substitutions at both the alkyne and alkene groups.

With the starting imines **1** in hand, we envisioned a synthetic route with diastereoselective propargylation of imines **1** as the key step in order to introduce the chiral information necessary for the rest of the sequence. To our surprise, we found that the asymmetric propargylation of this class of fluorinated imines remained undescribed in the scientific literature, despite similar non-fluorinated substrates being widely employed as electrophiles in diastereoselective addition reactions.[13]

We first assayed the addition of propargyl magnesium bromide to sulfinimine **1a** in CH_2Cl_2 using the conditions described by Zhang *et al*. for several non-fluorinated imines,[13a] however, the resulting homopropargyl amine **2a** was obtained with only slight diastereoselectivity (44:56). We therefore changed the solvent to THF and found that not only the diastereoselectivity was vastly improved (96:4), but the major diastereoisomer was actually the opposite of that observed in CH_2Cl_2.[14] The dramatic effect of the solvent in this kind of transformation is



Scheme 2. Rationale behind the solvent effects observed.

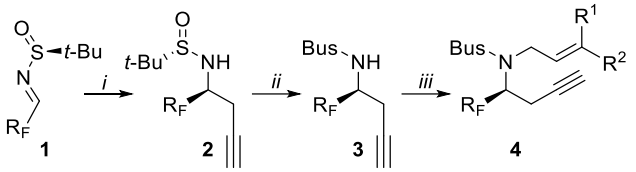
well documented, and is attributed to differing transition states according to the nature of the solvent (Scheme 2).[12d,13b,15] Nonetheless, it is clear that in our case the substrate also plays a role.

We hypothesize that the fluorinated group, given its strong electron-withdrawing character, increases the reactivity of the imine and decreases the difference in energy between the two transition states in non-coordinating solvents such as CH_2Cl_2. In coordinating solvents such as THF, the six-membered transition state is less favoured and therefore the reaction takes place *via* the open-chain transition state, resulting in much higher diastereoselectivity. Accordingly, the propargylation reaction was carried out at -78 °C in THF affording the corresponding homopropargyl sulfinamides **2a** and **2e-i** in moderate to good yields (60-87%) and excellent diastereomeric ratios (*dr* >20:1) (Table 1).

Allylation of the homopropargyl sulfinamides **2** to achieve the desired enynes proved problematic, and resulted in unsatisfactory yields (<30%). Fortunately, we found that after oxidation of the sulfinyl group with *m*-CPBA in CH_2Cl_2 at 0 °C,[16] the corresponding homopropargyl sulfonamides **3a** and **3e-i** successfully underwent allylation through reaction with the corresponding bromide in basic conditions at room temperature to give **4a-i** with good yields in general (Table 1).

With the goal of exploring the scope and limitations of the final Pauson-Khand reaction, we next synthesised *N*-tethered 1,7-enynes bearing an internal triple bond. To this end, we first attempted the preparation of phenyl-substituted **2j** through the addition of phenyl propargyl magnesium bromide to sulfinimine **1a**. However, in this case an inseparable mixture of the corresponding homopropargyl and allenyl products, **2j** and **2j'** respectively, was observed (Table 2). This has been described in several reports owing to the alkyne/allene equilibrium of the organometallic reagent in solution.[17] We found that this setback could be overcome to a certain degree modifying the reaction temperature; at higher temperatures, the desired propargylation reaction product **2j** was favoured by up to 11:1 (Table 2) (see Supporting Information for more details).

Table 1. Asymmetric synthesis of enynes **4a-g**.[a), b)]

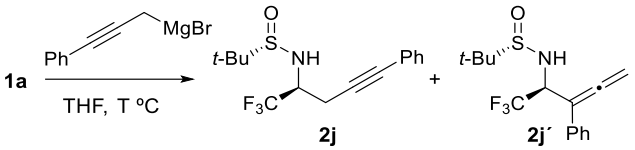


R_F	**2** (%) (*dr*)[c]	**3** (%)	R^1	R^2	**4** (%)
CF_3	**a** (87) (96:4)	**a** (82)	H	H	**a** (92)
CF_3 [d]	**a**	**a**	H	Me	**b** (93)
CF_3	**a**	**a**	H	Ph	**c** (84)
CF_3	**a**	**a**	Me	Me	**d** (93)
CHF_2	**e** (60) (95:5)	**e** (63)	H	H	**e** (53)
C_2F_5	**f** (65) (98:2)	**f** (81)	H	H	**f** (70)
C_3F_7	**g** (60) (97:3)	**g** (82)	H	H	**g** (55)
C_4F_9	**h** (60) (99:1)	**h** (83)	H	H	**h** (82)
CF_2Cl	**i** (74) (96:4)	**i** (84)	H	H	**i** (77)

Reaction conditions: *i*. Magnesium propargyl bromide (1.5 equiv), THF [0.1 M], -78 °C, 2-3 h. *ii*. *m*-CPBA (1.2 equiv), CH_2Cl_2 [0.1 M], 0 °C – r.t., 1-2 h. *iii*. Corresponding allyl bromide (2 equiv), K_2CO_3 (3 equiv), DMF [0.1 M], 0 °C – r.t., 5-12 h. [a] Yields refer to isolated yields in all cases. [b] Bus = *tert*-butanesulfonyl. [c] Diastereomeric ratios were determined by ^1H and ^{19}F NMR (see Supporting Information). [d] A 4:1 mixture of *E*/*Z*-crotyl bromide was used. We were unable to separate the resulting two isomers of **4b** by column chromatography, and as such continued with the isomeric mixture.

Despite this partial solution, in the end we decided to follow a different strategy and introduce an aryl group at the triple bond *via* Sonogashira reaction with **3a**, thereby eliminating completely allenyl derivative **2j'** from the resulting product. In this way, the corresponding homopropargyl sulfinamides were obtained in moderate to good yields. These derivatives were then subjected to the same

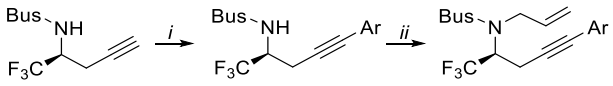
Table 2. Effect of temperature on alkyne vs allene selectivity.[a]



Entry	T (°C)	2j	:	2j'
1	-78	29	:	71
2	0	80	:	20
3	50	90	:	10
4	75	92	:	8

[a)] Selectivity was measured by ^{19}F NMR (see Supporting Information).

Table 3. Synthesis of enynes **4j-l**.[a), b)]



Entry	Ar	**3** (%)	**4** (%)
1	Ph	**3j** (87)	**4j** (81)
2	*p*-OMeC$_6$H$_4$	**3k** (40)	**4k** (99)
3	*p*-ClC$_6$H$_4$	**3l** (65)	**4l** (97)

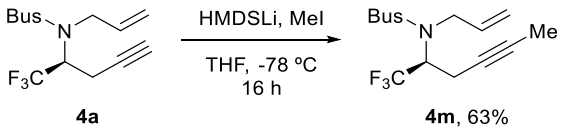
Reaction conditions: *i*. Ar-I (1.2 equiv), $Pd(Ph_3)_2Cl_2$ (4 mol%), CuI (8 mol%), $(i\text{-}Pr)_2NH$ [0.06 M], 50 °C, 2-3 h. *ii*. Allyl bromide (2 equiv), K_2CO_3 (3 equiv), DMF [0.1 M], 0 °C – r.t., 5-12 h. [a)] Yields refer to isolated yields in all cases. [b)] Bus = *tert*-butanesulfonyl.

oxidation/allylation sequence mentioned previously to prepare the target 4-aza-8-aryl-1,7-enynes **4j-l** (Table 3). Similarly, we attempted the synthesis of **4m** bearing a methyl substituent at the triple bond, firstly *via* propargylation analogous to that previously discussed. However, this resulted in poor yield and diastereoselectivity. We therefore opted to directly methylate the triple bond in **4a** using HMDSLi and methyl iodide, following a previously described prprocedure (Scheme 3).[18]

With a variety of chiral 1,7-enynes **4** in hand, we then explored their Pauson-Khand cyclisation to obtain adducts bearing stereodefined substitutions in various positions.

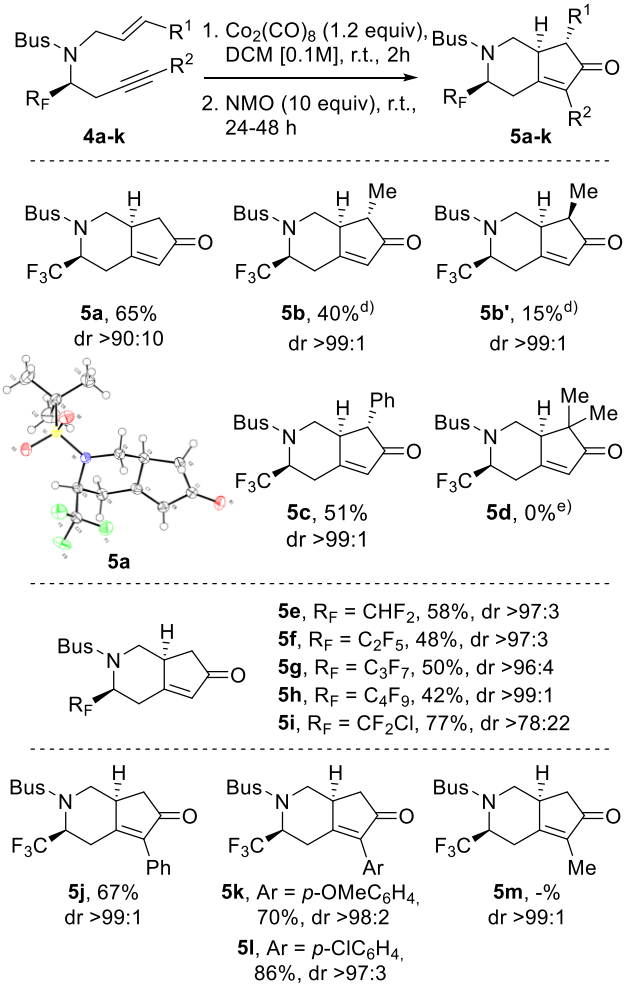
Treatment of **4a-m** with 1.2 equivalents of $Co_2(CO)_8$ resulted in their full conversion to the corresponding cobalt complexes after 2 hours in CH_2Cl_2 that, upon treatment with 10 equivalents of *N*-methylmorpholine-*N*-oxide (NMO) overnight at room temperature, underwent an efficient intramolecular PKR to afford the corresponding bicyclic derivatives **5a-m** as single diastereomers (Table 4).

The yields were moderate to good, and high diastereoselectivity was observed in almost all cases. In general, substrates with substituted olefin components (**4b-c**) or longer fluoroalkyl chains (**4f-h**) resulted in lower yields and higher diastereoselectivities (**5b-c** and **5f-h**, Table 4). Fortunately, when we carried out the PKR with the isomeric mixture of *E*/*Z*-**4b** we obtained only two diastereoisomers, indicating that the reaction took place stereospecifically. Furthermore, **5b** and **5b'** were separable by column chromatography, and their stereochemistry was determined according to NOESY experiments as well as previous literature reports involving similar substrates.[4] Enyne **4h** bearing the CF_2Cl substituent resulted in a higher yield but a low diastereoselectivity (**5i**, Table 4),



Scheme 3. Synthesis of 1,7-enyne **4m**.

Table 4. Pauson-Khand cyclisation of enynes **4a-m**. [a), b), c)]



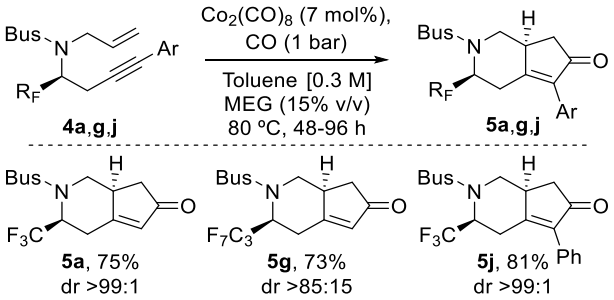
[a)] Yields refer to isolated yields in all cases. [b)] Diastereomeric ratios were determined by ^1H and ^{19}F NMR (see Supporting Information). [c)] Bus = *tert*-butanesulfonyl. [d)] Compounds **5b** and **5b'** were isolated from the same reaction mixture using the isomeric *E*/*Z* mixture of **4b** mentioned earlier, thus the global yield for this reaction was 55%. [e)] After addition of NMO, the cobalt complex reverted back to starting enyne **4d** (see text for details).

whereas enynes containing an internal alkyne group gave both higher yields and diastereoselectivities (**5j-m**, Table 4). An exception to this was enyne **4d**, bearing a

trisubstituted olefin. Curiously, after the formation of the cobalt complex, this substrate reverted back to the free enyne upon addition of the promotor, failing to cyclise into the expected Pauson-Khand product **5d**. In fact, a bibliographic search revealed documented instances of other similar interrupted Pauson-Khand reactions, in which trisubstituted alkenes failed to cyclise as required.[19]

The stereochemistry of the newly formed stereogenic centre in the bridgehead position was confirmed by X-ray crystallography of PK adduct **5a**.[20] In addition, **5a** was prepared starting from 1.2 grams of imine **1a** with no significant loss of yield or diastereoselectivity (global yield 36%, see Supporting Information for details).

Table 5. Catalytic Pauson-Khand cyclisation of selected enynes **4**.[a), b)]



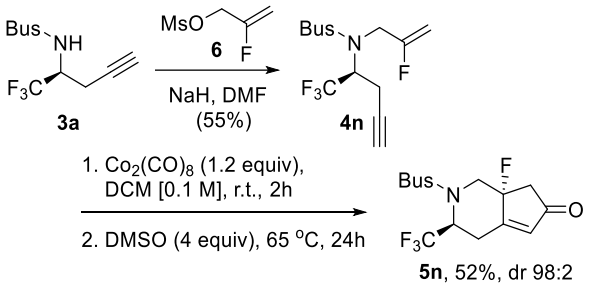
[a)] Yields refer to isolated yields in all cases. [b)] Bus = *tert*-butanesulfonyl.

We also explored the use of 1,7-enynes **4** in a catalytic version of the PKR, for which we selected a new synthetic protocol recently reported by Riera and co-workers.[21] This procedure is based on a biphasic system of ethylene glycol/toluene, and usually results in an enhancement of yield and selectivity for the PK adducts, as well as simplifying purification of the products. By applying these reaction conditions (7 mol% catalyst, low CO pressure, and 15% v/v of ethylene glycol in toluene) to enynes **4a**, **4g**, and **4j**, the corresponding bicyclic derivatives **5** were obtained (Table 5).

For adducts **5a** and **5j**, the yields and diastereoselectivities were clearly improved with respect to the stoichiometric version. However, **5g** was obtained with a higher yield but reduced diastereoselectivity. We suspect the higher yields were due to the simpler

purification arising from the reaction mixture containing only small amounts of cobalt compared with the stoichiometric version.

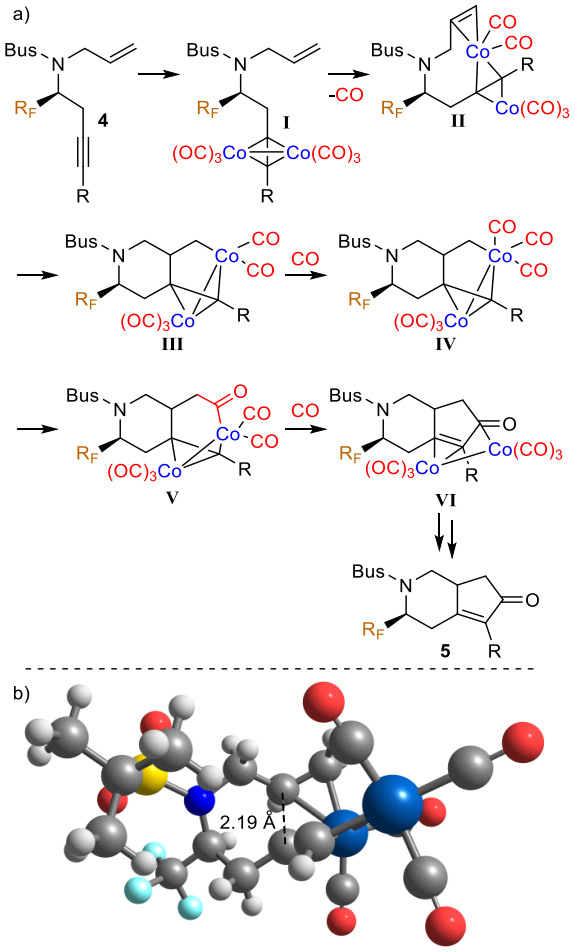
Furthermore, we tested the influence of the introduction a vinyl fluoride moiety on the Pauson-Khand cyclisation. To this end, the allylation reaction of the homopropargyl sulfonamine **3a** was carried out with 2-fluoroallyl mesylate **6** to afford enyne **4n** (Scheme 4).[22] For the cyclisation of this enyne derivative, we followed the reaction conditions previously applied by our group in analogous fluoro-



Scheme 4. Use of fluorinated mesylate **6** in the synthesis of PKR adducts bearing a stereodefined C—F bond at the bridgehead position. Bus = *tert*-butanesulfonyl.

Pauson-Khand reactions, in which DMSO is used as the promoter instead of NMO.[6, 23] It is worth noting that this transformation involves the asymmetric construction of a carbon-fluorine quaternary stereogenic centre, a goal that constitutes remarkable interest in organic synthesis.[24] Unfortunately, after several attempts, the catalytic version of the Pauson-Khand could not be applied to the synthesis of this class of previously reported quaternary C—F containing bicycles, such as **5n** (Scheme 4).[6, 23]

The mechanism of the Pauson-Khand reaction catalyzed by $Co_2(CO)_8$ was initially proposed by Magnus in 1985,[25] and the same mechanism has since been supported by theoretical studies.[26] In our case, 1,7-enyne **4** reacts with $Co_2(CO)_8$ through a ligand exchange reaction to form the alkyne-coordinated $Co_2(CO)_6$ complex **I** upon release of two molecules of CO (Scheme 5). Next, NMO provides a vacant site in the cobalt complex removing one CO.



Scheme 5. a) Plausible mechanism of our Pauson-Khand reaction. b) Most favourable transition state between complexes **II** and **III**, determining the configuration of the newly formed stereogenic centre (see Supporting Information).

Then, the alkene group coordinates to the electronically unsaturated cobalt centre, yielding complex **II** and releasing another molecule of CO. From here, the alkene is inserted into the Co—C bond, generating a new C—C bond in the six-membered cobaltacycle intermediate **III**. This cyclisation step occurs with high diastereoselectivity due to the energy difference between the two possible transition states shown by density functional theory (DFT) calculations (see Supporting Information for details), reinforcing the experimental results observed. The coordination of a CO molecule to the cobalt centre then generates complex **IV**, and subsequent CO insertion into the Co—C bond yields complex **V**. A second molecule

of CO then coordinates to the unsaturated cobalt centre in **V** to form complex **VI**, and a final reductive elimination releases the corresponding cyclopentenone product **5**.

In conclusion, the Pauson-Khand cycloaddition of fluoroalkyl substituted chiral 4-aza-1,7-enynes allows the synthesis of fluorinated derivatives of the 6*H*-cyclopenta[*c*]pyridine-6-one skeleton that is present in several classes of monoterpene alkaloids. The key step to access the enyne precursors is the diastereoselective propargylation of fluorinated *tert*-butanesulfinyl imines, which was explored here for the first time and took place in good yields and high diastereoselectivities, despite performing differently to their non-fluorinated counterparts. Substitution of both the reacting alkene and alkyne groups has been shown to be compatible with the Pauson-Khand reaction, allowing further functionalisation of the heterobicyclic core. This synthetic route was also carried out at gram scale maintaining high yields and diastereoselectivities throughout. A catalytic version of the Pauson-Khand reaction could also be used to produce the desired adducts, generally offering improved yields and diastereoselectivities. The process was also applied to the synthesis of a derivative bearing a fluorine atom at a fully substituted bridgehead carbon stereogenic center, an interesting feature given the difficulty in obtaining similar structures by alternative methods.

Experimental Section

General procedure for the stoichiometric Pauson-Khand reaction

Sulfonamides **4** (1 equiv.) were dissolved in DCM [0.1 M] at room temperature in a round-bottomed flask. Octacarbonyl dicobalt complex (1.2 equiv.) was then added and the mixture was stirred until the starting sulfonamide had been consumed (TLC analysis, typically 2 hours). At this time, *N*-methylmorpholine *N*-oxide (10 equiv.) was added and the reaction was stirred overnight at room temperature. Once the reaction had finished, the solvent was removed under reduced pressure and products **5** were purified by flash column chromatography (*n*-hexane:ethyl acetate).

General procedure for the catalytic Pauson-Khand reaction

Sulfonamides **4** (1 equiv.) were dissolved in anhydrous toluene [0.3 M] at room temperature in a flame-dried pressure tube containing a magnetic stirrer. Octacarbonyl dicobalt complex (7 mol%) was then added, followed by ethylene glycol (15% v/v). The vessel was then sealed and purged with N_2, and then three times with CO, before finally being charged with CO (1 bar) and heated to 80 °C for 2 days (TLC analysis, typically 2 hours). At this time, *N*-methylmorpholine *N*-oxide (1 mmol) was added and the reaction was stirred overnight at room temperature. Once the reaction had finished, the solvent was removed *in vacuo* and products **5** were purified by flash column chromatography (*n*-hexane:ethyl acetate).

Acknowledgements

The authors are grateful to the Spanish MICINN and the AEI (CTQ2017-84249-P) for financial support, the SCSIE (Universitat de València) for access to instrumental facilities. The technical and human support provided by SGIker (UPV/EHU, MINECO, GV/DJ, ERDF, and ESF) is also gratefully acknowledged.

References

[1] T.-S. Kam, K. Yoganathan, C. Wei. *J. Nat. Prod.* **1997**, *60*, 673–676.

[2] a) J. D. Ricker, L. M. Geary, *Top. Catal.* **2017**, *60*, 609-619; b) H. Lee, F. A. Kwong, *Eur. J. Org. Chem.* **2010**, 789–811; c) R. Rios Torres in *The Pauson-Khand Reaction. Scope, Variations and Applications*, Wiley, Chichester, **2012**.

[3] a) J. S. Clark, C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 4332–4335; b) K. Kaneda, R. Taira, T. Fukuzawa, *Synth. Commun.* **2017**, *47*, 1622–1629; c) Y. Kavanagh, M. O'Brien, P. Evans, *Tetrahedron*, **2009**, *65*, 8259–8268.

[4] D. A. Ockey, M. A. Lewis, N. E. Schore, *Tetrahedron*, **2003**, *59*, 5377–5381.

[5] M. Günter, H.-J. Gais, *J. Org. Chem.* **2003**, *68*, 8037–8041.

[6] A. Llobat, R. Román, N. Mateu, D. M. Sedgwick, P. Barrio, M. Medio-Simón, S. Fustero, *Org. Lett.* **2019**, *21*, 7294–7297.

[7] G. Mageur, J. Legros, F. Meyer, M. Ourévitch, B. Crousse, D. A. Bonnet-Delpon, *Eur. J. Org. Chem.* **2005**, *7*, 1258–1265.

[8] a) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819; b) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518; c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014***, 114*, 2432–2506; d) K. Uneyama in *Organofluorine Chemistry*, Blackwell Publishing Ltd., Oxford, **2006**; e) R. D. Chambers in *Fluorine in Organic Chemistry*, Blackwell Publishing Ltd., Oxford, **2004**; f) H. Hiyama in *Organofluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**.

[9] a) D. M. Sedgwick, R. Román, P. Barrio, A. Trabanco, S. Fustero in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals (*Eds. G, Haufe, F. Leroux), Academic Press, Oxford, **2019**, ch. 16, pp. 575–599; b) J. Dinges, C. Lamberth in *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, Wiley-VCH, Weinheim, **2012**.

[10] a) H. Mei, T. Hiramatsu, R. Takeda, H. Moriwaka, H. Abe, J. Han, V. A. Soloshonok, *Org. Process. Res. Dev.* **2019**, *23*, 629–634; b) S. Fustero, D. M. Sedgwick, R. Román, P. Barrio, *Chem. Commun.* **2018**, *54*, 9706–9725; c) M.-C. Belhomme, T. Besset, T. Poisson, X. Pannecouke, *Chem. Eur. J.* **2015**, *21*, 12836–12865; d) V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, *Chem. Rev.* **2015**, *115*, 973–1050. e) P. Bravo, A. Farina, M. Frigerio, S. V. Meille, F. Viani, V. A. Soloshonok, *Tetrahedron: Asymmetry*, **1994**, *5*, 987–1004.

[11] C. Xie, L. Zhang, H. Mei, J. Han, V. A. Soloshonok, Y. Pan, *ChemistrySelect*, **2016**, *1*, 4435–4439.

[12] a) S. Fustero, M. Rodenes, R. Román, D. M. Sedgwick, J. E. Aguado, V. A. Soloshonok, J. Han, H. Mei, M. Medio-Simón, P. Barrio, *Adv. Synth. Catal.* **2019**, *361*, 3860–3867; b) H. Mei, J. Han, S. Fustero, R. Román, R. Ruzziconi, V. A. Soloshonok, *J. Fluorine Chem.* **2018**, *216*, 57–70; c) A. Sanz-Vidal, J. Torres, V. A. Soloshonok, Y. Zhu, J. L. Han, S. Fustero, C. del Pozo, *Adv. Synth. Catal.* **2018**, *360*, 366–373; d) G. Mazzeo, G. Longhi, S. Abbate, F. Mangiavacchi, C. Santi, J. Han, V. A. Soloshonok, L. Melensi, R. Ruzziconi, *Org. Biomol.*

Chem. **2018**, *16*, 8742–8750; e) S. Fioravanti, *Tetrahedron*, **2016**, *72*, 4449–4489. f) N. Shibata, T. Nishimine, E. Tokunaga, K. Kawada, T. Kagawa, A. E. Sorochinsky, V. A. Soloshonok, *Chem. Commun.* **2012**, 48, 4124–4126.

[13] a) L. Cui, C. Li, L. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 9178–9181; b) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740.

[14] The absolute configuration of the stereogenic centre formed in the propargylation step was later confirmed by X-ray diffraction analysis in the final PKR adduct **5a** (see Table 2 and Supporting Information).

[15] D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron*, **1999**, *55*, 8883–8904.

[16] J. Hao, T. Milcent, P. Retailleau, V. A. Soloshonok, S. Ongeri, B. Crousse, *Eur. J. Org. Chem.* **2018**, 3688–3692.

[17] a) H. M. Wisniewska, E. Jarvo, *Chem. Sci.* 2011, **2**, 807–810; b) A. Yanagisawa, T. Suzuki, T. Koide, S. Okitsu, T. Arai, *Chem. Asian J.* **2008**, *3*, 1793–1800; c) H. P. Acharya, K. Miyoshi, Y. Kobayashi, *Org. Lett.* **2007**, *9*, 3535–3538.

[18] J. Otero-Fraga, J. R. Granja, *Org. Chem. Front.* **2017**, *4*, 460–464.

[19] L. Pérez-Serrano, J. Blanco-Urgoiti, L. Casarrubios, G. Domínguez, J. Pérez-Castells, *J. Org. Chem.* **2000**, *65*, 3513–3519.

[20] CCDC 1954729 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[21] A. Cabré, X. Verdaguer, A. Riera, *Synthesis*, **2018**, *50*, 3891–3896.

[22] A. N. Tkachenko, D. S. Radchenko, P. K. Mykhailiuk, O. O. Grygorenko, I. V. Komarov, *Org. Lett.* **2009**, *11*, 5674–5676.

[23] R. Román, N. Mateu, I. López, M. Medio-Simón, S. Fustero, P. Barrio, *Org. Lett.* **2019**, *21*, 2569–2573.

[24] a) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev.* **2018**, *118*, 3887–3964; b) C. Xie, L. Zhang, W. Sha, V. A. Soloshonok, J. Han, Y. Pan, *Org. Lett*. **2016**, *18*, 3270–3273; c) C. Xie, L. Wu, J. Han, V. A. Soloshonok, Y. Pan, *Angew. Chem. Int. Ed.* **2015**, *54*, 6019–6023; d) C. Xie, Y. Dai, H. Mei, J. Han, V. A. Soloshonok, Y. Pan, *Chem. Commun.* **2015**, *51*, 9149–9152.

[25] P. Magnus, L. M. Principe, *Tetrahedron Lett.* **1985**, *26*, 4851–4854.

[26] a) M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc*. 2001, *123*, 1703–1708; b) L. Zhua, Z. Wang, S. Liu, T. Zhang, Z. Yang, R. Bai, Y. Lan, *Chin. Chem. Lett*. **2019**, *60*, 889–894.

Supporting Information

Asymmetric synthesis of fluorinated monoterpenic alkaloid derivatives from chiral fluoroalkyl aldimines via the Pauson-Khand reaction

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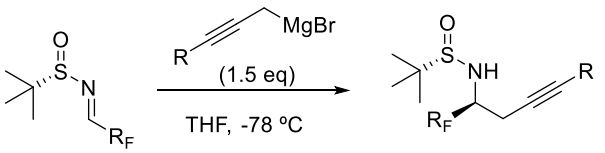
Content: **page**

I. General methods

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. CH_2Cl_2 was used without further purification. The reactions were monitored with the aid of TLC on 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. The abbreviation DCM stands for dichloromethane.

II. General procedure for the synthesis of sulfinamides 2.



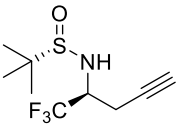
1a,d-i **2a,d-i**

For the synthesis of freshly 1M solution in THF of Grignard reagent, magnesium turnings (214 mg, 11 mmol), mercury chloride (II) (19 mg, 1.7 mol%), two iodine balls and Et_2O (5 mL, 1M) were added in a sealed tube under nitrogen atmosphere. This mixture as cooled at 0 °C and propargyl bromide was slowly added (0.56 mL, 5 mmol). The reaction mixture

was heated at 37 °C and stirred for 1h. At this time and at room temperature, this solution was used as a reagent in the next step without purification.

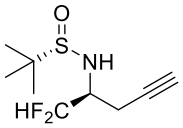
For the next asymmetric propargylation, a solution of the corresponding fluorinated imine **1** (1 mmol) in THF (0.1M) was cooled at -78 °C. The Grignard reagent freshly prepared (2.5 mmol) was added slowly and the reaction mixture was stirred at this temperature until the reaction was complete (TLC analysis, 2-3h). The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by column chromatography (*n*-hexane:AcOEt).

(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfinamide (2a)



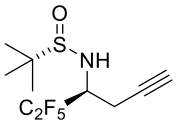
By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 31 mg (0.15 mmol) of **1a**, 22 mg of **2a** were obtained as a yellowish solid (87%, *dr* 96:4); $[\alpha]_D^{25}$ = +16.6 (*c* 1.0; $CHCl_3$); Mp: 55 - 57 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.08 (t, *J* = 2.7 Hz, 1H), 2.61 - 2.68 (m, 2H) 3.81 - 3.93 (m, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -74.97 (d, *J* = 6.4 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 22.4, 56.0 (q, $^2J_{CF}$ = 55.8 Hz), 57.4, 72.1, 77.6, 124.5 (q, $^1J_{CF}$ = 280.0 Hz). HRMS (ESI) calculated for $C_9H_{14}F_3NOS$ (M+H): 242.0821; found: 242.0821.

(*S*)-*N*-((*S*)-1,1-Difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfinamide (2e)



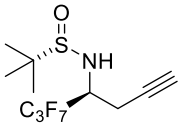
By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 44 mg (0.24 mmol) of **1d**, 33 mg of **2d** were obtained as a yellow oil (60%, *dr* 95:5); $[\alpha]_D^{25}$ = +23.5 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.57 - 2.62 (m, 2H), 3.60 - 3.75 (m, 2H), 6.02 (td, *J* = 55.3, 2.7 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 128.6 (ddd, J_{FF} = 286 Hz, $^1J_{FH}$ = 55.4 Hz, $^2J_{FH}$ = 7.8 Hz, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 22.5, 56.5 (t, $^2J_{CF}$ = 24 Hz), 56.9, 71.4, 78.6, 114.8 (t, $^1J_{CF}$ = 245 Hz). HRMS (ESI) calculated for $C_9H_{15}F_2NOS$ (M+H): 224.0915; found: 224.0916.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1,2,2-pentafluorohex-5-yn-3-yl)propane-2-sulfinamide (2f)



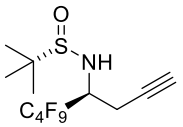
By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 100 mg (0.4 mmol) of **1e**, 72 mg of **2e** were obtained as a white solid (65%, *dr* 98:2); $[\alpha]_D^{25}$ = +20.4 (*c* 1.0; $CHCl_3$); Mp: 43 – 44 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.09 (t, *J* = 2.7 Hz, 1H), 2.59 - 2.80 (m, 2H), 3.91 - 4.00 (m, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 80.9 (s, 3F), -119.0 (d, *J* = 275.7 Hz, 1F), -122.0 (d, *J* = 275.7 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 22.4, 54.7 (t, $^2J_{CF}$ = 23.2 Hz), 57.5, 72.3, 77.6, 109 - 126 (C_2F_5 group). HRMS (ESI) calculated for $C_{10}H_{14}F_5NOS$ (M+NH_4): 309.1056; found: 309.1056.

(*S*)-2-Methyl-*N*-((*S*)-1,1,1,2,2,3,3-heptafluorohex-6-yn-3-yl)propane-2-sulfinamide (2g)



By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 300 mg (0.99 mmol) of **1f**, 202 mg of **2f** were obtained as a colourless oil (60% 53%, *dr* 97:3); $[\alpha]_D^{25}$ = +14.9 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.10 (t, *J* = 2.6 Hz, 1H), 2.72 (qdd, *J* = 16.9, 6.5, 2.8 Hz, 2H), 3.92 - 4.08 (m, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 80.6 – - 80.7 (t, *J* = 10.7 Hz, 3F), - 114.5 – - 120.5 (m, 2F), - 123.7 – -125.9 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.5, 55.2 (t, $^2J_{CF}$ = 22.8 Hz), 57.6, 72.3, 77.6, 108.6 – 119.9 (C_3F_7 group). HRMS (ESI) calculated for $C_{11}H_{14}F_7NOS$ (M+NH_4): 359.1020; found: 359.1023.

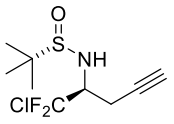
(*S*)-2-Methyl-*N*-((*S*)-1,1,1,2,2,3,3,4,4-nonafluorohex-7-yn-3-yl)propane-2-sulfinamide (2h)



By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 130 mg (0.37 mmol) of **1g**, 85 mg of **2g** were obtained as a white solid (60%, *dr* 99:1); $[\alpha]_D^{25}$ = +12.9 (*c* 1.0; $CHCl_3$); Mp: 63 – 65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.10 (t, *J* = 2.7 Hz, 1H), 2.72 (m, 2H), 3.95 (d, *J* = 9.8 Hz, 1H), 4.03 - 4.09 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 80.8 – - 80.9 (m, 3F), - 113.9 – - 119.9 (m, 2F), - 121.5 – - 121.5 (m, 2F), - 125.9 – - 126.2 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.5, 55.3 (t,

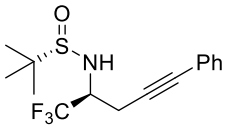
$^2J_{CF}$ = 22.5 Hz), 57.6, 72.3, 77.6, 107.6 - 119.6 (C_4F_9 group). HRMS (ESI) calculated for $C_{12}H_{14}F_9NOS$ (M+NH_4): 392.0730; found: 392.0725.

(*S*)-*N*-((*S*)-1-Chloro-1,1-difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfinamide (2i)



By means of general procedure **II** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (3:1)], from 200 mg (0.92 mmol) of **1h**, 176 mg of **2h** were obtained as a white solid (74%, *dr* 96:4); $[\alpha]_D^{25}$ = +3.7 (*c* 1.0; $CHCl_3$); Mp: 62 – 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 2.05 (t, *J* = 3.0 Hz, 1H), 2.53 – 2.76 (m, 2H), 3.82 – 3.92 (m, 1H), 3.97 – 4.04 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -59.3 (dd, *J* = 163.7, 5.6 Hz, 1F), -60.0 (dd, *J* = 163.7, 8.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 22.5, 57.6, 61.9 (t, $^2J_{CF}$ = 26.4 Hz), 72.2, 78.0, 128.7 (t, $^1J_{CF}$ = 298.9 Hz). HRMS (ESI) calculated for $C_9H_{14}ClF_2NOS$ (M+H): 258.0525; found: 258.0527.

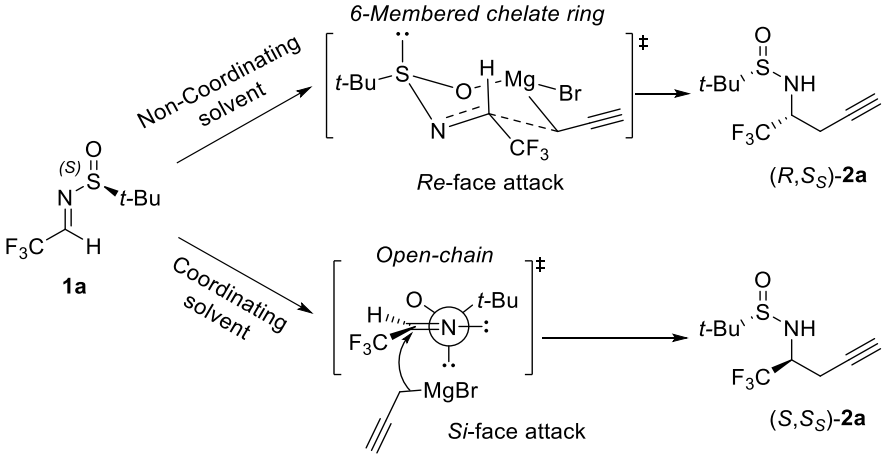
(*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-5-phenylpent-4-yn-2-yl)propane-2-sulfinamide (2j)



By means of general procedure **II** but heating at 75 °C for the addition step, and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (20:1)], from 50 mg (0.25 mmol) of **1a**, 42 mg of **2i** were obtained as a yellowish oil mixed in a 11:1 relationship with compound **2i'** (70%); $[\alpha]_D^{25}$ = +8.1 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.79 - 3.00 (qd, *J* = 17.3, 4.6 Hz, 2H), 3.88 - 4.02 (m, 2H), 7.29 -7.39 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -74.9 (d, *J* = 6.3 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 22.4, 56.5 (q, $^2J_{CF}$ = 31.0 Hz), 57.4, 82.9, 83.9, 122.7, 124.5 (q, $^1J_{CF}$ = 280.0 Hz), 128.3, 128.8, 131.6. HRMS (ESI) calculated for (M+H): 242.0821; found: 242.0821.

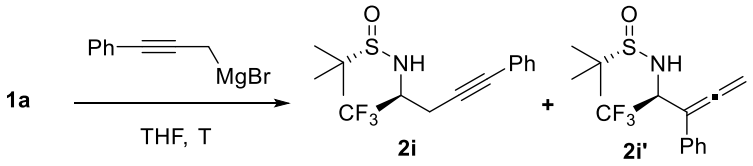
II.1 Solvent effects in the propargylation reaction

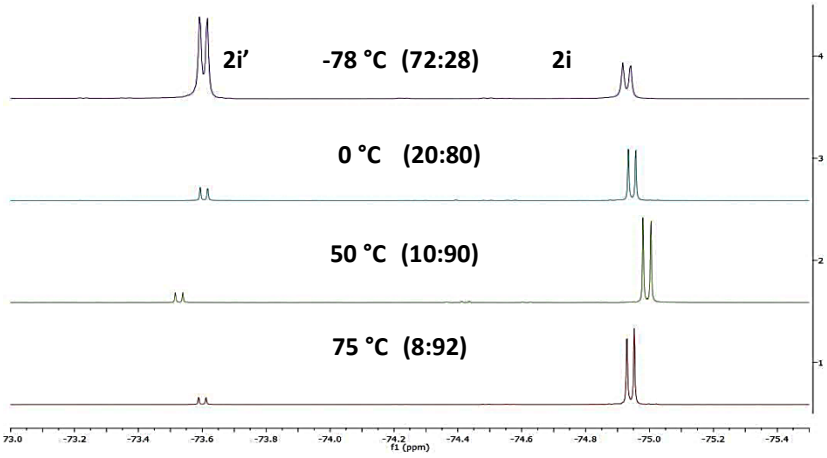
In non-coordinating solvents (DCM) the reaction takes place via a 6-membered chelate transition state, whereas in coordinating solvents (THF) this is disrupted and an open-chain transition state dominates (Scheme S1). We suspect that the open-chain transition state is preferred over the 6-membered ring for our substrates, although in DCM the two pathways compete and lower the diastereoselectivity of the reaction.



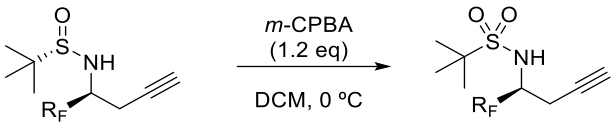
Scheme S1

II.2 Effect of temperature on 2i : 2i' selectivity





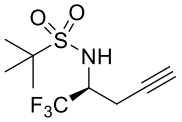
III. General procedure for the oxidation to sulfonamides 3.



2a,d-k **3a,d-k**

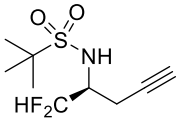
To a solution of corresponding *t*-butylsulfinylamides **2** (0.4 mmol) in DCM (0.1M) at 0 °C, *m*-CPBA was added (0.48 mmol) and the reaction mixture was stirred at toom temperature (TLC analysis, 1h), quenched with a saturated solution of $NaHCO_3$ aq. and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. Products **3** were purified by column chromatography (*n*-hexane:AcOEt).

(*S*)-2-Methyl-*N*-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamide (3a)



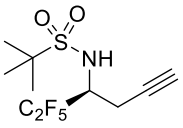
By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 442 mg (1.83 mmol) of **2a**, 386 mg of **3a** were obtained as a white solid (82%); $[\alpha]_D^{25}$ = +32.6 (*c* 1.0; $CHCl_3$); Mp: 55 - 57 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.16 (t, *J* = 2.7 Hz, 1H), 2.75 (qdd, *J* = 17.5, 5.3, 2.7 Hz, 2H), 4.06 - 4.12 (m, 1H), 4.77 (d, *J* = 10.5 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -74.1 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1, 24.0, 53.8 (q, $^2J_{CF}$ = 31.0 Hz), 60.9, 73.1, 84.1, 124.3 (q, $^1J_{CF}$ = 283.0 Hz). HRMS (ESI) calculated for $C_9H_{14}F_3NO_2S$ (M+H): 275.1035; found: 275.1036.

(*S*)-*N*-(1,1-Difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (3e)



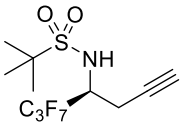
By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 73 mg (0.33 mmol) of **2d**, 49 mg of **3d** were obtained as a white solid (63%). $[\alpha]_D^{25}$ = +14.6 (*c* 1.0; $CHCl_3$); Mp: 58 - 61 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.13 (t, *J* = 2.7 Hz, 1H), 2.65 (dd, *J* = 6.3, 2.6 Hz, 2H), 3.77 - 3.88 (m, 1H), 4.51 (d, *J* = 10.2 Hz, 1H), 6.01 (td, *J* = 55.4, 2.7 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 128.5 (ddd, J_{FF} = 286 Hz, $^1J_{FH}$ = 55 Hz, $^2J_{FH}$ = 8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.1, 29.7, 54.5 (t, $^2J_{CF}$ = 23.1 Hz), 60.9, 72.4, 78.1, 114.4 (t, $^1J_{CF}$ = 246.0 Hz). HRMS (ESI) calculated for $C_9H_{15}F_2NO_2S$ (M+NH_4): 257.1130; found: 257.1137.

(*S*)-2-Methyl-*N*-(1,1,1,2,2-pentafluorohex-5-yn-3-yl)propane-2-sulfonamide (3f)



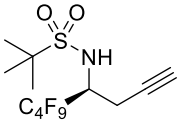
By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 138 mg (0.47 mmol) of **2e**, 118 mg of **3e** were obtained as a white solid (81%); $[\alpha]_D^{25}$ = +28.4 (*c* 1.0; $CHCl_3$); Mp: 54 – 55 °C . ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.17 (t, *J* = 2.7 Hz, 1H), 2.76 - 2.88 (m, 2H), 4.14 - 4.24 (m, 1H), 4.72 (d, *J* = 10.2 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -81.4 (s, 3F), -119.1 – -121.4 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1, 24.0, 52.0 (t, $^2J_{CF}$ = 23.0 Hz), 61.0, 73.2, 76.5, 109 – 125 (C_2F_5 group). HRMS (ESI) calculated for $C_{10}H_{14}F_5NO_2S$ (M+H): 325.1001; found: 325.1004.

(*S*)-*N*-(5,5,6,6,7,7,7-Heptafluorohept-1-yn-4-yl)-2-methylpropane-2-sulfonamide (3g)



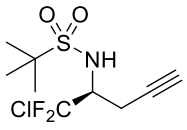
By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 180 mg (0.53 mmol) of **2f**, 154 mg of **3f** were obtained as a colourless oil (82%); $[\alpha]_D^{25}$ = +19.2 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.17 (t, *J* = 2.7 Hz, 1H), 2.83 (qdd, *J* = 17.1, 5.1, 2.3 Hz, 2H), 4.19 - 4.34 (m, 1H), 4.68 (d, *J* = 10.5 Hz). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 80.7 – - 80.8 (m, 3F), - 114.6 – - 119.5 (m, 2F), - 125.0 – - 125.1 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 24.0, 52.4 (t, $^2J_{CF}$ = 22.7 Hz), 61.0, 73.2, 76.5, 104.9 - 123.7 (C_3F_7 group). HRMS (ESI): It decomposes.

(S)-2-Methyl-*N*-(5,5,6,6,7,7,8,8,8-nonafluorooct-1-yn-4-yl)propane-2-sulfonamide (3h)



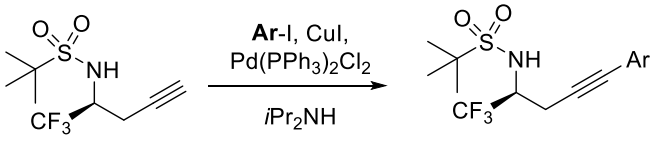
By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 85 mg (0.22 mmol) of **2g**, 73 mg of **3g** were obtained as a colourless oil (83%). $[\alpha]_D^{25}$ = +21.4 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.18 (t, *J* = 2.7 Hz, 1H), 2.73 - 2.96 (m, 2H), 4.21 - 4.33 (m, 1H), 4.62 (d, *J* = 10.6 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 80.9 – - 80.9 (m, 3F), - 113.9 – - 118.8 (m, 2F), - 121.7 – - 121.7 (m, 2F), - 125.9 – - 126.1 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.3, 24.0, 52.4 (t, $^2J_{CF}$ = 22.1 Hz), 61.0, 73.2, 76.5, 107.4 - 123.5 (C_4F_9 group). HRMS (ESI): It decomposes.

(*S*)-*N*-(1-Chloro-1,1-difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (3i)



By means of general procedure **III** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (7:1)], from 175 mg (0.68 mmol) of **2h**, 156 mg of **3h** were obtained as a white solid (84%). $[\alpha]_D^{25}$ = +13.3 (*c* 1.0; $CHCl_3$); Mp: 73 - 74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.19 (t, *J* = 3.0 Hz, 1H), 2.76 – 2.94 (m, 2H), 4.19 (br, 1H), 4.50 (br, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -58.3 (dd, *J* = 164.0, 5.6 Hz, 1F), -59.0 (dd, *J* = 164.0, 8.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 244.2, 58.5 (t, $^2J_{CF}$ = 26.4 Hz), 61.1, 73.4, 76.7, 128.3 (t, $^1J_{CF}$ = 297.5 Hz). HRMS (ESI) calculated for $C_9H_{14}ClF_2NO_2S$ ($M+NH_4$): 291.0740; found: 291.0746.

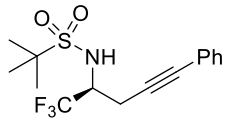
IV. General procedure for the Sonogashira coupling.



3a **3i-k**

CuI (8 mmol%), $Pd(PPh_3)_2Cl_2$ (4 mmol%) in iPr_2NH as solvent (0.06 M) were stirred at room temperature for 10 min. To this solution at 50 °C, sulfonamide **3a** (0.3 mmol) in $^iPr_2NH$ (0.06 M) was added slowly for 1h (slow addition pump). At this time, the reaction mixture was heated at 50 °C and stirred for 2h. The reaction was quenched with a saturated solution of NH_4Cl and extracted with AcOEt. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by column chromatography (*n*-hexane:AcOEt).

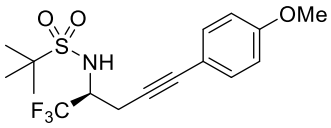
(*S*)-2-Methyl-*N*-(1,1,1-trifluoro-5-phenylpent-4-yn-2-yl)propane-2-sulfonamide (3j)



By means of general procedure **IV** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 100 mg (0.39 mmol) of **3a**, 68 mg of **3i** were obtained as a white solid (52%); $[\alpha]_D^{25}$ = +42.0 (*c* 1.0; $CHCl_3$); Mp: 71 - 73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.00 (qd, *J* = 17.2, 5.5 Hz, 2H), 4.12 - 4.26 (m, 1H), 4.51 (d, *J* = 10.6 Hz, 1H),

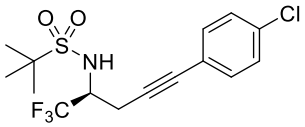
7.30 - 7.45 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ - 74.2 (d, *J* = 7.1 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2, 24.1, 54.1 (q, $^2J_{CF}$ = 30.0 Hz, CH), 61.0, 77.2, 81.5, 84.9, 124.4 (q, $^1J_{CF}$ = 286.3 Hz), 128.3, 128.5, 131.8. HRMS (ESI) calculated for $C_{15}H_{18}F_3NO_2S$ (M+NH_4): 351.1355; found: 351.1349.

(*S*)-2-Methyl-*N*-(1,1,1-trifluoro-5-(4-methoxyphenyl)pent-4-yn-2-yl)propane-2-sulfonamide (3k)



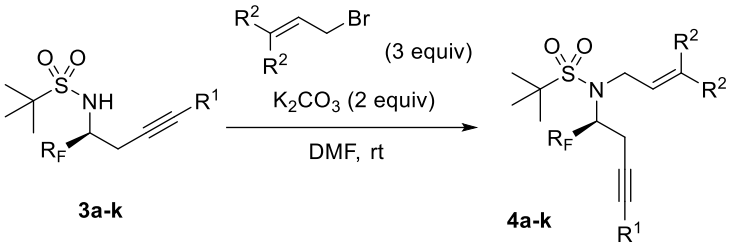
By means of general procedure **IV** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 150 mg (0.58 mmol) of **3a**, 116 mg of **3j** were obtained as a white solid (55%); $[\alpha]_D^{25}$ = +31.6 (*c* 1.0; $CHCl_3$); Mp: 101 – 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.98 (ddd, *J* = 23.0, 17.2, 5.2 Hz, 2H), 3.80 (s, 3H), 4.12 - 4.21 (m, 1H), 4.55 (d, *J* = 10.3 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -74.2 (d, *J* = 7.2 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1, 24.1, 54.2 (q, $^2J_{CF}$ = 30.3 Hz), 55.3, 60.9, 80.1, 84.8, 114.0, 114.6, 124.4 (q, $^1J_{CF}$ = 282.4 Hz), 133.2, 159.7. HRMS (ESI) calculated for $C_{16}H_{20}F_3NO_3S$ (M+NH_4): 381.1452; found: 381.1454.

(*S*)-*N*-(5-(4-Chlorophenyl)-1,1,1-trifluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (3l)



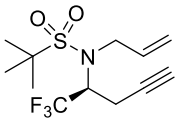
By means of general procedure **IV** and purification by flash chromatography of the reaction crude [*n*-hexane: AcOEt (8:1)], from 30 mg (0.12 mmol) of **3a**, 28 mg of **3k** were obtained as a white solid (65%); $[\alpha]_D^{25}$ = +33.5 (*c* 1.0; $CHCl_3$); Mp: 97 – 99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.91 (ddd, *J* = 23.2, 17.6, 5.2 Hz, 2H), 4.07-4.46 (m, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -74.19 (d, J_{FH} = 6.7 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2, 24.1, 54.2 (q, $^2J_{CF}$ = 30.6 Hz), 61.0, 82.7, 83.8, 121.0, 124.4 (q, $^1J_{CF}$ = 282.6 Hz), 128.7, 133.0, 134.6. HRMS (ESI) calculated for $C_{15}H_{17}ClF_3NO_2S$ (M+NH_4): 385.0954; found: 385.0959.

V. General procedure for the *N*-allylation of sulfonamides 3.



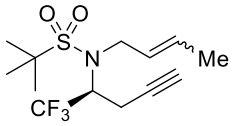
Sulfonamide **3** (0.3 mmol) was dissolved in DMF (0.1M) in a round-bottomed flask at room temperature, and then potassium carbonate (0.6 mmol) was added. After stirring, corresponding alkyl bromide (0.9 mmol) was added and the mixture was stirred at room temperature (5-12 h). When the reaction finished (TLC analysis), was quenched with a saturated solution of NH_4Cl aq. and extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by column chromatography (*n*-hexane:AcOEt).

(*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamide (4a)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 276 mg (0.93 mmol) of **3a**, 280 mg of **4a** were obtained as a colourless oil (92%). $[\alpha]_D^{25}$ = -31.5 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.14 (t, *J* = 2.7 Hz, 1H), 2.79 - 2.82 (m, 2H), 3.93 - 4.13 (m, 2H), 4.50 - 4.55 (m, 1H), 5.13 - 5.25 (m, 2H), 5.94 - 6.07 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.3 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 24.7, 49.6, 59.3 (q, $^2J_{CF}$ = 29.3 Hz), 63.0, 72.5, 78.0, 118.0, 124.6 (q, $^1J_{CF}$ = 282.0 Hz), 135.6. HRMS (ESI) calculated for $C_{12}H_{18}F_3NO_2S$ (M+NH_4): 315.1355; found: 315.1349.

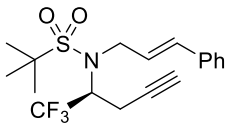
(*S*)-*N*-(But-2-en-1-yl)-2-methyl-N-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamide (4b)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 45 mg (0.17 mmol) of **3a**, 47.1 mg of **4b** were obtained as a colourless oil (93%), as mixture E:Z (4:1) (technical grade of reagent *trans*-1-bromo-2-

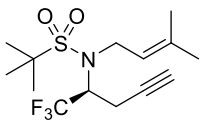
butene was 85%). $[\alpha]_D^{25}$ = -48.3 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H, *major*.), 1.44 (s, 9H, *minor*.), 1.64 (d, *J* = 6.0 Hz, 3H, *minor*.), 1.68 (d, *J* = 3.0 Hz, 3H, *major*.), 2.14 (t, *J* = 3.0 Hz, 1H), 2.72 – 2.68 (m, 2H), 33.833 – 4.07 (m, 2H), 4.46 – 4.60 (m, 1H), 5.56 – 5.70 (m, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.2 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7 (CH_3, *minor*.), 17.6 (CH_3, *major*.), 19.1 (CH_2, *minor*.), 19.6 (CH_2, *major*.), 24.7 ($3CH_3$, *minor*.), 24.8 ($3CH_3$, *major*.), 43.6 (CH_2, *minor.*), 49.0 (CH_2, *major*.), 59.3 (q, $^2J_{CF}$ = 30.9 Hz), 63.0, 72.3 (*major*.), 72.5 (*minor*.), 77.2 (*minor*.), 78.1 (*major*.), 124.7 (q, $^1J_{CF}$ = 286.1 Hz), 126.8 (*minor*.), 127.6 (*minor*.), 128.2 (*major*.), 129.7 (*major*.). HRMS (ESI) calculated for $C_{13}H_{20}F_3NO_2S$ ($M+NH_4$): 329.1505; found: 329.1510.

(*S*)-2-Methyl-*N*-(3-phenylallyl)-N-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamide (4c)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 60 mg (0.23 mmol) of **3a**, 72.5 mg of **4c** were obtained as a colourless oil (84%). $[\alpha]_D^{25}$ = -34.5 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.11 (t, *J* = 2.7 Hz, 1H), 2.68 – 2.87 (m, 2H), 4.01 (dd, *J* = 16.6, 7.9 Hz, 1H), 4.22 (ddd, *J* = 16.6, 5.6, 1.5 Hz, 1H), 4.45 – 4.58 (m, 1H), 6.22 – 6.32 (m, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 7.15 – 7.32 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.3 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.5, 24.9, 49.3, 59.3 (q, $^2J_{CF}$ = 30.1 Hz), 63.2, 72.6, 78.0, 122.8, 123.0-129.1 (CF_3 group), 126.6, 128.1, 128.7, 133.1, 136.2. HRMS (ESI) calculated for $C_{18}H_{22}F_3NO_2S$ ($M+NH_4$): 391.1662; found: 391.1669.

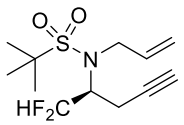
(*S*)-2-Methyl-N-(3-Methylbut-2-en-1-yl)-N-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamid (4d)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (6:1)], from 60 mg (0.23 mmol) of **3a**, 72.6 mg of **4c** were obtained as a colourless oil (97%). $[\alpha]_D^{25}$ = -34.2 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.63 (s, 3H), 1.71 (s, 3H), 2.14 (t, *J* = 2.7 Hz, 1H), 2.75 – 2.80 (m, 2H), 4.00 (d, *J* = 6.6 Hz, 2H), 4.48 – 4.60 (m, 1H), 5.35 (t, *J* = 6.4 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.5 (s, 3F). ^{13}C NMR (75.5

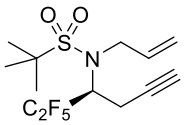
MHz, $CDCl_3$) δ 17.6, 19.2, 24.7, 25.7, 44.9, 59.3 (q, $^2J_{CF}$ = 29.8 Hz), 62.9, 72.3, 77.2, 121.8, 124.7 (q, $^1J_{CF}$ = 285.3 Hz, C), 135.0. HRMS (ESI) calculated for $C_{14}H_{22}F_3NO_2S$ (M+NH_4): 325.1323; found: 391.1669.

(*S*)-*N*-Allyl-*N*-(1,1-difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (4e)



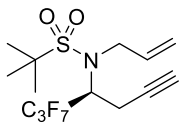
By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 29 mg (0.12 mmol) of **3d**, 18 mg of **4d** were obtained as a colourless oil (53%). $[\alpha]_D^{25}$ = -16.0 (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.13 (t, *J* = 2.65 Hz, 1H), 2.72 - 2.76 (m, 2H), 4.03 - 4.12 (m, 3H), 5.14 - 5.26 (m, 2H), 5.88 - 6.01 (m, 1H), 6.12 (td, *J* = 55.3 Hz, 2.8 Hz, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -119.3 – -128.11 (m, 2F).^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.8, 29.7, 49.9, 59.4 (t, $^2J_{CF}$ = 24.0 Hz), 62.9, 72.2, 79.4, 115.8 (t, $^1J_{CF}$ = 247.0 Hz), 118.1, 135.9. HRMS (ESI) calculated for $C_{12}H_{19}F_2NO_2S$ (M+NH_4): 297.1452; found: 297.1443.

(*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1,2,2-pentafluorohex-5-yn-3-yl)propane-2-sulfonamide (4f)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 140 mg (0.46 mmol) of **3e**, 108 mg of **4e** were obtained as a colourless oil (70%). $[\alpha]_D^{25}$ = -18.6 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.18 (t, *J* = 2.6 Hz, 1H), 2.64 (d, *J* = 18.0 Hz, 1H), 2.89 - 2.99 (m, 1H), 4.06 (ddd, *J* = 23.4, 16.7, 7.1 Hz, 2H), 4.68 (dd, *J* = 21.4, 8.4 Hz, 1H), 5.14 - 5.26 (m, 2H), 6.01 - 6.14 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -83.1 (s, 3F), -112.3 – -113.3 (m, 1F), -119.8 – -120.9 (m, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9, 24.8, 50.0, 57.1 (t, $^2J_{CF}$ = 22.0 Hz), 63.3, 73.0, 78.4, 112.8 - 124.6 (C_2F_5 group), 118, 135.5. HRMS (ESI) calculated for $C_{13}H_{18}F_5NO_2S$ (M+NH_4): 365.1313; found: 365.1317.

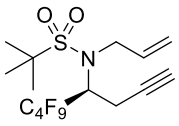
(*S*)-*N*-Allyl-*N*-(5,5,6,6,7,7,7-heptafluorohept-1-yn-4-yl)-2-methylpropane-2-sulfonamide (4g)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 154 mg (0.43 mmol) of **3f**, 90 mg of **4f** were obtained as a colourless oil

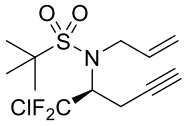
(55%). $[\alpha]_D^{25}$ = -18.6 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.19 (t, *J* = 2.6 Hz, 1H), 2.64 (d, *J* = 18.1 Hz, 1H), 2.96 (ddd, *J* = 17.7, 10.9, 2.3 Hz, 1H), 4.07 (ddd, *J* = 23.1, 17.0, 6.5 Hz, 2H), 4.79 (ddd, *J* = 23.4, 10.7, 3.5 Hz, 1H), 5.20 (dd, *J* = 23.4, 17.0 Hz, 1H), 6.02 - 6.15 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -80.4 (t, *J* = 10.9 Hz, 3F), -108.7 – -117.6 (m, 2F), -124.1 – -126.2 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.0, 24.8, 49.9, 57.1 (t, $^2J_{CF}$ = 20.4 Hz), 63.2, 73.0, 78.4, 104.8 - 123.7 (C_3F_7 group), 117.9, 135.5. HRMS (ESI) calculated for $C_{14}H_{18}F_7NO_2S$ (M+H): 415.1281; found: 415.1285.

(*S*)-*N*-Allyl-2-methyl-*N*-(5,5,6,6,7,7,8,8,8-nonafluorooct-1-yn-4-yl)propane-2-sulfonamide (4h)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 74 mg (0.18 mmol) of **3g**, 67 mg of **4g** were obtained as a colourless oil (82%). $[\alpha]_D^{25}$ = -10.7 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.19 (t, *J* = 2.6 Hz, 1H), 2.65 (d, *J* = 17.8 Hz, 1H), 2.97 (ddd, *J* = 17.8, 11.0, 2.6 Hz, 1H), 4.08 (ddd, *J* = 24.0, 16.9, 6.2 Hz, 2H), 4.81 (ddd, *J* = 24.2, 11.0, 3.8 Hz, 1H) 5.20 (dd, *J* = 22.9, 17.3 Hz, 2H), 6.03-6.16 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -80.9 (t, *J* = 9.7 Hz, 3F), -108.1 – -117.0 (m, 2F), -120.5 – -124.1 (m, 2F), -125.9 – -126.0 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.1, 24.9, 49.9, 57.3 (t, $^2J_{CF}$ = 20.3 Hz), 63.3, 73.0, 78.5, 107.9-126.2 (C_4F_9 group), 118.0, 135.5. HRMS (ESI) calculated for $C_{15}H_{18}F_9NO_2S$ (M+NH_4): 465.1250; found: 465.1253.

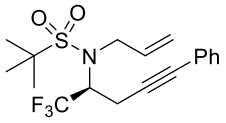
(*S*)-*N*-Allyl-*N*-(1-chloro-1,1-difluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (4i)



By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (4:1)], from 156 mg (0.57 mmol) of **3h**, 138 mg of **4h** were obtained as a colourless oil (77%). $[\alpha]_D^{25}$ = -24.9 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.15 (t, *J* = 2.7 Hz, 1H), 2.88 (dd, *J* = 7.6, 2.7 Hz, 2H), 3.94 (dd, *J* = 16.8, 7.5 Hz, 1H), 4.09 (dd, *J* = 16.8, 5.5 Hz, 1H), 4.60 – 4.67 (m, 1H), 5.13 (dd, *J* = 10.3, 1.3 Hz, 1H), 5. 17 (dd, *J* = 22.9, 1.3 Hz, 1H), 5.95 – 6.08 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -53.2 - -54.6 (m, 1F), -55.4 (dd, *J* = 161.7, 10.7 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.5, 24.9, 49.6, 63.3, 64.7 (t, $^2J_{CF}$ = 23.7

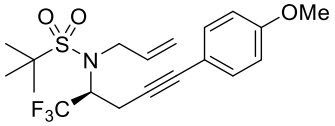
Hz), 72.7, 78.5, 117.9, 128.2 (t, $^{1}J_{CF}$ = 301.7 Hz), 135.6. HRMS (ESI) calculated for $C_{12}H_{18}ClF_2NO_2S$ (M+NH_4): 331.1053; found: 331.1063.

(*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluoro-5-phenylpent-4-yn-2-yl)propane-2-sulfonamide (4j)



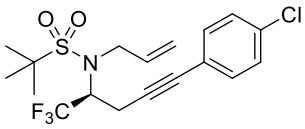
By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 50 mg (0.15 mmol) of **3i**, 48 mg of **4i** were obtained as a colourless oil (86%). $[\alpha]_D^{25}$ = -50.2 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.96 - 3.13 (m, 2H), 4.08 (ddd, *J* = 24.1, 16.7, 6.5 Hz, 2H), 4.58 - 4.70 (m, 1H), 5.16 - 5.29 (m, 2H), 6.01 - 6.14 (m, 1H), 7.29 - 7.45 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.3 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 24.8, 49.7, 59.5 (q, $^{2}J_{CF}$ = 31.2 Hz), 63.0, 83.4, 84.3, 118.0, 122.8, 127.8 (q, $^{1}J_{CF}$ = 121.0 Hz), 128.3, 128.7, 131.6, 135.8. HRMS (ESI) calculated for $C_{18}H_{22}F_3NO_2S$ (M+NH_4): 315.1355; found: 315.1349.

(*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluoro-5-(4-methoxyphenyl)pent-4-yn-2-yl)propane-2-sulfonamide (4k)



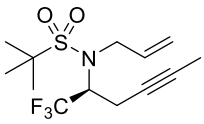
By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 28 mg (0.08 mmol) of **3j**, 32 mg of **4j** were obtained as a colourless oil (99%). $[\alpha]_D^{25}$ = -41.0 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.93 - 3.10 (m, 2H), 3.80 (s, 3H), 4.07 (ddd, *J* = 22.7, 16.7, 5.9 Hz, 2H), 4.55 - 4.68 (m, 1H), 5.21 (ddd, *J* = 27.1, 17.1, 1.3 Hz, 2H), 6.00 - 6.13 (m, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.4 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9, 24.8, 49.7, 55.3, 59.6 (q, $^{2}J_{CF}$ = 28.8 Hz), 63.1, 81.9, 84.2, 114.0, 115.0, 118.0, 124.7 (q, $^{1}J_{CF}$ = 285.2 Hz), 133.0, 135.8, 159.6. HRMS (ESI) calculated for $C_{19}H_{24}F_3NO_3S$ (M+NH_4): 421.1765; found: 421.1767.

(*S*)-*N*-Allyl-*N*-(5-(4-chlorophenyl)-1,1,1-trifluoropent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (4l)



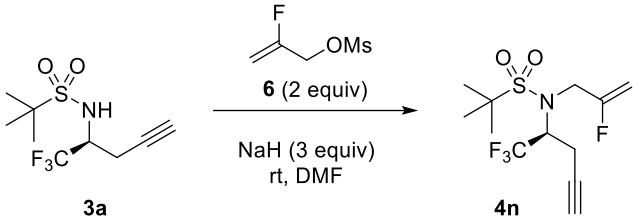
By means of general procedure **V** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 40 mg (0.11 mmol) of **3k**, 40 mg of **4k** were obtained as a colourless oil (97%). $[\alpha]_D^{25}$ = -64.6 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.02 (qd, *J* = 17.4, 12.7 Hz, 2H), 3.96 (dd, *J* = 16.7, 7.8 Hz, 1H), 4.15 (dd, *J* = 16.7, 5.3 Hz, 1H), 4.60 - 4.68 (m, 1H), 5.18 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.3 Hz, 1H), 6.05 - 6.07 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.3 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2, 24.8, 49.8, 59.5 (q, $^2J_{CF}$ = 29.3 Hz), 63.1, 83.2, 84.4, 118.1, 121.4, 124.8 (q, $^1J_{CF}$ = 285.3 Hz), 128.7, 132.9, 134.3, 135.8. HRMS (ESI) calculated for $C_{18}H_{21}ClF_3NO_2S$ (M+H): 408.0934; found: 408.0938.

(*S*)-*N*-Allyl-2-methyl-N-(1,1,1-trifluorohex-4-yn-2-yl)propane-2-sulfonamide (4m)



A solution lithium bis(trimethylsilyl)amide (1 M in THF, 0.34 mL, 0.336 mmol) was added dropwise to a solution of compound **4a** (50 mg, 0.168 mmol) in THF (0.4 mL) at -78 °C. After 20 min, MeI (52 uL, 0.84 mmol) was added at -78 °C and after further 10 min of stirring, the temperature was increased to -40 °C and the mixture was stirred for 12 h. After this time, the solvent was removed and the resulting crude was purified by flash chromatography [*n*-hexane:AcOEt (20:1)] and 35 mg of **4m** were obtained as a white solid (83%). $[\alpha]_D^{25}$ = -26.7 (*c* 1.0; $CHCl_3$). Mp: 42-44 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.77 (t, *J* = 2.6 Hz, 3H), 2.68 - 2.75 (m, 2H), 3.90 – 4.08 (m, 2H), 4.40 – 4.52 (m, 1H), 5.10 -5.22 (m, 2H), 5.91 – 6.05 (m, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.6 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.5, 19.0, 24.8, 49.1, 59.6 (q, $^2J_{CF}$ = 29.3 Hz), 63.0, 80.1, 117.8, 119.1, 122.8, 126.6, 130.4, 135.7. HRMS (ESI) calculated for $C_{13}H_{20}F_3NO_2S$ (M+H): 311.1167; found: 411.0938.

VI. *N*-Fluoroallylation of sulfonamide 3a.



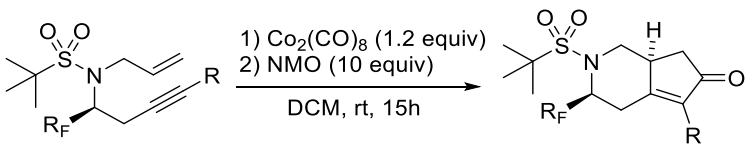
3a **4n**

To a solution of NaH (60%, 0.57 mmol) dissolved in DMF (0.1M) at 0 °C, sulfonamide **3a** was added slowly (0.19 mmol, 50 mg). The reaction mixture was stirred at this temperature for 15 minutes and 2-fluoroallyl methanesulfonate **6** was added (2 mmol). Finally, the reaction mixture was stirred at room temperature overnight. When the reaction finished (TLC analysis), was quenched with saturated solution of NH_4Cl aq. and extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by column chromatography [*n*-hexane:AcOEt (10:1)] to afford 33 mg of **4n** as a colourless oil (55%).

(S)-*N*-(2-Fluoroallyl)-2-methyl-N-(1,1,1-trifluoropent-4-yn-2-yl)propane-2-sulfonamide (4n)

$[\alpha]_D^{25}$ = -15.9 (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.16 (t, *J* = 2.7 Hz, 1H), 2.85 - 2.88 (m, 2H), 3.94 - 4.25 (m, 2H), 4.54 - 4.83 (m, 3H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.4 (s, 3F), -101.7 – -103.2 (m, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9, 24.6, 46.2 (d, $^2J_{CF}$ = 29.9 Hz), 59.5 (q, $^2J_{CF}$ = 29.9 Hz), 63.4, 72.5, 78.8, 95.6 (d, $^2J_{CF}$ = 17.8 Hz), 124.5 (q, $^1J_{CF}$ = 286.1 Hz), 160.5 (d, $^1J_{CF}$ = 260.6 Hz). HRMS (ESI) calculated for $C_{12}H_{17}F_4NO_2S$ ($M+NH_4$): 333.1252; found: 333.1254.

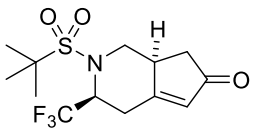
VII. Stoichiometric Pauson-Khand reaction of 4a-k to 5a-k.



4a-k **5a-k**

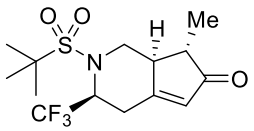
Sulfonamides **4** (0.1 mmol) were dissolved in DCM (0.1M) at room temperature in a round-bottomed flask. Then, octacarbonyl dicobalt complex was added (0.12 mmol) and after 2 hours the first stage was finished (TLC analysis). At this time, *N*-methylmorfoline-*N*-oxide (1 mmol) was added and the mixture was stirred overnight at room temperature. Once the reaction was finished (TLC analysis), solvent was removed and products **5** were purified by column chromatography (*n*-hexane:AcOEt).

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5a)



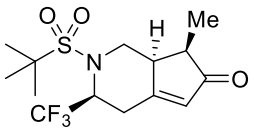
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 31 mg of **4a** (0.11 mmol), 22 mg of **5a** were obtained as a white solid (65%) $[\alpha]_D^{25}$ = -45.4 (*c* 1.0; $CHCl_3$). Mp: 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.93 (dd, *J* = 19.2, 2.5 Hz, 1H), 2.54 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.85 - 3.00 (m, 2H), 3.11 (d, *J* = 15 Hz, 2H), 4.04 - 4.11 (m, 1H), 4.67 - 4.78 (m, 1H), 6.05 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.4 (d, *J* = 7.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 29.4, 38.2, 40.2, 50.3, 55.6 (q, $^2J_{CF}$ = 36 Hz), 62.8, 125.1 (q, $^1J_{CF}$ = 286 Hz), 130.0, 174.2, 206.2. HRMS (ESI) calculated for $C_{13}H_{18}F_3NO_3S$ (M+H): 326.1029; found: 326.1021.

(*3S,7S,7aS*)-2-(*tert*-Butylsulfonyl)-7-methyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5b)



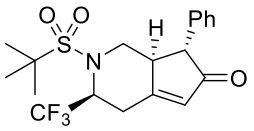
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 47 mg of **4b** (0.15 mmol), 20.3 mg of **5b** were obtained as a white solid (40 %). $[\alpha]_D^{25}$ = -49.8 (*c* 1.0; $CHCl_3$). Mp: 116 – 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.0 Hz, 3H), 1.43 (s, 9H), 1.93 (dq, *J* = 9.0, 3.0 Hz, 1H), 2.69 – 2.75 (m, 1H), 2.88 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.98 (dd, *J* = 15.0, 12.0 Hz, 1H), 3.10 (d, *J* = 15.0 Hz, 1H), 4.12 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.65 – 4.76 (m, 1H), 6.03 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.4 (d, *J* = 8.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 24.2, 29.3, 44.3, 48.5, 49.5, 55.4 (t, $^2J_{CF}$ = 30.9 Hz), 62.8, 125.2 (t, $^1J_{CF}$ = 285.4 Hz), 128.8, 171.6, 208.3. HRMS (ESI) calculated for $C_{14}H_{20}F_3NO_3S$ (M+H): 340.1189; found: 340.1197.

(*3S,7R,7aS*)-2-(*tert*-Butylsulfonyl)-7-methyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5b')



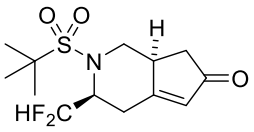
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (8:1)], from 47 mg of **4b** (0.15 mmol), 7.6 mg of **5b'** were obtained as a white solid (15 %). $[\alpha]_D^{25}$ = -23.6 (*c* 1.0; $CHCl_3$). Mp: 201 – 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.0 Hz, 3H), 1.44 (s, 9H), 2.51 – 2.61 (m, 1H), 2.89 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.03 – 3.21 (m, 3H), 3.95 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.65 – 4.76 (m, 1H), 6.06 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ – 68.5 (d, *J* = 8.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.9, 24.3, 29.7, 41.8, 43.2, 46.9, 55.6 (q, $^2J_{CF}$ = 30.9 Hz), 62.8, 125.1 (q, $^1J_{CF}$ = 285.4 Hz), 128.7, 173.0, 209.8. HRMS (ESI) calculated for $C_{14}H_{20}F_3NO_3S$ (M+H): 340.1189; found: 340.1198.

(*3S,7R,7aS*)-2-(*tert*-Butylsulfonyl)-7-phenyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5c)



By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 72.5 mg of **4c** (0.19 mmol), 38.8 mg of **5c** were obtained as a white solid (51 %). $[\alpha]_D^{25}$ = -127.0 (*c* 1.0; $CHCl_3$). Mp: 203 - 205 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.00 (d, *J* = 15.3, 7.4 Hz, 1H), 3.11 – 3.31 (m, 4H), 4.17 (dd, *J* = 13.5, 6.4 Hz, 1H), 4.70 – 4.81 (m, 1H), 6.14 (s, 1H), 7.13 – 7.37 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.3 (s, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 29.5, 48.8, 49.6, 55.5 (q, 2JCF = 31.2 Hz), 56.0, 62.8, 125.4 (q, 1JCF = 286.4 Hz), 127.5, 128.0, 128.8, 129.0, 136.9, 172.2, 205.1. HRMS (ESI) calculated for $C_{19}H_{22}F_3NO_3S$ (M+H): 402.1345; found: 402.1347.

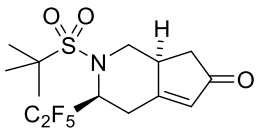
(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(difluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5e)



By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 30 mg of **4d** (0.11 mmol), 19.6 mg of **5d** were obtained as a white solid (58%). $[\alpha]_D^{25}$ = -70.3 (*c* 1.0; $CHCl_3$). Mp: 156 - 158 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.94 (dd, *J* = 16.2, 1.9 Hz, 1H), 2.55 (dd, J = 11.7, 6.8 Hz, 1H), 2.77 - 2.94 (m,

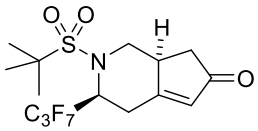
1H), 3.09 (d, *J* = 16 Hz, 2H), 4.05 - 4.11 (m, 1H), 4.32 - 4.41 (m, 1H), 5.90 (td, *J* = 51, 4.1 Hz, 1H), 6.04 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -123.6 (dd, *J* = 286, 55.2 Hz, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.4, 29.7, 38.3, 40.5, 50.4, 55.7 (t, $^2J_{CF}$ = 24.6 Hz), 62.3, 115.4 (t, $^1J_{CF}$ = 249 Hz), 129.8, 174.9, 206.1. HRMS (ESI) calculated for $C_{13}H_{19}F_2NO_3S$ (M+H): 308.1087; found: 308.1082.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoroethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5f)



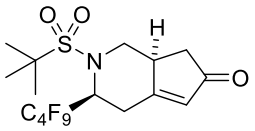
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 108 mg of **4e** (0.31 mmol), 55.8 mg of **5e** were obtained as a white solid (48%). $[\alpha]_D^{25}$ = -44.3 (*c* 1.0; $CHCl_3$). Mp: 124 – 126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.95 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.55 (dd, *J* = 18.6, 6.6 Hz, 1H), 2.91 - 3.17 (m, 4H), 4.09 (dd, *J* = 13.0, 5.4 Hz, 1H) 4.76 - 4.88 (m, 1H), 6.04 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -83.2 (s, 3F), -113.1 – -114.1 (m, 1F), -116.8 – -117.7 (m, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 30.3, 38.3, 40.4, 50.7, 53.9 (t, $^2J_{CF}$ = 19.9 Hz), 62.9, 114.5 - 121.0 (C_2F_5 group), 129.9, 173.9, 205.9. HRMS (ESI) calculated for $C_{14}H_{18}F_5NO_3S$ (M+NH_4): 393.1264; found: 393.1266.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoropropyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5g)



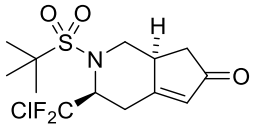
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 90 mg of **4f** (0.23 mmol), 48.8 mg of **5f** were obtained as a white solid (50%). $[\alpha]_D^{25}$ = -50.3 (*c* 1.0; $CHCl_3$). Mp: 130 – 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.94 (dd, *J* = 18.7, 2.8 Hz, 1H), 2.55 (dd, *J* = 18.7, 6.6 Hz, 1H), 2.90 - 3.14 (m, 4H), 4.10 (dd, *J* = 13.6, 6.1 Hz, 1H), 4.93 (dd, *J* = 25.8, 5.8 Hz, 1H), 6.03 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -80.3 (t, *J* = 10.8 Hz, 3F), -109.6 – -114.6 (m, 2F), -124.6 – -127.4 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 30.8, 38.2, 40.4, 50.7, 53.9 (t, $^2J_{CF}$ = 19.8 Hz), 62.9, 105.2 - 120.5 (C_3F_7 group), 129.9, 173.9, 205.9. HRMS (ESI) calculated for $C_{15}H_{18}F_7NO_3S$ (M+NH_4): 443.1233; found: 443.1234.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluorobutyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5h)



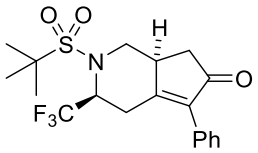
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 63 mg of **4g** (0.15 mmol), 30 mg of **5g** were obtained as a white solid (42%). $[\alpha]_D^{25}$ = -43.6 (*c* 1.0; $CHCl_3$). Mp: 133 – 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.95 (dd, *J* = 18.8, 2.8 Hz, 1H), 2.56 (dd, *J* = 18.8, 6.7 Hz, 1H), 2.91 - 3.15 (m, 4H), 4.11 (dd, *J* = 14.1, 6.4 Hz, 1H), 4.96 (dd, *J* = 25.6, 6.0 Hz, 1H), 6.04 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -80.8 – -80.9 (m, 3F), -108.9 – -113.9 (m, 2F), -121.1 – -124.2 (m, 2F), -125.8 – -125.9 (m, 2F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 30.8, 38.3, 40.5, 50.8, 54.1 (t, $^2J_{CF}$ = 19.1 Hz), 62.9, 107.8-120.3 (C_4F_9 group), 129.9, 173.9, 205.8. HRMS (ESI) calculated for $C_{16}H_{18}F_9NO_3S$ (M+NH_4): 493.1197; found: 493.1202.

(*3S,7aS*)-2-(*tert*-Butylsulfonyl)-3-(chlorodifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5i)



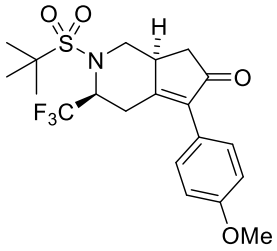
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (4:1)], from 138 mg of **4h** (0.44 mmol), 115.5 mg of **5h** were obtained as a colorless oil (77%). $[\alpha]_D^{25}$ = -16.5 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.91 (dd, *J* = 18.8, 2.7 Hz, 1H), 2.53 (dd, *J* = 18.8, 6.5 Hz, 1H), 2.88 – 3.00 (m, 2H), 3.11 – 3.16 (m, 1H), 3.30 (d, *J* = 15.3 Hz, 1H), 4.03 (dd, *J* = 13.7, 6.2 Hz, 1H), 4.71 – 4.81 (m, 1H), 6.03 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -53.5 (dd, *J* = 162.2, 8.0 Hz, 1F), -54.2 (dd, *J* = 162.2, 16.0 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.4, 30.0, 38.3, 40.1, 50.1, 61.0 (t, $^2J_{CF}$ = 23.7 Hz), 63.0, 129.2 (t, $^1J_{CF}$ = 300.4 Hz), 130.0, 174.1, 206.0. HRMS (ESI) calculated for $C_{13}H_{18}ClF_2NO_3S$ (M+H): 342.0737; found: 342.0746.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-5-phenyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5j)



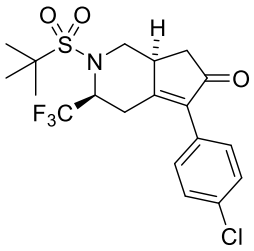
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 25 mg of **4i** (0.07 mmol), 18 mg of **5i** were obtained as a colourless oil (67%). $[\alpha]_D^{25}$ = -30.3 (*c* 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.09 (dd, *J* = 16.0, 2.8 Hz, 1H), 2.72 (dd, *J* = 12.0, 7.3 Hz, 1H), 2.90 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.01 - 3.09 (m, 1H), 3.18 - 3.29 (m, 2H), 4.14 (q, *J* = 6.2 Hz, 1H), 4.65 - 4.75 (m, 1H), 7.22 - 7.42 (m, 5H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.5 (d, J_{FH} = 8.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2, 27.9, 38.1, 38.7, 50.2, 55.3 (q, $^2J_{CF}$ = 31 Hz), 62.8, 125.2 (q, $^1J_{CF}$ = 288 Hz), 128.3, 128.6, 128.8, 130.0, 140.7, 166.6, 204.2. HRMS (ESI) calculated for $C_{19}H_{22}F_3NO_3S$ (M+NH_4): 419.1612; found: 419.1604.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-5-(4-methoxyphenyl)-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5k)



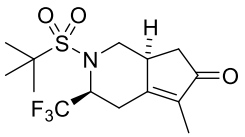
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 32 mg of **4j** (0.08 mmol), 24 mg of **5j** were obtained as a white solid (70%) $[\alpha]_D^{25}$ = -28.4 (*c* 1.0; $CHCl_3$). Mp: 61 - 63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.07 (dd, *J* = 18.9, 2.7 Hz, 1H), 2.70 (dd, *J* = 18.9, 6.7 Hz, 1H), 2.89 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.99 - 3.21 (m, 2H), 3.27 (d, *J* = 15.6 Hz, 1H), 3.82 (s, 3H), 4.13 (dd, *J* = 13.5, 6.1 Hz, 1H), 4.64 - 4.75 (m, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.6 (d, *J* = 8.3 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.3, 26.9, 37.1, 37.5, 49.1, 54.2, 54.3 (q, $^2J_{CF}$ = 30.7 Hz), 61.8, 113.1, 121.3, 124.2 (q, $^1J_{CF}$ = 286.1 Hz), 129.9, 139.1, 153.5, 164.6, 203.5. HRMS (ESI) calculated for $C_{20}H_{24}F_3NO_4S$ (M+NH_4): 449.1704; found: 449.1716.

(3*S*,7a*S*)-2-(tert-Butylsulfonyl)-5-(4-chlorophenyl)-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5l)



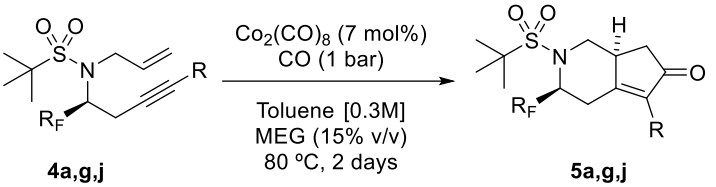
By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 40 mg of **4k** (0.10 mmol), 37 mg of **5k** were obtained as a white solid (86%). $[\alpha]_D^{25}$ = -37.0 (*c* 1.0; $CHCl_3$). Mp: 69 - 71 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.09 (dd, *J* = 18.9, 2.7 Hz, 1H), 2.72 (dd, *J* = 18.9, 6.7 Hz, 1H), 2.90 (dd, *J* = 15.5, 7.6 Hz, 1H), 3.00 - 3.08 (m, 1H), 3.22 (d, *J* = 15.5 Hz, 2H), 4.15 (dd, *J* = 14.0, 6.4 Hz, 1H), 4.66 - 4.76 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.6 (d, J_{FH} = 8.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.3, 28.0, 38.0, 38.8, 50.1, 55.3 (q, $^2J_{CF}$ = 30.8 Hz), 62.9, 125.2 (q, $^1J_{CF}$ = 285.3 Hz), 128.5, 128.9, 130.8, 134.4, 139.6, 167.2, 203.8. HRMS (ESI) calculated for $C_{19}H_{21}ClF_3NO_3S$ (M+NH_4): 453.1205; found: 453.1220.

(*3S*,7a*S*)-2-(tert-Butylsulfonyl)-5-methyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5m)



By means of general procedure **VII** and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 40 mg of **4m** (0.12 mmol), 37 mg of **5k** were obtained as a white solid (86%). $[\alpha]_D^{25}$ = -37.0 (*c* 1.0; $CHCl_3$). Mp: 69 - 71 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.09 (dd, *J* = 18.9, 2.7 Hz, 1H), 2.72 (dd, *J* = 18.9, 6.7 Hz, 1H), 2.90 (dd, *J* = 15.5, 7.6 Hz, 1H), 3.00 - 3.08 (m, 1H), 3.22 (d, *J* = 15.5 Hz, 2H), 4.15 (dd, *J* = 14.0, 6.4 Hz, 1H), 4.66 - 4.76 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.6 (d, J_{FH} = 8.5 Hz, 3F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.3, 28.0, 38.0, 38.8, 50.1, 55.3 (q, $^2J_{CF}$ = 30.8 Hz), 62.9, 125.2 (q, $^1J_{CF}$ = 285.3 Hz), 128.5, 128.9, 130.8, 134.4, 139.6, 167.2, 203.8. HRMS (ESI) calculated for $C_{14}H_{20}F_3NO_3S$ (M+NH_4): 339.1116; found: 453.1220.

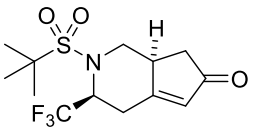
VIII. Catalytic Pauson-Khand reaction.



4a,g,j **5a,g,j**

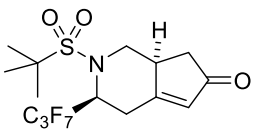
In a flame-dried pressure tube containing a magnetic stirrer, sulfonamides **4** (1.0 equiv.) were dissolved in anhydrous toluene [0.3M]. $Co_2(CO)_8$ (7 mol%) was then added, followed by ethylene glycol (15% v/v). The pressure vessel was closed, first purged with N_2 and then with CO (x3). Finally, it was charged with CO (1 bar) and heated to 80 °C; and the mixture was stirred for the indicated time. Afterwards, the CO was removed using a vacuum line and the biphasic solution was filtered on a small plug of celite and concentrated under reduced pressure. The products **5** were purified by column chromatography (hexanes/EtOAc mixtures of increasing polarity).

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5a).



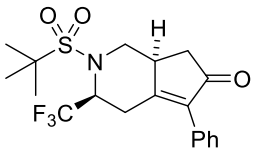
By means of general procedure **VIII** (catalytic) and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 51 mg of **4a** (0.171 mmol), 41 mg of **5a** were obtained as a white solid (75%). The spectroscopic data were in fully agreement with the described using the stoichiometric procedure.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoropropyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5f).



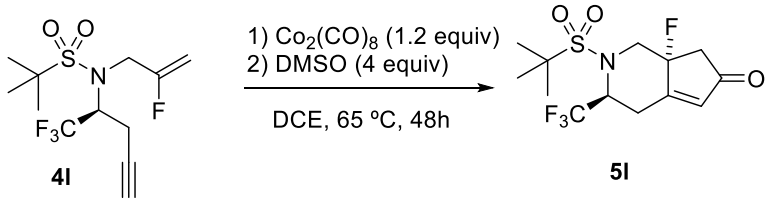
By means of general procedure **VIII** (catalytic) and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 74 mg of **4f** (0.186 mmol), 58 mg of **5f** were obtained as a white solid (73%). The spectroscopic data were in fully agreement with the described using the stoichiometric procedure.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-5-phenyl-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one (5i).



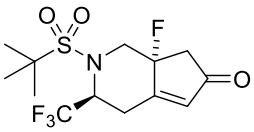
By means of general procedure **VII** (catalytic, stirring the reaction for 96 hours) and purification by flash chromatography of the reaction crude [*n*-hexane:AcOEt (10:1)], from 40 mg of **4i** (0.107 mmol), 35 mg of **5i** were obtained as a white solid (81%). The spectroscopic data were in fully agreement with the described using the stoichiometric procedure.

IX. Pauson-Khand reaction of 4l.

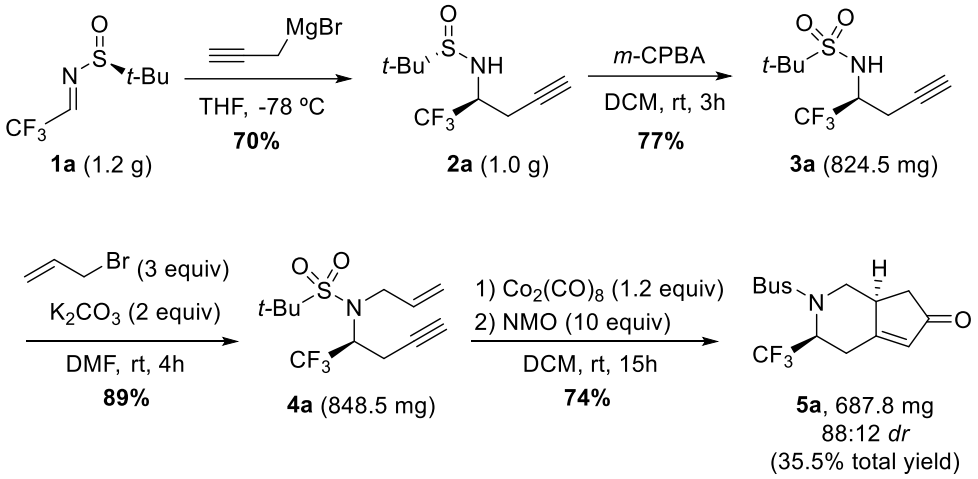


Sulfonamide **4l** (0.25 mmol) was dissolved in DCE (0.1M, 3 mL) at room temperature in a round-bottomed flask. Octacarbonyl dicobalt complex was added (0.28 mmol) and after 2 hours the first stage was finished (TLC analysis). At this time, DMSO (1 mmol) was added and the mixture was stirred for 48h at 65 °C. Solvent was removed and crude was purified by column chromatography [*n*-hexane:AcOEt (10:1)] to afford 45 mg of

(3*S*,7a*R*)-2-(*tert*-butylsulfonyl)-7a-fluoro-3-(trifluoromethyl)-1,2,3,4,7,7a-hexahydro-6H-cyclopenta[c]pyridin-6-one 5l By means of general procedure **IX**, compound **5l** was obtained as a white solid (52%). $[\alpha]_D^{25}$ = -15.5 (*c* 1.0; $CHCl_3$). Mp: 53 – 55 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.45 (dd, *J* = 18.7, 13.0 Hz, 1H), 2.75 (dd, *J* = 20.1, 18.8 Hz, 1H), 3.03 - 3.14 (m, 2H), 3.39 (dd, *J* = 33.8, 15.4 Hz, 1H), 4.35 - 4.44 (m, 1H), 4.67 - 4.71 (m, 1H), 6.18 (s, 1H). ^{19}F NMR (282.4 MHz, $CHCl_3$) δ -68.5 (s, 3F), -146.6 – -151.6 (m, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.4, 24.4, 42.1 (d, $^2J_{CF}$ = 23.4 Hz), 50.6 (d, $^2J_{CF}$ = 25.5 Hz), 54.6 (q, $^2J_{CF}$ = 30.8 Hz), 62.2, 124.1 (q, $^1J_{CF}$ = 268.8 Hz), 126.2 (d, $^1J_{CF}$ = 157.4 Hz), 131.7, 164.3 (d, $^2J_{CF}$ = 19.0 Hz), 199.6. HRMS (ESI) calculated for $C_{13}H_{17}F_4NO_3S$ (M+NH_4): 361.1198; found: 361.1204.



X. Gram-scale procedure for 5a



A freshly prepared 1M solution of propargylmagnesium bromide in Et_2O (1.5 equiv, 8.9 mmol) was added to a solution of the imine **1a** (5.96 mmol, 1.2 g) in THF (0.1 M, 60 mL) at −78 °C. After stirring for 3 h. at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with DCM and purified by flash column chromatography (*n*-hexane/EtOAc, 3:1). Sulfinamide **2a** was obtained with 70 % of chemical yield (1.0 g, 4.17 mmol).

m-CPBA (5.0 mmol) was added to a solution of this sulfinamide **2a** (1.0 g, 4.17 mmol) in DCM (40 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with DCM, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to afford sulfonamide **3a** (824.5 mg, 3.21 mmol) with 77 % of yield.

Sulfonamide **3a** (3.21 mmol) was dissolved in DMF (0.1M, 30 mL) in a round-bottomed flask at room temperature, and then potassium carbonate (6.42 mmol) was added. After stirring, allyl bromide (9.6 mmol) was added and the mixture was stirred for 4 h at room temperature. When the reaction finished (TLC analysis), was quenched with a saturated solution of NH_4Cl aq. and extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the crude mixture was purified by column

chromatography (*n*-hexane/EtOAc, 10:1) to afford 848.5 mg (2.86 mmol) of sulfonamide **4a** (89 %).

$Co_2(CO)_8$ (3.43 mmol) was added to a solution of sulfonamide **4a** (848.5 mg, 2.86 mmol) in DCM (25 mL) at room temperature. The reaction mixture was stirred for 2 h until complete formation of the alkyne-hexacarbonyldicobalt complex was observed by TLC. At this moment, NMO (28.6 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was removed in vacuum and the crude reaction was purified by flash column chromatography using *n*-hexane/EtOAc (8:1) as eluent to afford compound **5a** (687.8 mg, 74 % yield, *dr* 88:12).

XI. X-ray structure of compound 5a [1]

Single crystals of $C_{13}H_{18}F_3NO_3S$ were obtained using Et_2O and *n*-hexane (1:3), with slow evaporation in glass vial.

Crystal Data for $C_{13}H_{18}F_3NO_3S$ (*M* =325.34 g/mol): orthorhombic, space group P212121 (no. 19), *a* = 6.39098(7) Å, *b* = 9.46470(10) Å, *c* = 24.0400(2) Å, *V* = 1454.15(3) Å3, *Z* = 4, *T* = 150.00(10) K, μ(CuKα) = 2.401 mm^{-1}, *Dcalc* = 1.486 g/cm3, 10567 reflections measured (7.354° ≤ 2Θ ≤ 137.986°), 2708 unique (R_{int} = 0.0267, R_{sigma} = 0.0214) which were used in all calculations. The final *R*1 was 0.0247 (I > 2σ(I)) and wR^2 was 0.0657 (all data).

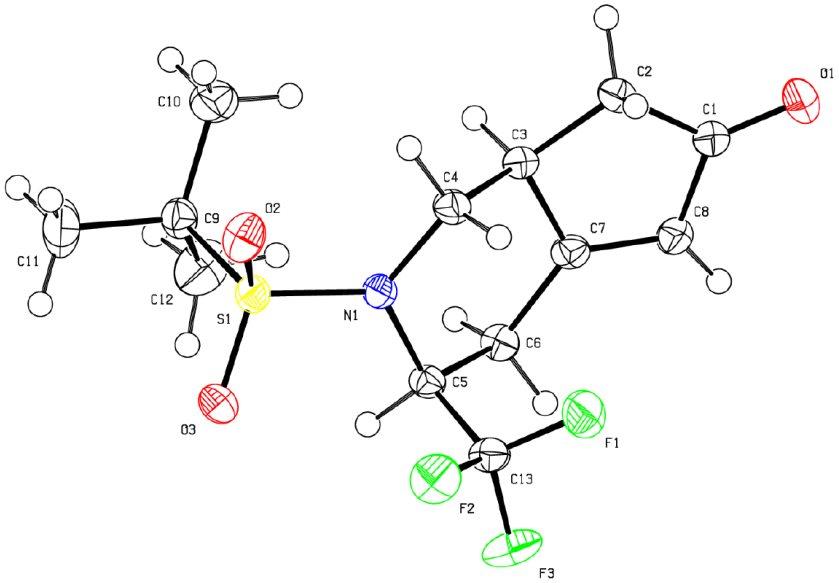


Figure S2. Ortep diagram for compound **5a**.

XII. Computational methods.

All the DFT calculations were carried out with the Gaussian 16 series of programs.[2] DFT method B3LYP [3] with a standard basis set 6-311+G(d,p) (LanL2DZ [4] basis set for Co) was used for geometry optimizations. Harmonic frequency calculations were performed for all stationary points to confirm them as a local minima or transition structures and to derive the thermochemical corrections for the enthalpies and free energies. The intrinsic reaction coordinate (IRC) path was traced to check the energy profiles connecting each transition state to the two associated minima of the proposed mechanism.

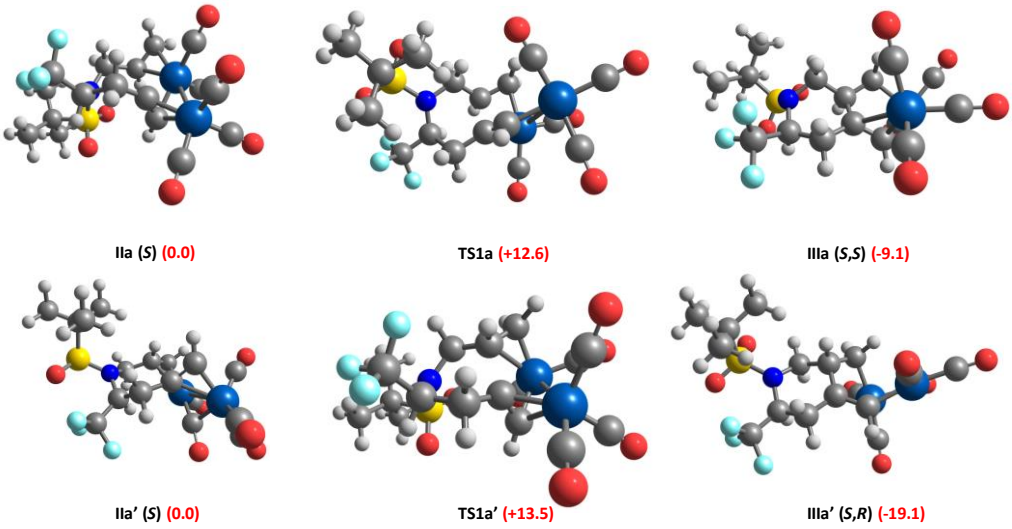


Figure S3. Optimized structures for reactant complex (II), transition state and product (III) for the cyclisation reaction from intermediate II to yield intermediate. Relative corrected electronic energies (in kcal/mol) are given in red.

XIII. Cartesian coordinates of optimized structures.

Intermediate IIa

6	-1.298121000	1.869206000	-0.038094000
6	-1.288311000	-0.460012000	-0.947911000
6	-0.385285000	-1.121710000	0.118641000
6	0.814364000	-0.280124000	0.444133000
6	-0.135569000	2.222872000	-0.932399000
6	0.823063000	3.111045000	-0.504938000
6	1.363187000	0.524799000	1.350459000
1	-1.991672000	2.710291000	-0.072068000
1	-0.959734000	-1.326763000	1.025436000
1	-0.045698000	-2.080572000	-0.272313000
1	1.382353000	3.695459000	-1.223220000
1	0.814342000	3.484340000	0.512716000
1	1.204093000	0.976206000	2.315912000
27	1.818860000	1.154787000	-0.444226000
6	2.030802000	0.665291000	-2.187689000
6	3.277463000	2.176996000	-0.131577000
8	2.197504000	0.354670000	-3.272991000
8	4.199313000	2.817563000	0.078569000
27	2.699020000	-0.812884000	0.759436000
6	4.272631000	-0.173751000	1.469897000
6	2.384533000	-2.111784000	1.944126000
6	3.150529000	-1.838209000	-0.680020000
8	5.239567000	0.187377000	1.951172000
8	3.430190000	-2.482200000	-1.577211000
8	2.158562000	-2.927896000	2.707926000
7	-2.082475000	0.682735000	-0.464823000
1	-0.606394000	-0.026544000	-1.681519000
6	-2.002324000	-1.518671000	-1.805315000

9	-2.773635000	-2.375568000	-1.110820000
9	-1.030858000	-2.279709000	-2.389500000
9	-2.715638000	-0.989016000	-2.801435000
16	-3.735088000	0.696009000	0.003940000
8	-4.068317000	2.122294000	0.059837000
8	-4.456422000	-0.195264000	-0.894151000
6	-4.000076000	0.038383000	1.758325000
6	-5.429997000	0.486363000	2.107331000
1	-6.157265000	0.087451000	1.397921000
1	-5.675287000	0.098241000	3.100441000
1	-5.517367000	1.572453000	2.124382000
6	-2.983534000	0.680265000	2.704394000
1	-1.963030000	0.352452000	2.496291000
1	-3.026260000	1.770073000	2.660284000
1	-3.222066000	0.378157000	3.728440000
6	-3.908226000	-1.488274000	1.755292000
1	-2.911064000	-1.851852000	1.506762000
1	-4.148720000	-1.848686000	2.760070000
1	-4.615297000	-1.925814000	1.051115000
1	-0.293226000	2.103965000	-1.999226000
1	-0.944510000	1.774682000	0.991296000

TS1 (yielding (*S*,*S*)-compound)

Frequency -278.0236

6	1.073215000	-0.662291000	0.845169000
6	0.015867000	-1.455741000	0.077608000
1	1.598032000	-1.359528000	1.494512000
6	0.292275000	0.568015000	-1.675418000
6	-0.889282000	0.016433000	-0.895660000
6	-2.143999000	-0.123139000	-1.471528000

1	-2.490157000	0.042505000	-2.481288000
27	-2.357296000	0.970622000	0.111885000
27	-2.250816000	-1.473296000	-0.167671000
6	-3.397357000	-1.743342000	1.126257000
6	-2.732110000	-2.704978000	-1.366622000
6	-4.176987000	1.020620000	0.144558000
6	-1.848879000	1.060802000	1.859444000
6	-2.118925000	2.648365000	-0.479683000
8	-4.156246000	-1.967585000	1.953296000
8	-3.115029000	-3.479831000	-2.112772000
8	-2.031674000	3.720963000	-0.853929000
8	-5.315538000	1.051837000	0.111096000
8	-1.568846000	1.117020000	2.964375000
1	0.605855000	-0.196332000	-2.395786000
1	-0.064889000	1.413871000	-2.267407000
6	1.580047000	0.999248000	-0.945006000
1	2.338978000	1.121164000	-1.720325000
6	-0.808874000	-2.332685000	0.893849000
1	-0.815658000	-2.137187000	1.963379000
1	-0.783051000	-3.390168000	0.654617000
1	0.612410000	0.089958000	1.485189000
7	2.082479000	0.006502000	0.005720000
6	1.522822000	2.381830000	-0.280762000
9	0.789731000	2.429315000	0.852490000
9	2.762461000	2.811132000	0.046775000
9	1.006074000	3.295566000	-1.132048000
16	3.398574000	-0.976173000	-0.515949000
6	4.825299000	-0.656432000	0.658620000
6	4.349761000	-0.889661000	2.095002000
1	3.592728000	-0.161993000	2.393200000

1	3.959255000	-1.899633000	2.232042000
1	5.206423000	-0.768536000	2.764169000
6	5.326198000	0.773460000	0.450837000
1	5.621709000	0.945767000	-0.584724000
1	4.576541000	1.511834000	0.732083000
1	6.203796000	0.924148000	1.086439000
6	5.891928000	-1.686093000	0.250993000
1	6.769477000	-1.537004000	0.886325000
1	5.536294000	-2.708059000	0.385905000
1	6.198737000	-1.553892000	-0.788147000
8	2.996453000	-2.375818000	-0.339549000
8	3.786755000	-0.484760000	-1.842825000
1	0.440618000	-1.956665000	-0.787294000

Intermediate IIIa

6	1.044195000	-0.457497000	0.971080000
6	-0.112649000	-0.833651000	0.032265000
1	1.397253000	-1.326698000	1.518667000
6	0.318604000	1.547569000	-0.798368000
6	-0.667926000	0.402953000	-0.635895000
6	-1.842865000	0.208434000	-1.347517000
1	-2.067156000	0.698250000	-2.292290000
27	-2.639012000	1.029319000	0.289382000
27	-2.840486000	-1.233568000	-0.537403000
6	-3.894377000	-2.216566000	0.612907000
6	-2.389393000	-2.402030000	-1.836006000
6	-4.385181000	0.738756000	0.320419000
6	-2.127586000	1.032078000	2.026730000
6	-2.668602000	2.765999000	-0.175254000
8	-4.500171000	-2.843643000	1.341159000
8	-2.060043000	-3.112757000	-2.660643000

8	-2.712650000	3.866422000	-0.477797000
8	-5.528431000	0.642138000	0.397330000
8	-1.868091000	1.086701000	3.140541000
1	0.109264000	2.105253000	-1.713205000
1	0.178083000	2.246794000	0.027723000
6	1.819732000	1.140807000	-0.815810000
1	2.106650000	0.809330000	-1.815483000
6	-1.233308000	-1.679538000	0.602644000
1	-1.501603000	-1.418872000	1.623268000
1	-1.050802000	-2.752079000	0.527190000
1	0.743275000	0.298071000	1.701271000
7	2.174470000	0.090578000	0.175114000
6	2.642100000	2.412316000	-0.552588000
9	2.453916000	2.890916000	0.699671000
9	3.963129000	2.227553000	-0.709358000
9	2.278855000	3.393616000	-1.413509000
16	3.277615000	-1.128521000	-0.386802000
6	4.674907000	-1.208623000	0.866534000
6	4.092761000	-1.537062000	2.244273000
1	3.466435000	-0.727005000	2.622550000
1	3.520297000	-2.465892000	2.230372000
1	4.923596000	-1.664241000	2.944329000
6	5.433840000	0.117111000	0.879298000
1	5.793878000	0.384046000	-0.114106000
1	4.820253000	0.932433000	1.261070000
1	6.298624000	0.005853000	1.540350000
6	5.564187000	-2.353778000	0.353141000
1	6.414034000	-2.455286000	1.033822000
1	5.025344000	-3.301649000	0.329201000
1	5.950625000	-2.141843000	-0.645227000

8	2.592842000	-2.427767000	-0.331290000
8	3.817371000	-0.653811000	-1.662970000
1	0.354892000	-1.420116000	-0.768873000

Intermediate IIa'

6	1.454418000	-0.582141000	1.680174000
6	0.235394000	-1.493425000	1.803361000
1	2.286132000	-1.146758000	2.114433000
6	-0.001598000	1.637970000	0.022950000
6	-0.903087000	0.500547000	-0.277949000
6	-1.124127000	-0.553901000	-1.047546000
1	-0.702062000	-1.152229000	-1.836304000
1	-0.025355000	-1.605551000	2.853281000
27	-2.803899000	0.456385000	-0.883933000
27	-1.671053000	-0.914642000	0.821879000
6	-2.021045000	0.022859000	2.329959000
6	-2.903447000	-2.242704000	0.852210000
6	-3.992501000	-0.753710000	-1.580560000
6	-3.735259000	1.532940000	0.248667000
6	-2.653733000	1.557270000	-2.282609000
8	-2.219781000	0.641170000	3.271120000
8	-3.700414000	-3.060952000	0.879258000
8	-2.531683000	2.259183000	-3.173711000
8	-4.714156000	-1.497095000	-2.054934000
8	-4.327033000	2.210979000	0.949793000
1	-0.175485000	2.451298000	-0.687097000
1	-0.241662000	2.040865000	1.008438000
6	1.516936000	1.295083000	-0.052817000
1	1.828108000	1.383462000	-1.094396000
6	-0.180751000	-2.495596000	0.955617000

1	-0.701144000	-3.349275000	1.368550000
1	0.265148000	-2.638866000	-0.014451000
1	1.311939000	0.277709000	2.334628000
7	1.892157000	-0.049990000	0.375334000
6	2.272385000	2.404391000	0.708189000
9	1.903781000	2.500707000	2.008435000
9	3.611918000	2.234875000	0.710326000
9	2.027599000	3.604279000	0.137765000
16	2.734927000	-1.063276000	-0.716043000
6	4.610319000	-0.807893000	-0.663262000
6	5.059948000	-0.722023000	0.796569000
1	4.667532000	0.162213000	1.297653000
1	4.768043000	-1.614664000	1.353542000
1	6.152026000	-0.660886000	0.819172000
6	4.987841000	0.425630000	-1.487196000
1	4.625956000	0.335881000	-2.511722000
1	4.615479000	1.352839000	-1.058678000
1	6.079622000	0.493037000	-1.515032000
6	5.168316000	-2.076246000	-1.333936000
1	6.256811000	-1.977925000	-1.380903000
1	4.921528000	-2.974041000	-0.768864000
1	4.795325000	-2.189375000	-2.353707000
8	2.514694000	-2.419099000	-0.206931000
8	2.286135000	-0.684876000	-2.060017000

TS1' (yielding (*S*,*R*)-compound)

Frequency -252.8591

6	-1.246423000	-0.190593000	-1.561563000
6	0.260265000	0.127839000	-1.588373000
1	-1.378208000	-1.265715000	-1.648809000

6	-0.129171000	1.771459000	0.407960000
6	0.742092000	0.551602000	0.201015000
6	1.165083000	-0.380386000	1.124975000
1	0.835269000	-0.633374000	2.120254000
1	0.478107000	1.140429000	-1.917095000
27	2.724681000	0.670256000	0.562282000
27	1.638615000	-1.268274000	-0.483025000
6	3.187491000	-1.831178000	-1.058403000
6	0.889037000	-2.834236000	-0.018743000
6	4.039947000	-0.280397000	1.389940000
6	3.396286000	1.358141000	-0.978712000
6	2.739672000	2.083664000	1.659570000
8	4.179214000	-2.255013000	-1.442948000
8	0.574845000	-3.884164000	0.290622000
8	2.774463000	2.985537000	2.358333000
8	4.838570000	-0.874074000	1.945724000
8	3.799351000	1.790068000	-1.956279000
1	0.034683000	2.138292000	1.421237000
1	0.201005000	2.559240000	-0.272271000
6	-1.661708000	1.527630000	0.224464000
1	-2.137068000	1.570618000	1.203438000
6	1.047982000	-0.861371000	-2.332548000
1	1.815269000	-0.470527000	-2.992866000
1	0.511037000	-1.705142000	-2.756117000
1	-1.702500000	0.277146000	-2.439983000
7	-1.985833000	0.235672000	-0.359345000
6	-2.285727000	2.674656000	-0.580079000
9	-1.772541000	2.784981000	-1.829878000
9	-3.620867000	2.543951000	-0.722747000
9	-2.063547000	3.852764000	0.043806000

16	-2.612158000	-0.970306000	0.683705000
6	-4.454075000	-1.121250000	0.355393000
6	-4.667222000	-1.241371000	-1.155488000
1	-4.372692000	-0.329762000	-1.678163000
1	-4.120254000	-2.089238000	-1.572225000
1	-5.732096000	-1.405647000	-1.343400000
6	-5.169350000	0.096269000	0.945117000
1	-4.975357000	0.189731000	2.014203000
1	-4.884144000	1.022246000	0.447768000
1	-6.245909000	-0.037539000	0.803678000
6	-4.872360000	-2.408995000	1.084103000
1	-5.951090000	-2.537223000	0.957407000
1	-4.367282000	-3.284213000	0.675469000
1	-4.662036000	-2.349997000	2.153808000
8	-2.009331000	-2.238321000	0.265110000
8	-2.436948000	-0.480509000	2.055371000

Intermediate IIIa'

6	1.285769000	0.159056000	1.615771000
6	-0.257096000	0.156690000	1.341676000
1	1.582708000	-0.762076000	2.112295000
6	0.342061000	1.973277000	-0.330042000
6	-0.528563000	0.779245000	-0.015307000
6	-1.114748000	-0.031287000	-0.975375000
1	-0.921079000	0.086640000	-2.038909000
1	-0.690356000	0.782027000	2.128739000
27	-2.739056000	0.922957000	-0.223288000
27	-2.143741000	-1.410480000	-0.174240000
6	-3.500061000	-2.222595000	0.795928000
6	-1.201041000	-2.807228000	-0.840695000

6	-4.058339000	0.288645000	-1.238076000
6	-3.282743000	0.992830000	1.491257000
6	-2.797590000	2.642080000	-0.723793000
8	-4.307487000	-2.707787000	1.431213000
8	-0.647165000	-3.672340000	-1.322630000
8	-2.828804000	3.741215000	-1.035305000
8	-4.948717000	-0.077080000	-1.863080000
8	-3.680657000	1.043554000	2.564372000
1	0.074718000	2.421560000	-1.286576000
1	0.201900000	2.740736000	0.437119000
6	1.843280000	1.546792000	-0.380770000
1	2.119871000	1.336355000	-1.413888000
6	-0.920238000	-1.231497000	1.410759000
1	-1.549833000	-1.352195000	2.292151000
1	-0.197128000	-2.039439000	1.349130000
1	1.536876000	0.981429000	2.288606000
7	2.124360000	0.340169000	0.409507000
6	2.732922000	2.713051000	0.060611000
9	2.570745000	3.033036000	1.367410000
9	4.047216000	2.464200000	-0.117127000
9	2.441392000	3.820045000	-0.658676000
16	2.605928000	-1.073597000	-0.432482000
6	4.359312000	-1.492550000	0.095753000
6	4.424396000	-1.499950000	1.625150000
1	4.236020000	-0.508722000	2.041598000
1	3.720098000	-2.214231000	2.055502000
1	5.431865000	-1.801581000	1.925857000
6	5.328002000	-0.477029000	-0.511114000
1	5.225716000	-0.428515000	-1.595844000
1	5.187197000	0.519710000	-0.097863000

1	6.347839000	-0.797346000	-0.277982000
6	4.604508000	-2.897293000	-0.480172000
1	5.627189000	-3.193547000	-0.230271000
1	3.916968000	-3.630882000	-0.059155000
1	4.505573000	-2.906161000	-1.567368000
8	1.761925000	-2.172118000	0.054806000
8	2.628508000	-0.740844000	-1.860696000

XIV. References

1. CCDC 1954729 contains the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2. Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

3. a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B: Condens. Matter*. **1988**, *37*, 785–789; b) A. D. Becke, *J. Chem. Phys*. **1993**, *98*, 1372–1377; c) A. D. Becke, *J. Chem. Phys*. **1993**, *98*, 5648–5652.

4. a) P. J. Hay, W. R. Wadt, *J. Chem. Phys*. **1985**, *82*, 270–283; b) P. J. Hay, W. R. Wadt, *J. Chem. Phys*. **1985**, *82*, 284–298; c) P. J. Hay, W. R. Wadt, *J. Chem. Phys*. **1985**, *82*, 299–310.

Scientific Article 4:

The Fluoro-Pauson-Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C-F Stereogenic Center

The Fluoro-Pauson-Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C—F Stereogenic Center.

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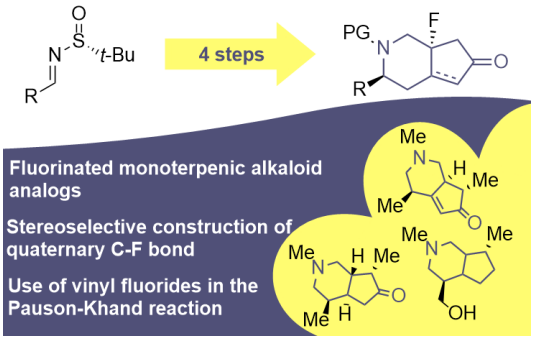
Supporting Information Placeholder



ABSTRACT: A variety of enantioenriched fluorinated 6*H*-cyclopenta[*c*]pyridin-6-one bicycles, a scaffold present in several classes of monoterpenic alkaloids with varied biological activity, were synthesized in just five steps starting from simple aldehyde starting materials. The synthesis presented wide functional group tolerance and moderate to high yields and diastereoselectivities, and could be carried out at gram-scale. These products were suitable for further transformations, such as hydrogenation and deprotection of the *tert*-butyl sulfonyl protecting group.

Nitrogen-containing heterocycles are highly prevalent in pharmaceuticals and agrochemicals, as well as in other bioactive molecules. This is immediately apparent when considering the alkaloid class of natural products; morphine, caffeine, nicotine, and atropine all belong to this diverse family and present a wide range of biological activities. A somewhat understudied scaffold is the cyclopenta[*c*]pyridin-6-one bicycle, present in various natural products such as Tecomanine, Tecostanine and certain compounds belonging to the Kinabalurine series (Figure 1).[1,2] Both Tecomanine and Tecostanine are present in the leaves of *Tecoma stans*, a species of bush native to Latin America, infusions of which have long been used in Mexico to treat symptoms of diabetes. In fact, extracts of this plant have been shown to exert a significant hypoglycemic response in both rabbits and dogs, attributed to the action of these two monoterpenic alkaloids.[3,4] Given this activity, compounds presenting this bicyclic structure could be useful in the search for new antidiabetic compounds; a class of pharmaceuticals that is increasingly important in the modern world.[5]

In terms of synthesis, racemic Tecomanine has been synthesized through a variety of synthetic methods, including a Pauson-Khand reaction which allows the prior introduction of all necessary substituents directly into the precursor, creating the bicyclic molecular complexity in just one reaction (Scheme 1a).[6] Series of enantioenriched products with similar structures have been prepared by both Gais[7] and Evans,[1] again through the use of a Pauson-Khand reaction as the key step to form the bicyclic scaffold.

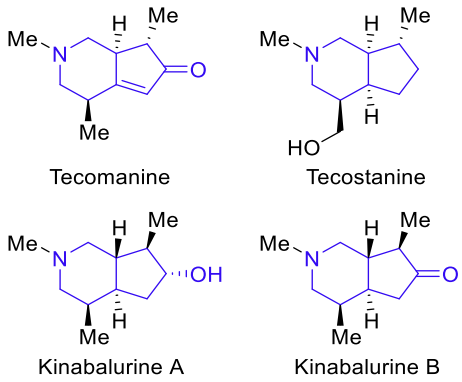


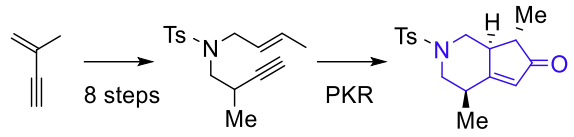
Figure 1. Structures of monoterpenic alkaloids bearing the target bicyclic structure.

On the other hand, fluorine has become increasingly important in several key industrial fields, including but not limited to medicinal and pharmaceutical chemistry, agrochemistry and materials science. The strategic incorporation of fluorine into biologically active molecules can improve the drug-like properties of a given compound, such as the metabolic stability or lipophilicity.[8-10] However, given the scarcity of natural products containing fluorine atoms, any advance in this field relies on the development of new methods to synthesize new fluorine-bearing structures. A recent trend in medicinal organic chemistry, denominated the *escape from flatland*, refers to a shift from the more common aromatic and similar C_{sp2} tethers towards C_{sp3} carbon centers in an attempt to provide greater 3D molecular diversity.[11] In particular, after approximately a decade of exhaustive research on the formation of C_{sp2}—F and C_{sp2}—R_F bonds,[12] the asymmetric introduction of fluorine or fluorinated groupings into sp^3 carbon centers is gaining more attention in recent years.[13] Regarding this objective, perhaps the most challenging is the selective construction of a quaternary stereogenic carbon center containing a C—F bond. In fact, pharmaceutical drugs containing a stereogenic C—F bond constitute just 1% of the drugs currently on the market as a direct result of this problem.

We recently reported the first Pauson-Khand reactions using enyne substrates containing a vinyl fluoride moiety as the olefin coupling partner, an effective way to construct molecular complexity and the coveted quaternary C—F group in one step, albeit in a racemic manner.[14] Owing to the complete diastereoselectivity observed in this process, we foresaw that enantiopure products bearing a stereodefined quaternary C—F unit within a similar monoterpenic skeleton could be obtained by using a suitable enantioenriched substrate.

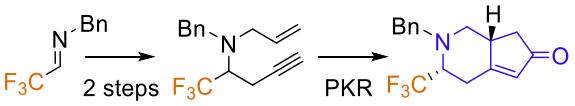
Scheme 1. a, b) Previous related work; racemic synthesis of Tecomanine precursor and other trifluoromethylated derivatives via the Pauson-Khand reaction. c) This work; the synthesis of enantioenriched fluorinated Tecomanine analogues.

a) Racemic synthesis of Tecomanine precursor[6]



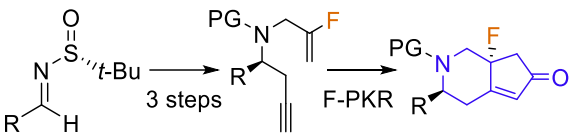
Racemic

b) Synthesis of trifluoromethyl-bearing Tecomanine analogue[15]



trans/*cis*: 85/15
Racemic, only one example

c) ***This work***



R = Ar, Alk, HetAr
Single enantiomer obtained

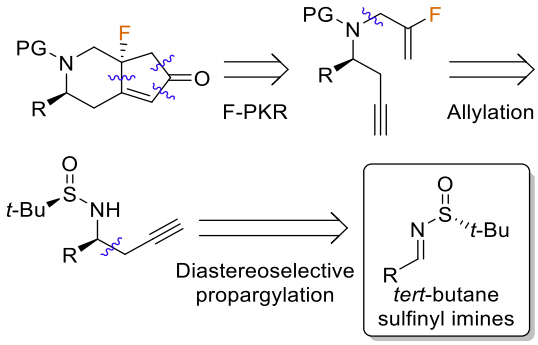
We were surprised to find that fluorinated examples of this class of structure had not yet been studied, the only example in the literature being a single racemic analogue based on the same 6*H*-cyclopenta[*c*]pyridin-6-one scaffold bearing a trifluoromethyl substituent, which was also synthesized using the Pauson-Khand reaction (Scheme 1b).[15]

Therefore, we decided to apply our method to the synthesis of enantioenriched compounds presenting the same bicyclic skeleton as seen in the aforementioned natural products, bearing an all-important C—F bond at the bridged stereogenic center (Scheme 1c).

We first carried out a retrosynthetic analysis of our target structures (Scheme 2). The bicyclic core could be constructed via fluoro-Pauson-Khand reaction of the *N*-tethered

fluoroenyne precursor. The vinyl fluoride could be introduced using a suitable building block for the alkylation of the amine group, which could in turn be synthesized through stereoselective propargylation to the corresponding imine.

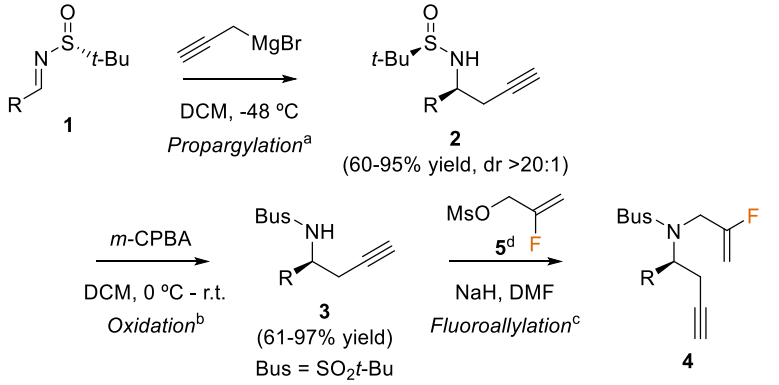
Scheme 2. Retrosynthetic analysis of target bicyclic structures.



We then decided that Ellman's *tert*-butane sulfinyl imines would be suitable starting materials for our goal of synthesising Tecomanine analogues, since they can be used as electrophiles in many diastereoselective addition reactions with a variety of nucleophiles such as organometallic reagents.[16,17] Specifically, the diastereoselective addition of propargyl magnesium bromide to this class of imines is well documented. Therefore, we followed the procedure reported by Zhang *et al.* to obtain a variety of sulfinylamide intermediates **2** in good yields and high diastereoselectivities.[18] Aromatic, heteroaromatic and aliphatic aldimines participated in the propargylation step uneventfully.

From there, the final step to form the precursors for the Pauson-Khand reaction was the introduction of the fluoroallyl group via alkylation of the nitrogen atom. Unfortunately, the direct alkylation of the sulfinylamides resulted in unsatisfactory yields (<20%). However, we found that after oxidation to the corresponding sulfonamides, the reaction took place much more successfully.[19] In this way, a series of *N*-tethered fluorinated enynes **4** was synthesized in good to high yields (Scheme 3).

Scheme 3. Synthesis of fluoro-Pauson-Khand precursors 4.



4a, Ar = C_6H_5, 72%
4b, Ar = 4-MeC_6H_4, 45%
4c, Ar = 4-$OMeC_6H_4$,83%
4d, Ar = 4-*t*-BuC_6H_4, 60%
4e, Ar = 3-$OMeC_6H_4$, 75%
4f, Ar = 4-BrC_6H_4, 50%
4g, HetAr = 3-Benzofuranyl, 84%
4h, HetAr = 2-Thiophenyl, 76%
4i, HetAr = 3-Thiophenyl, 71%
4j, HetAr = 3-Pyridinyl, 46%[e]
4k, Alk = *c*-C_6H_{11}, 95%
4l, Alk = *c*-C_3H_5, 82%
4m, Alk = $Ph(CH_2)_2$, 94%
4n, Alk = *n*-C_6H_{13}, 84%

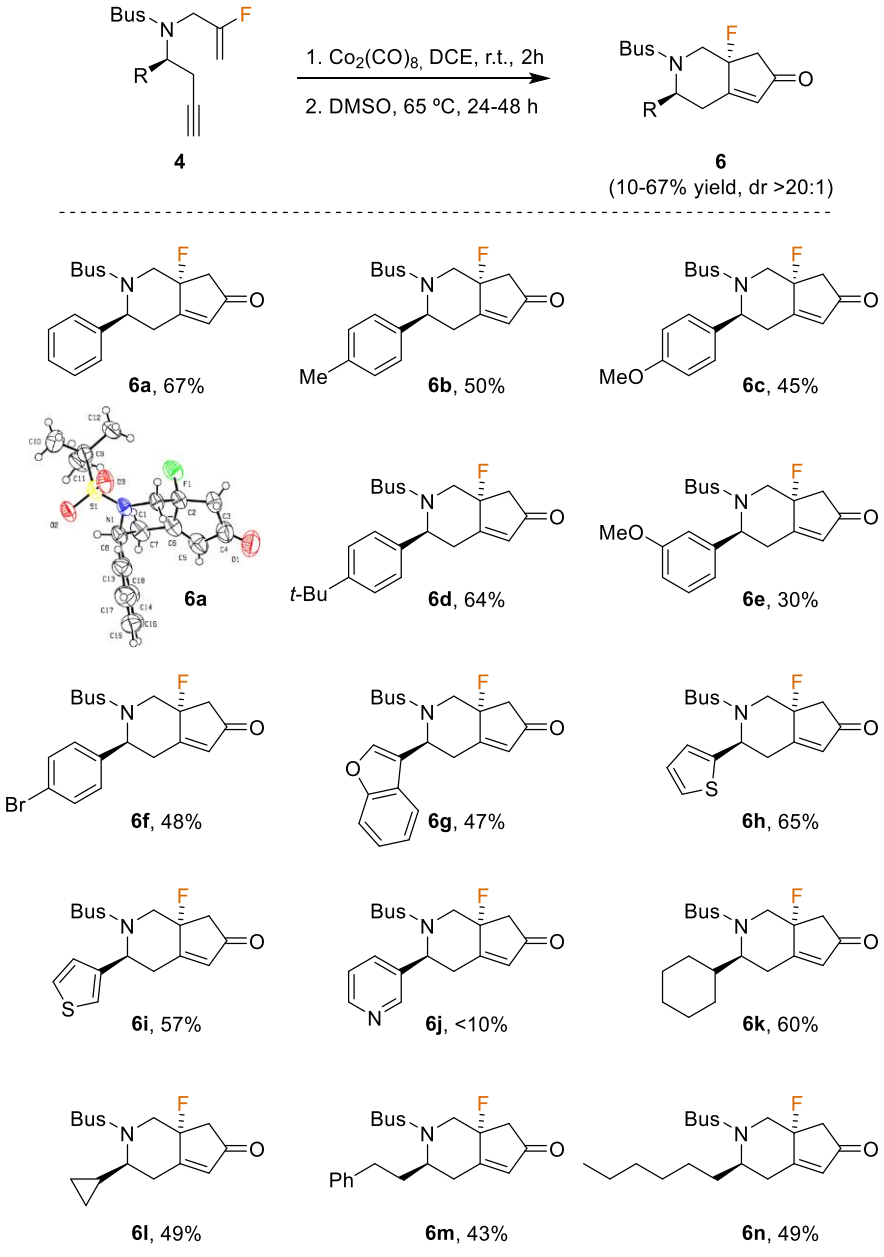
Yields refer to the isolated yields of the final fluoroallylation step.[a] Reaction carried out as described by Zhang *et al*.[18] Standard conditions for the propargylation step: aldimine **1** (1 equiv), freshly prepared propargyl magnesium bromide (1.5 equiv), dichloromethane (0.1 M), -48 °C, 16 h. [b] Standard conditions for the oxidation step: **2** (1 equiv), *m*-CPBA (1.2 equiv), dichloromethane (0.1 M), 0 °C – r.t., 2 h. [c] Standard conditions for the fluoroallylation step: **3** (1 equiv), NaH (3 equiv), **5** (2 equiv), DMF (0.2 M), 0 °C – r.t., 16 h. [d] Mesylate **5** prepared following the procedure described by Mykhailiuk *et al*.[20] [e] An extra reduction step was necessary for the synthesis of **4j** (see Supporting Information for details).

We then applied our fluoro-Pauson-Khand procedure to the desired precursors **4** (Scheme 4).[14] However, our previously reported conditions using dichloromethane at 40 °C for the second reaction step were unsuccessful for these substrates. Instead, we found

we had to switch the solvent to dichloroethane and increase the temperature slightly to 65 °C. The final bicyclic products were obtained in moderate to good yields and excellent diastereoselectivities (*dr* >20:1). The reaction was tolerant of a variety of electron-neutral and electron-rich aromatic rings with several substitution patterns (**6a-e**). The presence of a halogen atom on the aromatic ring was also tolerated (**6f**). Heteroaromatic substituents at the stereogenic center resulted in interesting scaffolds combining two potential pharmacophores (**6g-j**). However, pyridine-based **6j** resulted in a low yield. Substrates derived from aliphatic aldehydes, both linear and cyclic, were also successfully used (**6k-n**). The absolute stereochemistry of product **6a** was determined to be (*S*, *R*) by X-ray crystallography (see Supporting Information for details) (Scheme 4).[22]

The double bond in the resulting bicyclic products **6** could be efficiently and diastereoselectively (*dr* >20:1) hydrogenated using palladium over activated charcoal under an atmosphere of hydrogen.[23] However, it is worth noting that the resulting saturated product **7** was unstable in acidic conditions, and rapidly lost HF during column chromatography using both standard silica gel and aluminum oxide (Scheme 5a).

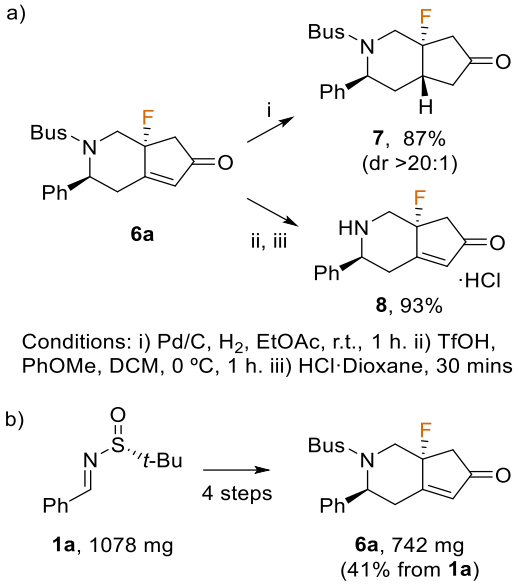
Scheme 4. Scope and limitations of the fluoro-Pauson-Khand reaction



Nonetheless, using FluoroFlash® silica gel we were able to purify the desired saturated cyclopentanones **7** successfully, with no loss of HF. Furthermore, the *tert*-butyl sulfonyl group could be removed through treatment of the resulting Pauson-Khand adduct with trifluoromethylsulfonic acid in the presence of anisole to form **8** (Scheme 5a).[24] The resulting amine was isolated as the hydrochloride salt, as the intermediate free amine was found to be unstable. A gram-scale synthesis of **6a** was carried out successfully in good yield and no detectable decrease diastereoselectivity (Scheme 5b).

In summary, the power of the intramolecular Pauson-Khand reaction for the stereoselective construction of enantioenriched bicyclic cyclopentenones has been showcased by the concise asymmetric synthesis of fluorinated Tecomanine analogues. Noteworthy is the use of vinyl fluorides as olefin counterparts in the Pauson-Khand reaction, allowing the stereoselective introduction of a fluorine atom in an otherwise synthetically challenging bridgehead quaternary stereocenter. Several synthetic transformations have been carried out on the obtained products, including hydrogenation of the unsaturated bicyclic system to generate the corresponding saturated derivative, and the removal of the Bus protecting group. A gram-scale synthesis has also been successfully achieved in five steps starting from the corresponding aldehyde.

Scheme 5. a) Examples of further modifications to the final Pauson-Khand adducts. b) Gram-scale synthesis of 6a



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, characterization of all new compounds, and their corresponding NMR spectra (PDF).

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

[1] Kavanagh, Y.; O'Brien, M.; Evans, P. Stereocontrolled preparation of bicyclic alkaloid analogues: an approach towards the kinabalurine skeleton. *Tetrahedron*, **2009**, *65*, 8259-8268.

[2] Kam, T.-S.; Yoganathan, K.; Wei, C. Monoterpene Alkaloids from Kopsia pauciflora. *J. Nat. Prod*. **1997**, *60*, 673-676.

[3] Hammouda, Y.; Rashid, A.-K.; Amer, M.-S. Hypoglycaemic properties of tecomine and tecostanine. *J. Pharm. Pharmacol*. **1964**, *16*, 833-834.

[4] Lozoya-Meckes, M.; Mellado-Campos, V. Is the Tecoma Stans infusion an antidiabetic remedy? *J. Ethnopharmacol*. **1985**, *14*, 1-9.

[5] Lamos, E. M.; Hedrington, M.; Davis, S. N. An update on the safety and efficacy of oral antidiabetic drugs: DPP-4 inhibitors and SGLT-2 inhibitors. *Expert Opin. Drug Saf*. **2019**, DOI: 10.1080/14740338.2019.1626823

[6] Ockey, D. A.; Lewis, M. A.; Schore, N. E. A short synthesis of (±)-Tecomanine via a Pauson–Khand-based route. *Tetrahedron*, **2003**, *59*, 5377-5381.

[7] Günter, M.; Gais, H.-J. Asymmetric Synthesis of Fused Bicyclic α-Amino Acids Having a Hexahydro-cyclopenta[*c*]pyridine Skeleton via Intramolecular Pauson-Khand Reaction of 1-Sulfonimidoyl-Substituted 5-Azaoct-1-en-7-ynes. *J. Org. Chem*. **2003**, *68*, 8037-8041.

[8] Purser, S.; Moore, P. M.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320-330.

[9] Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev*. **2014**, *114*, 2432-2506.

[10] Yamazaki, T.; Taguchi, T.; Ojima, I. Unique Properties of Fluorine and Their Relevance to Medicinal Chemistry and Chemical Biology. In Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed; Wiley-Blackwell: Chippenham, **2009**; pp 1-47.

[11] (a) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *MedChemComm*, **2013**, *4*, 515-519. (b) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem*. **2009**, *52*, 6752-6756.

[12] Neumann, C. N.; Ritter, T. Late-Stage Fluorination: Fancy Novelty or Useful Tool? *Angew. Chem. Int. Ed.* **2015**, *54*, 3216-3221.

[13] (a) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073-9174. (b) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon−Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev*. **2018**, *118*, 3887-3964.

[14] Román, R.; Mateu, N.; López, I.; Medio-Simon, M.; Fustero, S.; Barrio, P. Vinyl Fluorides: Competent Olefinic Counterparts in the Intramolecular Pauson−Khand Reaction. *Org. Lett*. **2019**, *21*, 2569-2573.

[15] Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. A One-Pot Synthesis of Doubly Unsaturated Trifluoromethyl Amines: Easy Access to CF_3-Substituted Piperidines. *Eur. J. Org. Chem*. **2005**, *7*, 1258-1265.

[16] Cogan, D. A.; Liu, G.; Ellman, J. Asymmetric synthesis of chiral amines by highly diastereoselective 1,2-additions of organometallic reagents to *N*-*tert*-butanesulfinyl imines. *Tetrahedron*, **1999**, *55*, 8883-8904.

[17] Sedgwick, D. M.; Barrio, P.; Simón, T.; Román, R.; Fustero, S. Asymmetric Allylation/RCM-Mediated Synthesis of Fluorinated Benzo-Fused Bicyclic Homoallylic Amines As Dihydronaphthalene Derivatives. *J. Org. Chem.* **2016**, *81*, 8876-8887.

[18] Cui, L.; Li, C.; Zhang, L. A Modular, Efficient, and Stereoselective Synthesis of Substituted Piperidin-4-ols. *Angew. Chem. Int. Ed*. **2010**, *49*, 9178-9181.

[19] Hao, J.; Milcent, T.; Retailleau, P.; Soloshonok, V. A.; Ongeri, S.; Crousse, B. Asymmetric Synthesis of Cyclic Fluorinated Amino Acids. *Eur. J. Org. Chem*. **2018**, 3688-3692.

[20] Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. K.; Grygorenko, O. O.; Komarov, I. V. 4-Fluoro-2,4-methanoproline. *Org. Lett*. **2009**, *11*, 5674-5676.

[21] Rubio-Presa, R.; Fernández-Rodríguez, M. A.; Pedrosa, M. R.; Arnáiz, F. J.; Sanz, R. Molybdenum-Catalyzed Deoxygenation of Heteroaromatic *N*-Oxides and Hydroxides using Pinacol as Reducing Agent. *Adv. Synth. Catal*. **2017**, *359*, 1752-1757.

[22] The stereochemistry of **7** was tentatively assigned by a series of 2D NMR experiments.

[23] Sun, P.; Weinreb, S. M. *tert*-Butylsulfonyl (Bus), a New Protecting Group for Amines. *J. Org. Chem*. **1997**, *62*, 8604-8608.

Supporting Information

The Fluoro-Pauson-Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C—F Stereogenic Center.

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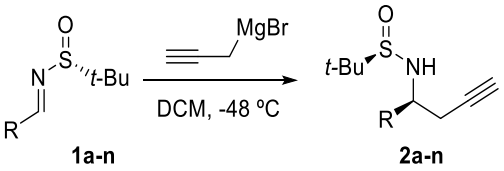
I. General methods

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. CH_2Cl_2 was used without further purification. The reactions were monitored with the aid of TLC on 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz or 500 MH spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. The abbreviation DCM stands for dichloromethane.

N-tert-Butanesulfinyl aldimines **1a-n** were synthesized according to literature procedures.[1]

Spectroscopic data of these compounds were in agreement with those previously reported: **1a**,**b**,**c**[2]; **1d**[3]; **1e**,**k**[4]; **1f**,**l**[5]; **1g**[6]; **1h**[7]; **1i**[8]; **1j**[9]; **1m**[10]; **1n**[11].

II. General procedure for the propragylation reaction to sulfinamides 2.



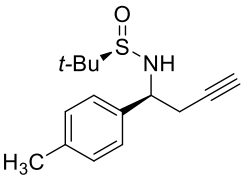
1a-n **2a-n**

Compounds **2a-n** were prepared according to the known procedure.[12]

A 1M solution of propargylmagnesium bromide in THF was prepared by stirring propargyl bromide (14 mmol) and activated Mg (28 mmol) in anhydrous THF (1M, 14 mL) at 50 °C for 2 h. This freshly prepared solution was then added (1.5 equiv, 13.5 mmol) to a solution of corresponding imine **1** (9.0 mmol) in dichloromethane (0.1 M, 90 mL) at −48 °C. After stirring for 18h at −48 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM. The resulting sulfinamides **2a-n** were purified by flash column chromatography.

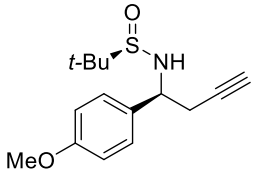
Spectroscopic data of compound **2a** is in agreement with previously reported data.[13]

(*R*)-2-Methyl-*N*-((*S*)-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfinamide (2b)



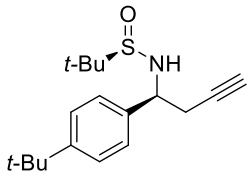
By means of general procedure **II**, from 2.0 g (9.0 mmol) of imine **1b**, 2.2 g of **2b** were obtained as a white solid (93% yield). Mp: 92 - 94 °C; R_f = 0.27 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 121.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 4.51 – 4.57 (m, 1H), 4.01 (d, *J* = 3.0 Hz, 1H), 2.59 – 2.76 (m, 2H), 2.34 (s, 3H), 2.11 (t, *J* = 3.0 Hz, 1H), 2.05 (t, *J* = 3.0 Hz, 1H), 1.22 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.3, 129.3, 127.4, 80.0, 72.1, 56.6, 55.8, 28.8, 22.6, 21.2 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{21}NOS$ [M+H]: 264.1417; found: 264.1410.

(*R*)-*N*-((*S*)-1-(4-Methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2c)



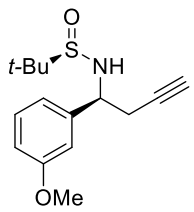
By means of general procedure **II**, from 3.2 g (13.4 mmol) of imine **1c**, 3.4 g of **2c** were obtained as a colorless oil (93% yield); $[\alpha]^{25}_{D}$ = – 76.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.56 – 4.51 (m, 1H), 3.99 (d, *J* = 3.0 Hz, 1H), 3.80 (s, 3H), 2.75-2.58 (m, 2H), 2.11 (t, *J* = 3.0 Hz, 1H), 1.22 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 132.2, 128.6, 113.9, 80.1, 72.0, 56.3, 55.7, 55.2, 28.7, 22.6 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{21}NO_2S$ [M+H]: 280.1366; found: 280.1355.

(*R*)-*N*-((*S*)-1-(4-(*tert*-Butyl)phenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2d)



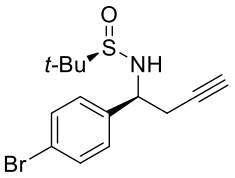
By means of general procedure **II**, from 200 mg (0.75 mmol) of imine **1d**, 172 mg of **2d** were obtained as a colorless oil (75% yield). R_f = 0.27 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_{D}$ =– 80.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 4.58 – 4.52 (m, 1H), 4.04 (d, *J* = 3.5 Hz, 1H), 2.78 – 2.60 (m, 2H), 2.11 (t, *J* = 3.0 Hz, 1H), 1.31 (s, 9H), 1.23 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 28.7, 31.3, 55.9, 56.5, 72.1, 80.1, 125.5, 127.0, 137.2, 150.9 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{27}NOS$ [M+H]: 306.1886; found: 306.1883.

(*R*)-*N*-((*S*)-1-(3-Methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2e)



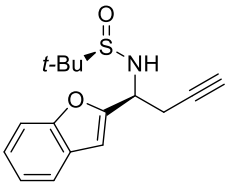
By means of general procedure **II**, from 200 mg (0.84 mmol) of **1e**, 147 mg of **2e** were obtained as a colorless oil (63% yield). R_f = 0.29 (*n*-hexane/EtOAc, 1:1); $[\alpha]^{25}_{D}$ =– 102.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.78 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.49 (ddd, *J* = 8.2, 5.2, 3.3 Hz, 1H), 3.95 (d, *J* = 3.0 Hz, 1H), 3.73 (s, 3H), 2.68 (ddd, *J* = 16.8, 5.2, 2.6 Hz, 1H), 2.58 (ddd, *J* = 16.8, 7.9, 2.6 Hz, 1H), 2.06 (t, *J* = 2.6 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 142.0, 129.6, 119.7, 113.44, 113.0, 79.8, 72.1, 56.7, 55.8, 55.2, 28.7, 22.6; HRMS (ESI): m/z calcd for $C_{15}H_{21}NO_2S$ [M+H]: 280.1366; found: 280.1355.

(*R*)-*N*-((*S*)-1-(4-Bromophenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2f)



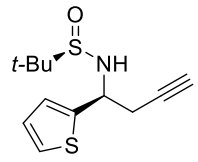
By means of general procedure **II**, from 700 mg (2.42 mmol) of **1f**, 524 mg of **2f** were obtained as a white solid (66% yield). R_f = 0.26 (*n*-hexane/EtOAc, 2:1); Mp = 75 – 77 °C; $[\alpha]^{25}_D$ = –91.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 4.58 – 4.47 (m, 1H), 3.99 (d, *J* = 2.54 Hz, 1H), 2.72 (ddd, *J* = 16.8, 5.4, 2.6 Hz, 1H), 2.62 (ddd, *J* = 16.8, 7.6, 2.5 Hz, 1H), 2.11 (t, *J* = 2.5 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 131.7, 129.1, 122.0, 79.3, 72.4, 56.2, 55.9, 28.5, 22.5; HRMS (ESI): m/z calcd for $C_{14}H_{18}BrNOS$ [M+H]: 328.0365; found: 328.0354.

(*R*)-*N*-((*S*)-1-(Benzofuran-2-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2g)



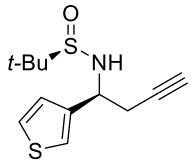
By means of general procedure **II**, from 500 mg (2.00 mmol) of **1g**, 458 mg of **2g** were obtained as a white solid (74% yield). R_f = 0.29 (*n*-hexane/EtOAc, 2:1); Mp = 118 – 120 °C; $[\alpha]^{25}_D$ = – 91.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 1H), 7.47 – 7.42 (m, 2H), 7.31 – 7.18 (m, 2H), 6.72 (t, *J* = 0.8 Hz, 2H), 4.77 (q, *J* = 6.0 Hz, 1H), 4.04 (d, *J* = 6.4 Hz, 1H), 3.00 – 2.96 (m, 4H), 2.10 (t, *J* = 2.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 154.9, 127.8, 124.3, 122.8, 121.1, 111.1, 104.8, 79.0, 72.4, 56.2, 52.6, 25.7, 22.5; HRMS (ESI): m/z calcd for $C_{16}H_{19}NO_2S$ [M+H]: 290.1209; found: 290.1206.

(*R*)-2-Methyl-*N*-((*S*)-1-(thiophen-2-yl)but-3-yn-1-yl)propane-2-sulfinamide (2h)



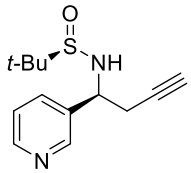
By means of general procedure **II**, from 392 mg (1.82 mmol) of imine **1h**, 278 mg of **2h** were obtained as a white solid (60% yield). Mp: 80 - 81 °C; R_f = 0.30 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ = – 67.6 (*c* 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 6.96 (dd, *J* = 4.8, 3.3 Hz, 1H), 4.86 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.10 (d, *J* = 4.5 Hz, 1H), 2.91 – 2.74 (m, 2H), 2.13 (t, *J* = 2.4 Hz, 1H), 1.24 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 126.8, 125.6, 125.5, 79.4, 72.6, 56.2, 53.5, 29.2, 22.6 ppm. HRMS (ESI): m/z calcd for $C_{12}H_{17}NOS_2$ [M+H]: 256.0824; found: 256.0822.

(*R*)-2-Methyl-*N*-((*S*)-1-(thiophen-3-yl)but-3-yn-1-yl)propane-2-sulfinamide (2i)



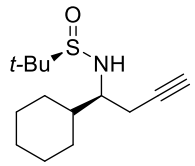
By means of general procedure **II**, from 750 mg (3.5 mmol) of imine **1i**, 730 mg of **2i** were obtained as a white solid (82% yield). Mp: 60 - 61 °C; R_f = 0.22 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ = – 90.3 (*c* 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 6.98 (dd, *J* = 5.1, 1.5 Hz, 1H), 4.60 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.94 (d, *J* = 4.5 Hz, 1H), 2.77-2.61 (m, 2H), 2.05 (t, *J* = 5.4 Hz, 1H), 1.16 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 126.3, 126.2, 122.9, 79.8, 72.6, 55.9, 53.2, 28.1, 22.6 ppm. HRMS (ESI): m/z calcd for $C_{12}H_{17}NOS_2$ [M+H]: 256.0824; found: 256.0833.

(*R*)-2-Methyl-*N*-((*S*)-1-(pyridin-3-yl)but-3-yn-1-yl)propane-2-sulfinamide (2j)



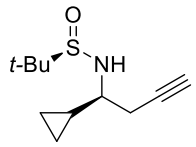
By means of general procedure **II**, from 680 mg (3.23 mmol) of **1j**, 486 mg of **2j** were obtained as a colorless oil (60% yield). R_f = 0.26 (EtOAc/MeOH, 10:1); $[\alpha]^{25}_D$ = – 120.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.43 (s, 1H), 7.59 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.18 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.50 (td, *J* = 6.4, 4.0 Hz, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 3.05 (s, 1H), 2.74 – 2.57 (m, 2H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.7, 135.7, 134.9, 123.2, 78.8, 72.5, 55.8, 54.8, 28.0, 22.3; HRMS (ESI): m/z calcd for $C_{13}H_{18}N_2OS$ [M+H]: 251.1213; found: 251.1212.

(*R*)-*N*-((*S*)-1-Cyclohexylbut-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2k)



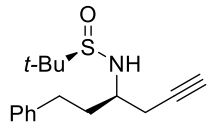
By means of general procedure **II**, from 803 mg (3.73 mmol) of **1k**, 808 mg of **2k** were obtained as a colorless oil (85% yield). R_f = 0.29 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ = – 2.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (d, *J* = 8.9 Hz, 1H), 3.15 – 3.05 (m, 1H), 2.62 (qdd, *J* = 16.9, 5.1, 2.6 Hz, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.81 – 1.59 (m, 6H), 1.23 (s, 9H), 1.18 – 1.09 (m, 1H), 0.95 (ddd, *J* = 24.4, 12.3, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.3, 71.4, 59.8, 56.3, 40.9, 29.5, 29.0, 26.4, 26.1, 26.0, 23.8, 22.8; HRMS (ESI): m/z calcd for $C_{14}H_{25}NOS$ [M+H]: 256.1730; found: 256.1740.

(*R*)-*N*-((*S*)-1-Cyclopropylbut-3-yn-1-yl)-2-methylpropane-2-sulfinamide (2l)



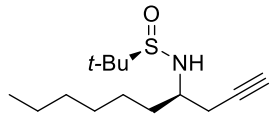
By means of general procedure **II**, from 783 mg (4.51 mmol) of **1l**, 750 mg of **2l** were obtained as a colorless oil (78% yield). R_f = 0.36 (*n*-hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ = – 46.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (d, *J* = 4.6 Hz, 1H), 2.71 – 2.59 (m, 2H), 2.55 – 2.43 (m, 1H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.21 (s, 9H), 0.97 – 0.84 (m, 1H), 0.67 – 0.40 (m, 3H), 0.26 – 0.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.4, 71.4, 58.6, 55.6, 26.8, 22.6, 15.6, 4.8, 2.7; HRMS (ESI): m/z calcd for $C_{11}H_{19}NOS$ [M+H]: 214.1260; found: 214.1255.

(*R*)-2-Methyl-*N*-((*R*)-1-phenylhex-5-yn-3-yl)propane-2-sulfinamide (2m)



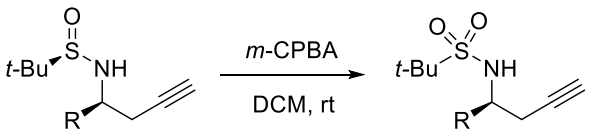
By means of general procedure **II**, from 615 mg (2.59 mmol) of **1m**, 582 mg of **2m** were obtained as a colorless oil (81% yield). R_f = 0.28 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ = – 14.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.16 – 7.08 (m, 3H), 3.51 (d, *J* = 8.8 Hz, 1H), 3.39 – 3.26 (m, 1H), 2.74 – 2.52 (m, 3H), 2.45 (ddd, *J* = 16.8, 4.4, 2.7 Hz, 1H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.88 (dddd, *J* = 8.7, 7.5, 6.0, 2.5 Hz, 2H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$*d*) δ 141.3, 128.4, 128.3, 125.9, 79.8, 71.7, 56.1, 54.2, 36.6, 31.9, 26.6, 22.6; HRMS (ESI): m/z calcd for $C_{16}H_{23}NOS$ [M+H]: 278.1573; found: 278.1576.

(*R*)-*N*-((*R*)-Dec-1-yn-4-yl)-2-methylpropane-2-sulfinamide (2n)



By means of general procedure **II**, from 758 mg (3.49 mmol) of **1n**, 664 mg of **2n** were obtained as a colorless oil (74% yield). R_f = 0.29 (*n*-hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ = –19.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (d, *J* = 8.4 Hz, 1H), 3.40 – 3.26 (m, 1H), 2.63 (ddd, *J* = 16.7, 5.7, 2.7 Hz, 1H), 2.46 (ddd, *J* = 16.7, 4.6, 2.7 Hz, 1H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.63 – 1.53 (m, 2H), 1.34 – 1.23 (m, 8H), 1.21 (s, 10H), 0.90 – 0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.2, 71.4, 56.0, 54.8, 34.8, 31.7, 28.9, 26.6, 25.6, 22.6, 22.5, 14.00. HRMS (ESI): m/z calcd for $C_{14}H_{27}NOS$ [M+H]: 258.1886; found: 258.1891.

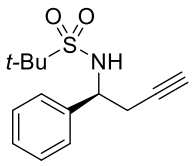
III. General procedure for oxidation reaction to sulfonamides 3.



2a-n **3a-n**

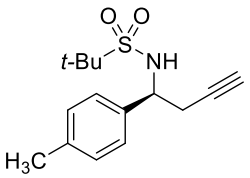
To a solution of corresponding sulfinamide **2** (12.3 mmol) in DCM (120 mL) at 0 °C, *m*-CPBA (14.8 mmol) was added and the mixture was stirred at room temperature for 2 h. After this time, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography affording sulfonamides **3a-n**.

(*S*)-2-Methyl-*N*-(1-phenylbut-3-yn-1-yl)propane-2-sulfonamide (3a)



By means of general procedure **III**, from 1166 mg (4.68 mmol) of **2a**, 1206 mg of **3a** were obtained as a white solid (97% yield). R_f = 0.21 (*n*-hexane/EtOAc, 5:1); Mp = 65 – 67 °C; $[\alpha]^{25}_D$ = – 42.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 4.93 (d, *J* = 9.5 Hz, 1H), 4.73 – 4.58 (m, 1H), 2.78 (ddd, *J* = 16.8, 6.2, 2.7 Hz, 1H), 2.64 (ddd, *J* = 16.8, 5.1, 2.6 Hz, 1H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 128.6, 127.8, 126.3, 79.3, 72.3, 60.0, 56.3, 29.1, 24.1; HRMS (ESI): m/z calcd for $C_{14}H_{19}NO_2S$ [M+H]: 266.1209; found: 266.1211.

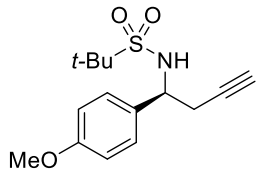
(*S*)-2-Methyl-*N*-(1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (3b)



By means of general procedure **III**, from 468 mg (1.77 mmol) of **2b**, 388 mg of **3b** were obtained as a colorless oil (78% yield). R_f = 0.29 (*n*-hexane/EtOAc, 6:1); $[\alpha]^{25}_D$ = – 31.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 4.85 (d, *J* = 9.0 Hz, 1H), 4.66 – 4.73 (m, 2H), 2.67 – 2.90 (m, 2H), 2.36 (s, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.5, 129.4,

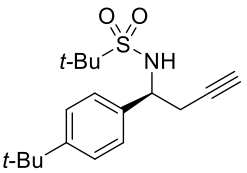
126.3, 79.4, 72.3, 60.1, 56.1, 29.2, 24.2, 21.1 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{21}NO_2S$ [M+NH_4]: 297.1631; found: 297.1636.

(*S*)-*N*-(1-(4-Methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3c)



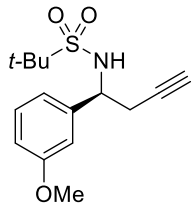
By means of general procedure **III**, from 3.4 g (12.4 mmol) of **2c**, 3.0 g of **3c** were obtained as a white solid (83% yield); Mp: 78 - 80 °C; R_f = 0.31 (*n*-hexane/EtOAc, 7:1); $[\alpha]^{25}_D$ – 38.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.80 (d, *J* = 9.0 Hz, 1H), 4.71-4.64 (m, 1H), 3.80 (s, 3H), 2.89-2.66 (m, 2H), 2.05 (t, *J* = 3.0 Hz, 1H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.8, 127.6, 114.0, 79.5, 72.3, 60.1, 55.8, 55.3, 29.2, 24.2 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{21}NO_3S$ [M+NH_4]: 313.1580; found: 313.1585.

(*S*)-*N*-(1-(4-(*tert*-Butyl)phenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3d)



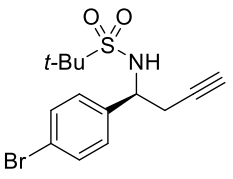
By means of general procedure **III**, from 132 mg (0.43 mmol) of **2d**, 113 mg of **3d** were obtained as a white solid (78% yield); Mp: 120 - 122 °C; R_f = 0.31 (*n*-hexane/EtOAc, 6:1); $[\alpha]^{25}_D$ = – 46.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 4.82 (d, *J* = 9.0 Hz, 1H), 4.74 – 4.67 (m, 1H), 2.92 – 2.67 (m, 2H), 2.06 (t, *J* = 3.0 Hz, 1H), 1.34 (s, 9H), 1.31 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 137.5, 125.9, 125.6, 79.6, 72.3, 60.1, 56.0, 34.5, 31.3, 28.9, 24.2 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{27}NO_2S$ [M+NH_4]: 339.2101; found: 339.2102.

(*S*)-*N*-(1-(3-Methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3e)



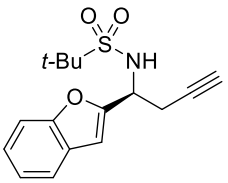
By means of general procedure **III**, from 103 mg (0.37 mmol) of **2e**, 83 mg of **3e** were obtained as a white solid (76% yield). R_f = 0.30 (*n*-hexane/EtOAc, 3:1); Mp = 95 – 97 °C; $[\alpha]^{25}_D$ = – 37.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.88 – 6.80 (m, 1H), 4.87 (d, *J* = 9.5 Hz, 1H), 4.69 (dt, *J* = 9.7, 5.5 Hz, 1H), 3.81 (s, 3H), 2.87 (ddd, *J* = 16.8, 6.1, 2.6 Hz, 1H), 2.71 (ddd, *J* = 16.8, 4.9, 2.6 Hz, 1H), 2.06 (t, *J* = 2.6 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 142.2, 129.7, 118.6, 113.0, 112.3, 79.2, 72.4, 60.1, 56.2, 55.2, 29.1, 24.1; HRMS (ESI): m/z calcd for $C_{15}H_{21}NO_3S$ [M+K]: 334.0874; found: 334.0864.

(*S*)-*N*-(1-(4-Bromophenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3f)



By means of general procedure **III**, from 522 mg (1.59 mmol) of **2f**, 336 mg of **3f** were obtained as a white solid (61% yield). R_f = 0.29 (*n*-hexane/EtOAc, 5:1); Mp = 84 – 86 °C; $[\alpha]^{25}_D$ = – 46.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.25 – 7.20 (m, 2H), 4.93 (d, *J* = 9.5 Hz, 1H), 4.75 – 4.62 (m, 1H), 2.84 (ddd, *J* = 16.8, 6.2, 2.7 Hz, 1H), 2.68 (ddd, *J* = 16.8, 5.0, 2.6 Hz, 1H), 2.07 (t, *J* = 2.6 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 131.8, 128.1, 121.8, 78.8, 72.7, 60.1, 55.8, 28.9, 24.1; HRMS (ESI): m/z calcd for $C_{14}H_{18}BrNO_2S$ [M+NH_4]: 361.0580; found: 361.0570.

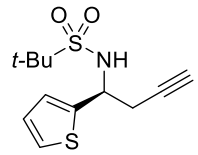
(*S*)-*N*-(1-(Benzofuran-2-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3g)



By means of general procedure **III**, from 367 mg (1.27 mmol) of **2g**, 303 mg of **3g** were obtained as a white solid (78% yield). R_f = 0.29 (*n*-hexane/EtOAc, 5:1); Mp = 108 – 110 °C; $[\alpha]^{25}_D$ = – 79.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1H), 7.43 – 7.36 (m, 1H), 7.26 – 7.13 (m, 2H), 6.72 (s, 1H), 4.91 – 4.71 (m, 2H), 2.91 (dd, *J* = 5.0, 2.6 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 154.8, 127.9, 124.4, 123.0, 121.2, 111.2, 104.3, 78.6, 72.4, 60.4, 51.5, 26.2, 24.1; HRMS (ESI): m/z calcd for $C_{16}H_{19}NO_3S$ [M+NH_4]: 323.1424; found: 323.1418.

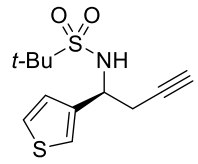
(*S*)-2-Methyl-*N*-(1-(thiophen-2-yl)but-3-yn-1-yl)propane-2-sulfonamide (3h)

By means of general procedure **III**, from 370 mg (1.45 mmol) of **2h**, 306 mg of **3h** were



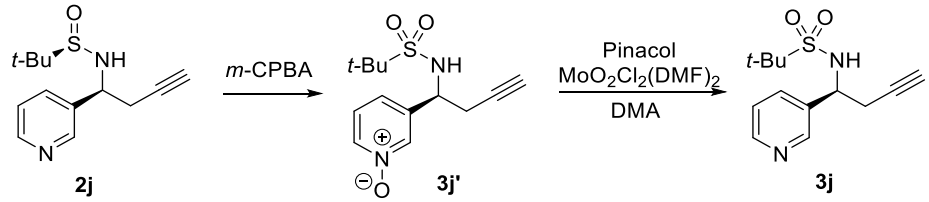
obtained as a colorless oil (78% yield); R_f = 0.33 (*n*-hexane/EtOAc, 7:1); $[\alpha]^{25}_D$ = – 19.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.07 (dt, *J* = 3.6, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.64 (d, *J* = 10.0 Hz, 1H), 3.03 – 2.81 (m, 2H), 2.10 (t, *J* = 2.7 Hz, 1H), 1.40 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 127.0, 125.0, 124.9, 78.9, 72.9, 60.4, 52.7, 29.1, 24.1 ppm. HRMS (ESI): m/z calcd for $C_{12}H_{17}NO_2S_2$ [M+NH_4]: 289.11039; found: 289.1040.

(*S*)-2-Methyl-*N*-(1-(thiophen-3-yl)but-3-yn-1-yl)propane-2-sulfonamide (3i)



By means of general procedure **III**, from 720 mg (2.86 mmol) of **2i**, 535 mg of **3i** were obtained as a white solid (70% yield); Mp: 78 - 80 °C; R_f = 0.30 (*n*-hexane/EtOAc, 7:1); $[\alpha]^{25}_D$ =– 42.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H), 7.12 (dd, *J* = 4.8, 1.5 Hz, 1H), 4.84 - 4.73 (m, 2H), 2.94 – 2.72 (m, 2H), 2.07 (t, *J* = 2.4 Hz, 1H), 1.36 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 126.5, 126.0, 121.9, 79.4, 72.4, 60.2, 52.6, 28.3, 24.2 ppm. HRMS (ESI): m/z calcd for $C_{12}H_{17}NO2S_2$ [M+NH_4]: 289.1038; found: 289.1039.

Synthesis of (*S*)-2-methyl-*N*-(1-(pyridin-3-yl)but-3-yn-1-yl)propane-2-sulfonamide (3j)

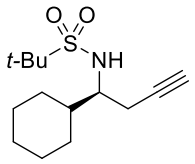


By means of general procedure **III** and adding 3 equiv of *m*-CPBA, from 380 mg (1.52 mmol) of **2j**, 212 mg of (*S*)-3-(1-((1,1-dimethylethyl)sulfonamido)but-3-yn-1-yl)pyridine 1-oxide **3j'** were obtained as a white solid (49% yield). R_f = 0.21 (EtOAc:MeOH, 5:1); Mp = 205 – 207 °C; $[\alpha]^{25}_D$ = - 34.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, MeOD) δ 8.50 (t, *J* = 1.6 Hz, 1H), 8.31 (dq, *J* = 6.3, 1.0 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 8.0, 6.3 Hz, 1H), 4.77 (t, *J* = 7.1 Hz, 1H), 2.89 – 2.70 (m, 2H), 2.52 (t, *J* = 2.6 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, MeOD) δ 144.5, 139.3, 139.2, 129.2, 127.8, 80.29, 73.5, 61.2, 56.1, 28.0, 24.5; HRMS (ESI): m/z calcd for $C_{13}H_{19}N_2O_3S$ [M+H]: 283.1111; found: 283.1111.

To a stirred solution of **3j'** (212 mg, 0.75 mmol) in DMA (1.5 mL), pinacol (98 mg, 0.77 mmol) and $MoO_2Cl_2(DMF)_2$ (12 mg, 5 mol%) were added and the mixture was stirred at 130 °C overnight. After completion, the reaction mixture was cooled to room temperature, treated with 0.3 M aqueous NaOH and extracted with EtOAc (x3). The combined organic layers were washed with 0.3 M aqueous NaOH and brine and then dried over Na_2SO_4, filtered and the solvents evaporated under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc, 1:2) to yield 198 mg of **3j** (99%) as a white solid. R_f = 0.21 (*n*-hexane/EtOAc, 1:2); Mp = 95 – 97 ºC; $[\alpha]^{25}_D$ = -

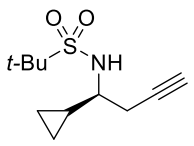
38.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 19.7 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 5.45 (d, *J* = 9.5 Hz, 1H), 4.77 (dt, *J* = 9.9, 5.7 Hz, 1H), 2.88 (ddd, *J* = 16.8, 6.2, 2.5 Hz, 1H), 2.74 (ddd, *J* = 16.9, 5.0, 2.6 Hz, 1H), 2.08 (t, *J* = 2.5 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.0, 136.5, 134.2, 123.6, 78.6, 72.9, 60.2, 54.4, 28.7, 24.1; HRMS (ESI): m/z calcd for $C_{13}H_{22}N_3O_2S$ [M+NH_4]: 284.1433; found: 284.1440.

(*S*)-*N*-(1-Cyclohexylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3k)



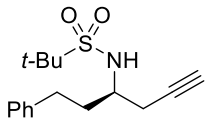
By means of general procedure **III**, from 339 mg (1.33 mmol) of **2k**, 324 mg of **3k** were obtained as a colorless oil (90% yield). R_f = 0.31 (*n*-hexane/EtOAc, 7:1); $[\alpha]^{25}_D$ = + 40.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, *J* = 10.2 Hz, 1H), 3.30 (dddd, *J* = 10.1, 7.6, 5.3, 4.0 Hz, 1H), 2.69 – 2.49 (m, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.84 – 1.72 (m, 3H), 1.71 – 1.61 (m, 2H), 1.41 (s, 9H), 1.31 – 1.13 (m, 3H), 1.09 – 0.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.0, 71.3, 59.9, 57.5, 41.0, 29.6, 29.3, 26.1, 26.0, 26.0, 24.2, 23.4; HRMS (ESI): m/z calcd for $C_{14}H_{25}NO_2S$ [M+H]: 272.1679; found: 272.1675.

(*S*)-*N*-(1-Cyclopropylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (3l)



By means of general procedure **III**, from 745 mg (3.49 mmol) of **2l**, 640 mg of **3l** were obtained as a white solid (80% yield). R_f = 0.31 (*n*-hexane/EtOAc, 5:1); Mp = 64 – 66 °C; $[\alpha]^{25}_D$ = + 31.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, *J* = 8.9 Hz, 1H), 2.89 (tdd, *J* = 9.0, 5.1, 3.9 Hz, 1H), 2.67 (ddd, *J* = 16.7, 5.2, 2.7 Hz, 1H), 2.54 (ddd, *J* = 16.7, 3.8, 2.7 Hz, 1H), 2.07 (t, *J* = 2.6 Hz, 1H), 1.40 (s, 9H), 1.22 – 1.08 (m, 1H), 0.68 – 0.51 (m, 3H), 0.36 – 0.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.0, 71.5, 59.8, 57.3, 26.5, 24.3, 16.4, 4.4, 4.3; HRMS (ESI): m/z calcd for $C_{11}H_{19}NO_2S$ [M+NH_4]: 247.1475; found: 247.1471.

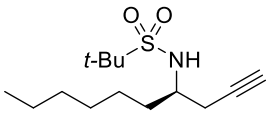
(*S*)-2-Methyl-*N*-(1-phenylhex-5-yn-3-yl)propane-2-sulfonamide (3m)



By means of general procedure **III**, from 451 mg (1.63 mmol) of **2m**, 391 mg of **3m** were obtained as a colorless oil (82% yield). R_f = 0.23 (*n*-hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = + 13.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 2H), 7.18 – 7.10 (m, 3H), 4.18 (d, *J* = 9.9 Hz, 1H), 3.52 (dddd, *J* = 12.4, 6.9, 4.3, 2.8 Hz, 1H), 2.72 – 2.54 (m, 3H), 2.47 (ddd, *J* = 17.0, 3.8, 2.7 Hz, 1H), 2.03 (t, *J* = 2.6 Hz, 1H), 2.01 – 1-90 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9,

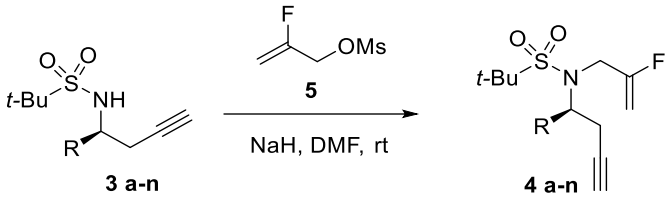
128.4, 128.2, 126.0, 79.3, 71.8, 59.8, 52.6, 36.4, 32.3, 25.7, 24.2. HRMS (ESI): m/z calcd for $C_{16}H_{23}NO_2S$ [M+H]: 294.1522; found: 294.1521.

(*S*)-*N*-(Dec-1-yn-4-yl)-2-methylpropane-2-sulfonamide (3n)



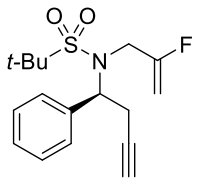
By means of general procedure **III**, from 300 mg (1.17 mmol) of **2n**, 268 mg of **3n** were obtained as a colorless oil (84% yield). R_f = 0.34 (*n*-hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = + 35.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (d, *J* = 10.0 Hz, 1H), 3.57 – 3.44 (m, 1H), 2.60 (ddd, *J* = 16.9, 5.4, 2.7 Hz, 1H), 2.44 (ddd, *J* = 16.9, 3.7, 2.6 Hz, 1H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.73 – 1.61 (m, 2H), 1.39 (s, 9H), 1.36 – 1.21 (m, 8H), 0.92 – 0.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.6, 71.5, 59.8, 53.0, 34.9, 31.6, 29.0, 26.0, 25.7, 24.2, 22.5, 14.0. HRMS (ESI): m/z calcd for $C_{14}H_{27}NO_2S$ [M+H]: 274.1835; found: 274.1838.

IV. General procedure for fluoro-allylation reaction.



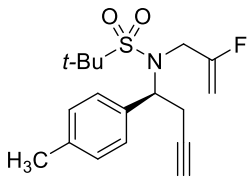
To a suspension of NaH (60%, 6.8 mmol) in dry DMF (40 mL), sulfonamide **3** (4.54 mmol) was added dropwise at 0 °C. After stirring at this temperature for 20 minutes, fluorinated mesylate **5** (9.1 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH_4Cl aq. and extracted with diethyl ether. The organic layer was then dried over anhydrous Na_2SO_4, concentrated under vacuum and the crude reaction mixture was then purified by flash column chromatography.

(*S*)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-phenylbut-3-yn-1-yl)propane-2-sulfonamide (4a)



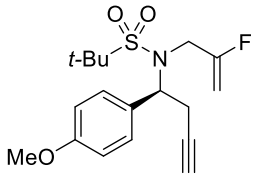
By means of general procedure **IV**, from 1206 mg (4.54 mmol) of **3a**, 1058 mg of **4a** were obtained as a colorless oil (72% yield). R_f = 0.34 (*n*-hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = – 32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.45 – 7.28 (m, 3H), 5.28 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.69 (dd, *J* = 16.1, 3.1 Hz, 1H), 4.41 (dd, *J* = 48.3, 3.0 Hz, 1H), 4.13 – 3.95 (m, 1H), 3.43 (dd, *J* = 18.9, 16.6 Hz, 1H), 3.32 – 3.17 (m, 1H), 3.11 – 2.95 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.47 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.27 (dq, *J* = 48.9, 15.8 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, *J* = 261.0 Hz), 136.2, 128.8, 128.5, 128.3, 95.0 (d, *J* = 18.0 Hz), 80.7, 71.5, 62.4, 61.1, 45.9 (d, *J* = 27.7 Hz), 24.8, 23.0; HRMS (ESI): m/z calcd for $C_{17}H_{22}FNO_2S$ [M+NH_4]: 341.1694; found: 341.1699.

(S)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (4b)



By means of general procedure **IV**, from 110 mg (0.39 mmol) of **3b**, 59 mg of **4b** were obtained as a colorless oil (45% yield). R_f = 0.32 (*n*-hexane/EtOAc, 6:1); $[\alpha]^{25}_D$ = – 30.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 5.26 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.69 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.41 (dd, *J* = 48.0, 3.0, 1H), 4.04 (dd, *J* = 18.0, 15.0 Hz, 1H), 3.41 (dd, *J* = 18.0, 15.0 Hz, 1H), 3.27 – 3.17 (m, 1H), 3.02 – 2.94 (m, 1H), 2.35 (s, 3H), 1.97 (t, *J* = 3.0 Hz, 1H), 1.47 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.1 – -101.5 (m, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, J^1_{CF} = 261.2 Hz), 138.1, 133.1, 129.2, 128.8, 94.9 (d, J^2_{CF} = 18.1 Hz), 80.8, 71.4, 62.4, 60.9, 45.7 (d, J^2_{CF} = 27.9 Hz), 24.8, 23.0 (d, J^3_{CF} = 3.0 Hz), 21.1 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{24}FNO_2S$ [M+NH_4]: 355.1850; found: 355.1835.

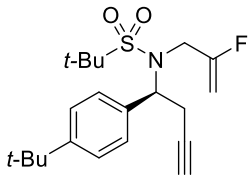
(*S*)-*N*-(2-Fluoroallyl)-*N*-(1-(4-methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4c)



By means of general procedure **IV**, from 460 mg (1.56 mmol) of **3c**, 456 mg of **4c** were obtained as a colorless oil (83% yield). R_f = 0.32 (*n*-hexane/EtOAc, 6:1); $[\alpha]^{25}_D$ = – 22.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.24 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.69 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.43 (dd, *J* = 48.0, 3.0

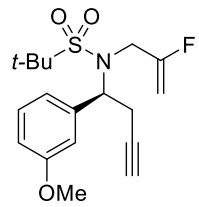
Hz, 1H), 4.03 (t, *J* = 15.0 Hz, 1H), 3.41 (dd, *J* = 18.0, 15.0 Hz, 1H), 3.26 – 3.15 (m, 1H), 3.01 – 2.93 (m, 1H), 1.97 (t, *J* = 3.0 Hz, 1H), 1.46 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.2 – -101.5 (m, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, J^1_{CF} = 261.2 Hz), 159.4, 130.2, 128.1, 113.8, 94.9 (d, J^2_{CF} = 18.1 Hz), 80.8, 71.4, 62.4, 60.7, 55.3, 45.7 (d, J^2_{CF} = 28.0 Hz), 24.8, 23.1 (d, *J* = 3.0 Hz) ppm. HRMS (ESI): m/z calcd for $C_{18}H_{24}FNO_3S$ [M+NH_4]: 371.1799; found: 371.1797.

(*S*)-*N*-(1-(4-(*tert*-Butyl)phenyl)but-3-yn-1-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4d)



By means of general procedure **IV**, from 104 mg (0.32 mmol) of **3d**, 74 mg of **4d** were obtained as a colorless oil (60% yield). R_f = 0.32 (*n*-hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ = – 22.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 5.25 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.68 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.41 (dd, *J* = 48.0, 3.0 Hz, 1H), 4.04 (t, *J* = 15 Hz, 1H), 3.41 (t, *J* = 18 Hz, 1H), 3.27 – 3.17 (m, 1H), 2.95 – 3.03 (m, 1H), 1.99 (t, *J* = 3.0 Hz, 1H), 1.47 (s, 9H), 1.32 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.0 – -101.4 (m, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J^1_{CF} = 260.5 Hz), 151.2, 133.1, 128.4, 125.4, 94.9 (d, J^2_{CF} = 18.1 Hz), 80.0, 71.4, 62.4, 60.9, 45.8 (d, J^2_{CF} = 28.0 Hz), 34.6, 31.2, 24.8 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{30}FNO_2S$ [M+NH_4]: 397.2320; found: 397.2338.

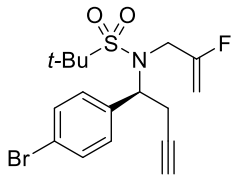
(*S*)-*N*-(2-Fluoroallyl)-*N*-(1-(3-methoxyphenyl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4e)



By means of general procedure **IV**, from 57 mg (0.19 mmol) of **3e**, 51 mg of **4e** were obtained as a colorless oil (75% yield). R_f = 0.35 (*n*-hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ = – 41.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.11 (m, 2H), 6.91 – 6.83 (m, 1H), 5.25 (dd, *J* = 10.8, 4.3 Hz, 1H), 4.69 (dd, *J* = 16.1, 3.1 Hz, 1H), 4.43 (dd, *J* = 48.3, 3.1 Hz, 1H), 4.05 (t, *J* = 15.8 Hz, 1H), 3.82 (s, 3H), 3.44 (dd, *J* = 18.6, 16.7 Hz, 1H), 3.21 (dddd, *J* = 17.0, 10.8, 2.5, 0.9 Hz, 1H), 3.06 – 2.90 (m, 1H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.47 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.16 (dq, *J* = 49.0, 16.2 Hz, 1F);

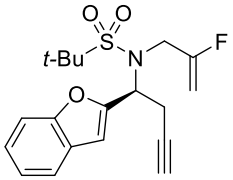
^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, *J* = 260.8 Hz), 159.7, 137.8, 129.3, 120.8, 114.5, 113.9, 95.0 (d, *J* = 18.1 Hz), 80.7, 71.5, 62.4, 61.0, 55.2, 45.8 (d, *J* = 27.7 Hz), 24.8, 23.0; HRMS (ESI): m/z calcd for $C_{18}H_{24}FNO_3S$ [M+K]: 392.1093; found: 392.1079.

(*S*)-*N*-(1-(4-Bromophenyl)but-3-yn-1-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4f)



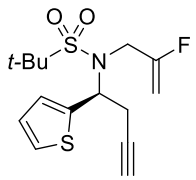
By means of general procedure **IV**, from 336 mg (0.96 mmol) of **3f**, 193 mg of **4f** were obtained as a white solid (50% yield). R_f = 0.21 (*n*-hexane/EtOAc, 15:1); Mp = 75 – 77 °C; $[\alpha]^{25}_D$ = – 17.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 4H), 5.22 (dd, *J* = 10.9, 4.4 Hz, 1H), 4.71 (dd, *J* = 16.0, 3.2 Hz, 1H), 4.43 (dd, *J* = 48.2, 3.2 Hz, 1H), 4.05 (t, *J* = 15.8 Hz, 1H), 3.41 (dd, *J* = 18.6, 16.7 Hz, 1H), 3.20 (dddd, *J* = 17.0, 10.9, 2.5, 0.9 Hz, 1H), 2.97 (ddd, *J* = 17.1, 4.1, 4.0 Hz, 1H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.46 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.29 (dq, *J* = 49.1, 16.4 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (d, *J* = 260.9 Hz), 135.3, 131.6, 130.6, 122.5, 95.3 (d, *J* = 18.1 Hz), 80.3, 71.9, 62.4, 60.5, 45.9 (d, *J* = 27.5 Hz), 24.7, 22.8; HRMS (ESI): m/z calcd for $C_{17}H_{21}BrFNO_2S$ [M+NH_4]: 419.0799; found: 419.0787.

(*S*)-*N*-(1-(Benzofuran-2-yl)but-3-yn-1-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4g)



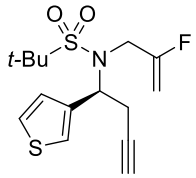
By means of general procedure **IV**, from 165 mg (0.54 mmol) of **3g**, 178 mg of **4g** were obtained as a white solid (91% yield). R_f = 0.21 (*n*-hexane/EtOAc, 10:1); Mp = 72 – 74 °C; $[\alpha]^{25}_D$ = + 16.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 1H), 7.46 – 7.39 (m, 1H), 7.31 – 7.15 (m, 2H), 6.85 (s, 1H), 5.25 (dd, *J* = 10.3, 4.8 Hz, 1H), 4.60 (dd, *J* = 15.8, 3.1 Hz, 1H), 4.40 (dd, *J* = 47.7, 3.0 Hz, 1H), 4.09 (dd, *J* = 16.4, 11.9 Hz, 1H), 3.50 (dd, *J* = 19.5, 16.6 Hz, 1H), 3.16 (ddd, *J* = 16.8, 10.3, 2.5 Hz, 1H), 3.00 (ddd, *J* = 16.8, 4.8, 2.8 Hz, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.48 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.03 – -101.54 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.63 (d, *J* = 261.5 Hz), 154.7, 152.9, 127.6, 124.8, 123.1, 121.4, 111.2, 107.6, 94.5 (d, *J* = 17.8 Hz), 79.9, 71.6, 63.0, 56.9, 46.1 (d, *J* = 30.1 Hz), 24.6, 23.2; HRMS (ESI): m/z calcd for $C_{19}H_{22}FNO_3S$ [M+NH_4]: 381.1643; found: 381.1641.

(*S*)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-(thiophen-2-yl)but-3-yn-1-yl)propane-2-sulfonamide (4h)



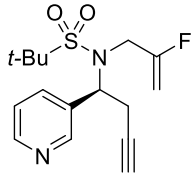
By means of general procedure **IV**, from 130 mg (0.48 mmol) of **3h**, 120 mg of **4h** were obtained as a colorless oil (76% yield). R_f = 0.32 (*n*-hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = – 13.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.22 (dt, *J* = 3.6, 1.2 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.37 (dd, *J* = 10.2, 4.8 Hz, 1H), 4.69 (dd, *J* = 16.0, 3.0 Hz, 1H), 4.49 (dd, *J* = 48.0, 3.0 Hz, 1H), 4.09 (t, *J* = 16.0 Hz, 1H), 3.52 (dd, *J* = 18.0, 16.0 Hz, 1H), 3.23 – 3.01 (m, 2H), 2.04 (t, *J* = 2.4 Hz, 1H), 1.48 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.1 (br, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, J^1_{CF} = 259.5 Hz), 140.2, 127.9, 126.6, 126.5, 95.0 (d, J^2_{CF} = 18.1 Hz), 80.3, 71.7, 62.5, 58.1, 45.3 (d, J^2_{CF} = 28.7 Hz), 25.1, 24.7 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{20}FNO_2S_2$ [M+NH_4]: 347.1258; found: 347.1253.

(*S*)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-(thiophen-3-yl)but-3-yn-1-yl)propane-2-sulfonamide (4i)



By means of general procedure **IV**, from 200 mg (0.74 mmol) of **3i**, 172 mg of **4i** were obtained as a colorless oil (71% yield). R_f = 0.32 (*n*-hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ = – 24.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.41 (m, 1H), 7.33 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.67 (dd, *J* = 15.9, 3.0 Hz, 1H), 4.38 (dd, *J* = 48.0, 3.0 Hz, 1H), 4.06 (t, *J* = 16.8 Hz, 1H), 3.42 (t, *J* = 16.8 Hz, 1H), 3.19 – 2.94 (m, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.47 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.2 – -101.5 (m, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, J^1_{CF} = 261.2 Hz), 138.3, 128.2, 126.0, 124.6, 94.9 (d, J^2_{CF} = 18.1 Hz), 80.7, 71.6, 62.3, 57.9, 45.6 (d, J^2_{CF} = 27.2 Hz), 24.7, 24.2 (d, *J* = 3.0 Hz) ppm. HRMS (ESI): m/z calcd for $C_{15}H_{20}FNO_2S_2$ [M+NH_4]: 347.1258; found: 347.1255.

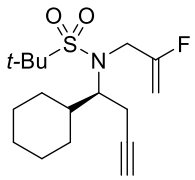
(*S*)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-(pyridin-3-yl)but-3-yn-1-yl)propane-2-sulfonamide (4j)



By means of general procedure **IV**, from 100 mg (0.38 mmol) of **3j**, 56 mg of **4j** were obtained as a colorless oil (46% yield). R_f = 0.29 (*n*-hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ = -17.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 8.00 – 7.87 (m, 1H), 7.33

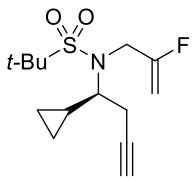
(dd, *J* = 7.9, 4.8 Hz, 1H), 5.25 (dd, *J* = 10.6, 4.8 Hz, 1H), 4.72 (dd, *J* = 16.0, 3.2 Hz, 1H), 4.47 (dd, *J* = 48.1, 3.2 Hz, 1H), 4.07 (t, *J* = 16.0 Hz, 1H), 3.52 (t, *J* = 17.0 Hz, 1H), 3.27 (ddd, *J* = 17.0, 10.7, 2.1 Hz, 1H), 3.04 (ddd, *J* = 17.1, 4.7, 2.7 Hz, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.45 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.28 (dq, *J* = 48.9, 15.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (d, *J* = 261.0 Hz), 150.0, 149.5, 136.8, 132.2, 123.4, 95.5 (d, *J* = 18.0 Hz), 79.9, 72.3, 62.6, 59.5, 46.3 (d, *J* = 27.6 Hz), 24.7, 22.47; HRMS (ESI): m/z calcd for $C_{16}H_{21}FN_2O_2S$ [M+H]: 325.1381; found: 325.1381.

(*S*)-*N*-(1-Cyclohexylbut-3-yn-1-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4k)



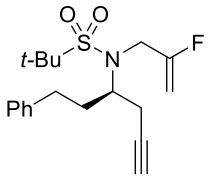
By means of general procedure **IV**, from 200 mg (0.74 mmol) of **3k**, 230 mg of **4k** were obtained as a colorless oil (95% yield). R_f = 0.28 (*n*-hexane/EtOAc, 15:1); $[\alpha]^{25}_D$ = + 15.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, *J* = 16.0, 2.9 Hz, 1H), 4.63 (dd, *J* = 48.0, 2.8 Hz, 1H), 4.18 (dd, *J* = 19.0, 16.2 Hz, 1H), 4.00 (dd, *J* = 18.1, 16.2 Hz, 1H), 3.57 (dt, *J* = 10.2, 5.2 Hz, 1H), 2.77 – 2.57 (m, 2H), 2.10 (t, *J* = 2.7 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.83 – 1.64 (m, 4H), 1.40 (s, 9H), 1.28 – 1.07 (m, 4H), 0.98 (qd, *J* = 12.0, 3.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -99.46 (dq, *J* = 50.3, 17.7 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, *J* = 261.5 Hz), 95.4 (d, *J* = 18.4 Hz), 81.9, 71.8, 63.3, 62.5, 45.7 (d, *J* = 28.0 Hz), 41.0, 31.4, 30.6, 26.6, 26.3, 26.3, 24.9, 23.7; HRMS (ESI): m/z calcd for $C_{17}H_{28}FNO_2S$ [M+H]: 330.1898; found: 330.1894.

(*S*)-*N*-(1-Cyclopropylbut-3-yn-1-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4l)



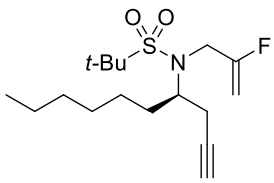
By means of general procedure **IV**, from 46 mg (0.20 mmol) of **3l**, 47 mg of **4l** were obtained as a white solid (82% yield). R_f = 0.35 (*n*-hexane/EtOAc, 5:1); Mp = 44 – 46 °C; $[\alpha]^{25}_D$ = – 4.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 – 4.57 (m, 2H), 4.26 – 4.06 (m, 2H), 3.23 (dt, *J* = 9.3, 7.4 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.41 (s, 9H), 1.21 – 1.08 (m, 1H), 0.80 – 0.69 (m, 1H), 0.69 – 0.60 (m, 1H), 0.60 – 0.43 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -100.63 (dq, *J* = 47.7, 15.9 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, *J* = 261.4 Hz), 94.5 (d, *J* = 18.1 Hz), 81.3, 71.0, 63.8, 62.3, 46.3 (d, *J* = 29.2 Hz), 24.9, 24.8, 14.8, 7.1, 4.0; HRMS (ESI): m/z calcd for $C_{14}H_{22}FNO_2S$ [M+H]: 288.1428; found: 288.1425.

(*S*)-*N*-(2-Fluoroallyl)-2-methyl-*N*-(1-phenylhex-5-yn-3-yl)propane-2-sulfonamide (4m)



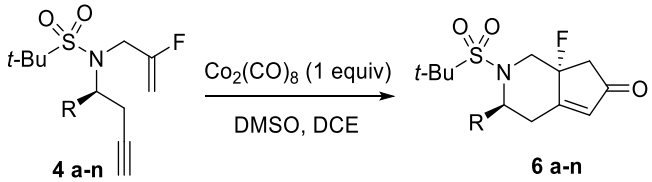
By means of general procedure **IV**, from 110 mg (0.37 mmol) of **3m**, 124 mg of **4m** were obtained as a colorless oil (94% yield). R_f = 0.32 (*n*-hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ = + 16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.10 (m, 5H), 4.75 – 4.45 (m, 2H), 4.02 (d, *J* = 17.1 Hz, 2H), 3.86 (p, *J* = 6.8 Hz, 1H), 2.73 – 2.57 (m, 4H), 2.23 – 1.93 (m, 3H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 100.54 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, *J* = 261.3 Hz), 141.1, 128.4, 128.3, 126.1, 94.7 (d, *J* = 18.1 Hz), 81.0, 71.7, 62.2, 58.4, 45.0 (d, *J* = 28.8 Hz), 35.2, 33.3, 24.6, 23.8. HRMS (ESI): m/z calcd for $C_{19}H_{26}FNO_2S$ [M+NH_4]: 369.2007; found: 369.2005.

(*S*)-*N*-(Dec-1-yn-4-yl)-*N*-(2-fluoroallyl)-2-methylpropane-2-sulfonamide (4n)



By means of general procedure **IV**, from 200 mg (0.73 mmol) of **3n**, 204 mg of **4n** were obtained as a colorless oil (84% yield). R_f = 0.29 (*n*-hexane/EtOAc, 15:1); $[\alpha]^{25}_D$ = + 10.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 – 4.50 (m, 2H), 4.14 – 3.90 (m, 2H), 3.83 (p, *J* = 6.9 Hz, 1H), 2.69 – 2.50 (m, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.90 – 1.60 (m, 2H), 1.40 (s, 9H), 1.36 – 1.20 (m, 8H), 0.91 – 0.81 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -100.15 – -100.86 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, *J* = 261.5 Hz), 94.6 (d, *J* = 18.2 Hz), 81.3, 71.3, 62.2, 59.0, 44.8 (d, *J* = 29.1 Hz), 33.3, 31.6, 29.1, 26.9, 24.7, 23.9, 22.5, 14.0. HRMS (ESI): m/z calcd for $C_{17}H_{30}FNO_2S$ [M+H]: 332.2054; found: 332.2064.

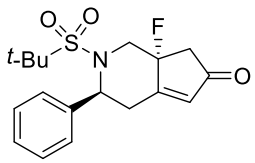
V. General procedure for the intramolecular Pauson-Khand reaction.



$Co_2(CO)_8$ (3.8 mmol) was added to a solution of the corresponding fluorinated enyne **4** (3.15 mmol) in DCE (30 mL) at room temperature (no inert atmosphere required). The reaction mixture was stirred for two hours until complete formation of the alkyne-hexacarbonyldicobalt complex was observed by TLC. Then, DMSO (9.5 mmol) was added

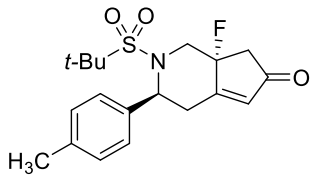
and the reaction was heated to 65 ºC and stirred for another 24-48 hours at this temperature. Upon completion, the solvent was removed in vacuum and the crude reaction mixture was purified by flash column chromatography using mixtures of *n*-hexane and EtOAc as eluent. [14]

(3*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-phenyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6a)



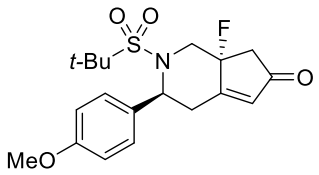
By means of general procedure **V**, from 1020 mg (3.15 mmol) of **4a**, 742 mg of **6a** were obtained as a white solid (67% yield). R_f = 0.26 (*n*-hexane/EtOAc, 3:1); Mp = 155 – 157 °C; $[\alpha]^{25}_D$ = – 88.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H), 6.01 (s, 1H), 5.46 (d, *J* = 4.9 Hz, 1H), 4.34 (dd, *J* = 14.9, 11.2 Hz, 1H), 3.50 – 3.36 (m, 2H), 3.27 (dd, *J* = 34.7, 15.1 Hz, 1H), 2.75 – 2.59 (m, 1H), 2.29 (dd, *J* = 18.8, 11.9 Hz, 1H), 1.53 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -148.00 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 167.9 (d, *J* = 17.8 Hz), 136.2, 132.8, 129.0, 127.8, 126.9, 94.1 (d, *J* = 182.4 Hz), 62.6, 58.0, 51.3 (d, *J* = 24.8 Hz), 43.3 (d, *J* = 23.4 Hz), 30.7, 24.5; HRMS (ESI): m/z calcd for $C_{18}H_{22}FNO_3S$ [M+NH_4]: 369.1643; found: 369.1649.

(*3S,7aR*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(*p*-tolyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[c]pyridin-6-one (6b)



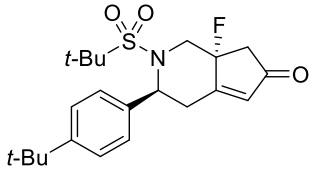
By means of general procedure **V**, from 42 mg (0.13 mmol) of **4b**, 24 mg of **6b** were obtained as a white solid (50% yield); Mp: 148 - 150 °C; R_f = 0.21 (*n*-hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = – 85.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.00 (s, 1H), 5.42 (br, 1H), 4.32 (dd, *J* = 15.0, 12.0 Hz, 1H), 3.44 – 3.33 (m, 2H), 3.25 (dd, *J* = 36.0, 15.0 Hz, 1H), 2.66 (dd, *J* = 18.0, 16.0 Hz, 1H), 2.31 (s, 3H), 2.28 (dd, *J* = 18.0, 12.0 Hz, 1H), 1.52 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.8 (s, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3 (d, *J* = 1.0 Hz), 168.2 (d, J^2_{CF} = 18.1 Hz), 137.5, 133.0, 132.8 (d, *J* = 4.5 Hz), 129.7, 126.9, 95.2 (d, J^1_{CF} = 181.9 Hz), 62.6, 57.8, 51.2 (d, J^2_{CF} = 25.0 Hz), 43.4 (d, J^2_{CF} = 23.4 Hz), 30.8, 24.5, 20.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{24}FNO_3S$ [M+NH_4]: 383.1799; found: 383.1792.

(*3S,7aR*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(4-methoxyphenyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[c]pyridin-6-one (6c)



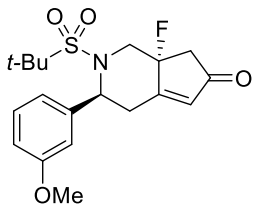
By means of general procedure **V**, from 370 mg (1.048 mmol) of **4c**, 170 mg of **6c** were obtained as a white solid (45% yield); Mp: 80 - 82 °C; R_f = 0.22 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 85.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.03 (s, 1H), 5.40 (br, 1H), 4.30 (dd, *J* = 15.0, 12.0 Hz, 1H), 3.78 (s, 3H), 3.42 – 3.15 (m, 3H), 2.66 (dd, *J* = 21.0, 18.0 Hz, 1H), 2.29 (dd, *J* = 18.0, 12.0 Hz, 1H), 1.52 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.6 (s, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 168.2 (d, J^2_{CF} = 17.4 Hz), 158.9, 132.9 (d, *J* = 4.5 Hz), 128.3, 128.0, 114.4, 94.2 (d, J^1_{CF} = 183.5 Hz), 62.6, 57.5, 55.3, 51.0 (d, J^2_{CF} = 24.2 Hz), 43.4 (d, J^2_{CF} = 22.6 Hz), 30.7, 24.6 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{24}FNO_4S$ [M+NH_4]: 399.17448; found: 399.1745.

(3*S*,7a*R*)-3-(4-(*tert*-Butyl)phenyl)-2-(*tert*-butylsulfonyl)-7a-fluoro-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[c]pyridin-6-one (6d)



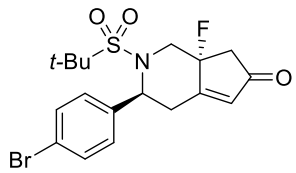
By means of general procedure **V**, from 51 mg (0.13 mmol) of **4d**, 35 mg of **6d** were obtained as a white solid (64% yield); Mp: 204 - 206 °C; R_f = 0.19 (*n*-hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = – 116 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 6.02 (s, 1H), 5.40 (s, 1H), 4.31 (t, J = 12.0 Hz, 1H), 3.41-3.18 (m, 3H), 2.66 (t, J = 18.0, 12.0 Hz, 1H), 1.52 (s, 9H), 1.29 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.9 (s, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 168.3 (d, J^2_{CF} = 18.1 Hz), 150.6, 132.9, 132.8, 126.3, 126.0, 94.2 (d, J^1_{CF} = 183.5 Hz), 62.5, 57.8, 51.1 (d, J^2_{CF} = 24.1 Hz), 43.4 (d, J^2_{CF} = 20.2 Hz), 34.4, 31.2, 24.4 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{30}FNO_3S$ [M+NH_4]: 425.2269; found: 425.2267.

(3*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(3-methoxyphenyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6e)



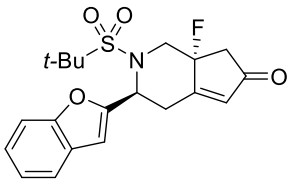
By means of general procedure **V**, from 25 mg (0.07 mmol) of **4e**, 8 mg of **6e** were obtained as a white solid (30% yield). R_f = 0.34 (*n*-hexane/EtOAc, 2:1); Mp = 118 – 120 °C; $[\alpha]^{25}_D$ = – 42.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.1 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.85 – 6.75 (m, 1H), 6.02 (s, 1H), 5.42 (s, 1H), 4.33 (dd, *J* = 14.7, 11.4 Hz, 1H), 3.79 (s, 3H), 3.46 – 3.37 (m, 2H), 3.28 (dd, *J* = 34.8, 15.1 Hz, 1H), 2.67 (t, *J* = 19.0, 1H), 2.30 (dd, *J* = 18.8, 11.9 Hz, 1H), 1.52 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.62 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 167.9 (d, *J* = 17.3 Hz), 160.2, 137.9, 132.8, 130.0, 119.06, 113.4, 112.7, 94.1 (d, *J* = 185.0 Hz), 62.6, 57.8, 55.2, 51.3 (d, *J* = 24.9 Hz), 43.3 (d, *J* = 23.2 Hz), 30.7, 24.5; HRMS (ESI): m/z calcd for $C_{19}H_{24}FNO_4S$ [M+NH_4]: 399.1748; found: 399.1741.

(3*S*,7a*R*)-3-(4-Bromophenyl)-2-(*tert*-butylsulfonyl)-7a-fluoro-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6f)



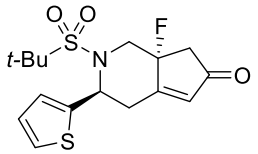
By means of general procedure **V**, from 98 mg (0.24 mmol) of **5f**, 50 mg of **6f** were obtained as a white solid (48% yield). R_f = 0.24 (*n*-hexane/EtOAc, 3:1); Mp = 78 – 80 °C; $[\alpha]^{25}_D$ = – 83.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.02 (s, 1H), 5.39 (s, 1H), 4.32 (dd, *J* = 14.6, 11.2 Hz, 1H), 3.39 (s, 2H), 3.19 (dd, *J* = 34.5, 15.1 Hz, 1H), 2.68 (t, *J* = 19.5 Hz, 1H), 2.31 (dd, *J* = 18.8, 12.1 Hz, 1H), 1.53 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.83 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 167.2 (d, *J* = 17.8 Hz), 135.3, 132.9, 132.2, 128.8, 122.0, 94.1 (d, *J* = 182.8 Hz), 62.7, 57.5, 51.2 (d, *J* = 24.9 Hz), 43.3 (d, *J* = 23.3 Hz), 30.4, 24.5; HRMS (ESI): m/z calcd for $C_{18}H_{21}BrFNO_3S$ [M+NH_4]: 447.0748; found: 447.0734.

(3*S*,7a*R*)-3-(Benzofuran-2-yl)-2-(*tert*-butylsulfonyl)-7a-fluoro-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6g)



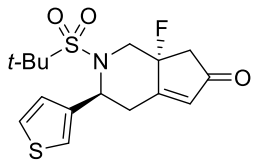
By means of general procedure **V**, from 145 mg (0.40 mmol) of **5g**, 73 mg of **6g** were obtained as a colorless oil (47% yield). R_f = 0.27 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 75.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.56 – 7.49 (m, 1H), 7.44 – 7.38 (m, 1H), 7.32 – 7.19 (m, 3H), 6.68 (s, 1H), 6.13 (s, 1H), 5.54 (s, 1H), 4.45 – 4.27 (m, 1H), 3.48 – 3.29 (m, 2H), 2.72 (dd, *J* = 19.9, 19.0 Hz, 1H), 2.36 (dd, *J* = 18.8, 11.8 Hz, 1H), 1.53 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ - 149.1 (br, 1F) ppm; ^{13}C NMR (75 MHz, $CHCl_3$) δ 201.1, 154.8, 153.4, 132.8, 127.8, 124.7, 123.3, 121.3, 111.2, 106.2, 62.6, 53.7, 51.6 (d, *J*= 25.3 Hz), 43.3 (d, *J*= 23.7 Hz), 29.7, 24.4 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{22}FNO_4S$ $[M+NH_4]$: 409.1592; found: 409.1509.

(*3S,7aR*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(thiophen-2-yl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[c]pyridin-6-one (6h)



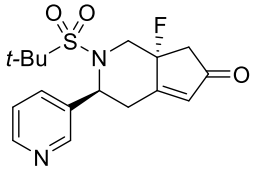
By means of general procedure **V**, from 55 mg (0.17 mmol) of **4h**, 37 mg of **6h** were obtained as a colorless oil (65% yield); R_f = 0.22 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 62.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 4.2 Hz, 1H), 7.01 (d, *J* = 3.3 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.16 (s, 1H), 5.58 (d, *J* = 5.1 Hz, 1H), 4.27 (dd, *J* = 14.4, 11.1 Hz, 1H), 3.42 – 3.29 (m, 3H), 2.70 (dd, *J* = 20.1, 18.9 Hz, 1H), 2.35 (dd, *J* = 18.6, 12.3 Hz, 1H), 1.51 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.9 (s, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 167.5 (d, J^2_{CF} = 17.4 Hz), 140.7, 133.8, 127.2, 125.9, 93.8 (d, J^1_{CF} = 150.7 Hz), 62.6, 55.1, 50.8 (d, J^2_{CF} = 24.2 Hz), 43.3 (d, J^2_{CF} = 23.4 Hz), 32.2, 24.5, 24.4 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{20}FNO_3S_2$ $[M+NH_4]$: 375.1207; found: 375.1195.

(*3S,7aR*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(thiophen-3-yl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[c]pyridin-6-one (6i)



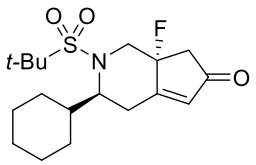
By means of general procedure **V**, from 60 mg (0.19 mmol) of **4i**, 36 mg of **6i** were obtained as a colorless oil (57% yield); R_f = 0.22 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 50.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.16 – 7.11 (m, 2H), 6.11 (s, 1H), 5.39 (br, 1H), 4.25 (dd, *J* = 12.0, 9.0 Hz, 1H), 3.32 (br, 2H), 3.20 (dd, *J* = 36.0, 15.0 Hz, 1H), 2.68 (dd, *J* = 21.0, 18.0 Hz, 1H), 2.32 (dd, *J* = 18.0, 12.0 Hz, 1H), 1.51 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.8 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 168.1 (d, J^2_{CF} = 17.4 Hz), 138.4, 133.2 (d, *J* = 4.5 Hz), 127.2, 126.8, 123.5, 94.3 (d, J^1_{CF} = 183.5 Hz), 62.5, 55.1, 50.9 (d, J^2_{CF} = 24.2 Hz), 43.3 (d, J^2_{CF} = 24.2Hz), 31.3, 24.5 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{20}FNO_3S_2$ [M+NH_4]: 375.1207; found: 375.1202.

(3*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-(pyridin-3-yl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6j)



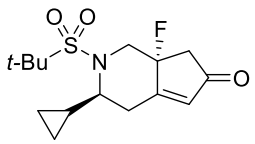
By means of general procedure **V**, from 40 mg (0.12 mmol) of **4j**, 2 mg of **6j** were obtained as a colorless oil (5% yield). R_f = 0.2 (*n*-hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ = – 32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 2H), 7.79 (d, *J*= 7.9 Hz, 1H), 7.36 (s, 1H), 6.08 (s, 1H), 5.48 (d, *J* = 3.2 Hz, 1H), 4.34 (dd, *J* = 14.9, 10.8 Hz, 1H), 3.45 (s, 2H), 3.17 (dd, *J* = 34.2, 15.1 Hz, 1H), 2.70(dd, *J* = 19.0Hz, 1H), 2.44 –2.23 (m, 1H), 1.54 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.84 (br, 1F); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7, 148.2 (d, *J* = 22.0 Hz), 134.9, 133.3, 94.1 (d, *J* = 182.7 Hz), 89.9, 62.9, 56.3, 51.2 (d, *J* = 24.1 Hz), 43.3 (d, *J* = 22.6 Hz), 30.1, 29.7, 24.5 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{21}FN_2O_3S$ [M+H]: 353.1330 ; found: 353.1322.

(3*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-3-cyclohexyl-7a-fluoro-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6k)



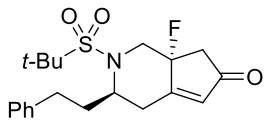
By means of general procedure **V**, from 91 mg (0.28 mmol) of **4k**, 59 mg of **6k** were obtained as a white solid (60% yield). R_f = 0.22 (*n*-hexane/EtOAc, 5:1); Mp = 168 – 170 °C; $[\alpha]^{25}_D$ = – 31.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.10 (dd, *J* = 15.3, 11.6 Hz, 1H), 3.79 – 3.61 (m, 1H), 2.98 (dd, *J* = 34.4, 15.3 Hz, 1H), 2.84 (s, 2H), 2.60 (t, *J* = 19.6 Hz, 1H), 2.33 (dd, *J* = 18.8, 12.3 Hz, 1H), 1.74 – 1.51 (m, 5H), 1.35 (s, 9H), 1.22 – 1.11 (m, 2H), 1.08 – 0.83 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.12 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 169.2 (d, *J* = 17.8 Hz), 133.0 (d, *J* = 4.5 Hz), 94.48 (d, *J* = 182.2 Hz), 62.5, 60.2, 51.2 (d, *J* = 24.7 Hz), 43.6 (d, *J* = 23.5 Hz), 36.2, 30.6, 29.7, 29.0, 26.4, 26.2, 26.0, 24.7; HRMS (ESI): m/z calcd for $C_{18}H_{28}FNO_3S$ [M+H]: 358.1847; found: 358.1836.

(3*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-3-cyclopropyl-7a-fluoro-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6l)



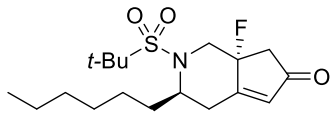
By means of general procedure **V**, from 24 mg (0.08 mmol) of **4l**, 13 mg of **6l** were obtained as a colorless oil (49% yield). R_f = 0.23 (*n*-hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ = – 24.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 4.27 (dd, *J* = 14.8, 11.4 Hz, 1H), 3.59 – 3.35 (m, 2H), 3.08 (ddt, *J* = 13.4, 5.4, 2.3 Hz, 1H), 2.89 – 2.67 (m, 2H), 2.48 (dd, *J* = 18.8, 11.7 Hz, 1H), 1.44 (s, 9H), 1.00 – 0.83 (m, 2H), 0.71 – 0.51 (m, 2H), 0.36 – 0.27 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -149.53 (br, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 169.0 (d, *J* = 18.1 Hz), 133.1, 94.3 (d, *J* = 182.9 Hz), 62.1, 60.1, 51.2 (d, *J* = 24.8 Hz), 43.6 (d, *J* = 23.3 Hz), 32.4, 24.5, 12.0, 5.3, 5.0; HRMS (ESI): m/z calcd for $C_{15}H_{22}FNO_3S$ [M+H]: 316.1377; found: 316.1372.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-phenethyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6m)



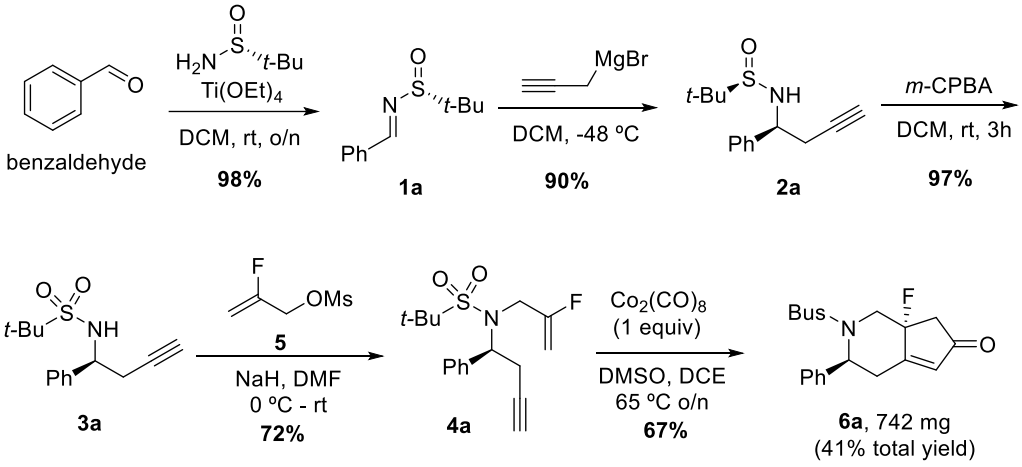
By means of general procedure **V**, from 45 mg (0.13 mmol) of **4m**, 19 mg of **6m** were obtained as a colorless oil (43% yield). R_f = 0.39 (*n*-hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ = – 47.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.27 – 7.05 (m, 5H), 6.01 (s, 1H), 4.27 – 4.06 (m, 2H), 3.16 (dd, *J* = 34.1, 15.0 Hz, 1H), 2.98 (dd, *J* = 14.5, 5.7 Hz, 1H), 2.78 – 2.50 (m, 4H), 2.37 (dd, *J* = 18.8, 11.2 Hz, 1H), 1.93 – 1.67 (m, 2H), 1.36 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 150.26 (br, 1F); ^{13}C NMR (75 MHz, $CHCl_3$) δ 201.2, 168.4 (d, *J* = 18.6 Hz), 140.4, 133.1, 126.4, 62.1, 50.7 (d, *J* = 25.7 Hz), 32.8, 32.7, 29.9, 24.3. HRMS (ESI): m/z calcd for $C_{20}H_{26}FNO_3S$ [M+H]: 380.1690; found: 380.1684.

(3*S*,7a*S*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-hexyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (6n)



By means of general procedure **V**, from 100 mg (0.30 mmol) of **4n**, 53 mg of **6n** were obtained as a colorless oil (49% yield). R_f = 0.37 (*n*-hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ = – 47.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 6.10 (s, 1H), 4.21 (dd, *J* = 15.0, 11.5 Hz, 1H), 4.08 (q, *J* = 6.5 Hz, 1H), 3.21 (dd, *J* = 34.2, 15.0 Hz, 1H), 3.09 – 2.91 (m, 1H), 2.82 – 2.61 (m, 2H), 2.43 (dd, *J* = 18.8, 11.2 Hz, 1H), 1.69 – 1.46 (m, 2H), 1.42 (s, 9H), 1.36 – 1.19 (m, 8H), 0.86 (t, *J* = 6.1 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -148.7 – -152.5 (br); ^{13}C NMR (75 MHz, $CHCl_3$) δ 201.3, 168.8 (d, *J* = 18.1 Hz), 133.0 (d, *J* = 4.0 Hz), 93.85 (d, *J* = 183.5 Hz), 62.0, 55.6, 50.6 (d, *J* = 25.3 Hz), 43.5 (d, *J* = 23.1 Hz), 31.6, 30.7, 29.8, 28.9, 26.4, 24.3, 22.5, 14.0. HRMS (ESI): m/z calcd for $C_{18}H_{30}FNO_3S$ [M+K]: 398.1562; found: 398.1548.

VI. Gram-scale procedure for 6a.



A solution of benzaldehyde (560 mg, 5.3 mmol) and $Ti(OEt)_4$ (20 mmol) in DCM (0.1 M, 53 mL) was stirred for 5 min at room temperature. To the resulting solution, (*R*)-*N*-(tert-butanesulfinyl)amine was added (770 mg, 6.4 mmol) and the mixture was stirred at room temperature for 12 h. After this time, saturated aqueous $NaHCO_3$ was added until white titanium salts precipitated. The suspension was filtered through a short pad of Celite washing with small portions of dichloromethane. The filtrate was extracted with dichloromethane and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 5:1) to afford imine **1a** (1078 mg, 5.2 mmol, 98%).

A freshly prepared 1M solution of propargylmagnesium bromide in THF (1.5 equiv, 7.8 mmol) was added to a solution of the imine **1a** (5.2 mmol) in dichloromethane (0.1 M, 52 mL) at −48 °C. After stirring for 18 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with DCM and purified by flash column chromatography (*n*-hexane/EtOAc, 3:1). Sulfinamide **2a** was obtained with 90% of chemical yield (1166 mg, 4.7 mmol).

m-CPBA (5.62 mmol) was added to a solution of this sulfinamide **2a** (1166 mg, 4.68 mmol) in DCM (47 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with DCM, dried over

anhydrous Na_2SO_4 and purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to afford sulfonamide **3a** (1206 mg, 4.54 mmol) with 97% of yield.

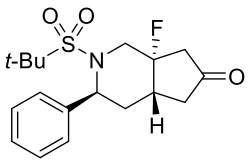
To a suspension of NaH (60%, 6.81 mmol) in dry DMF (40 mL) at 0 °C, sulfonamide **3a** (1206 mg, 4.54 mmol) was added dropwise. After stirring at this temperature for 20 minutes, fluorinated mesylate **5** (9.12 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with NH_4Cl aq., extracted with diethyl ether, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (*n*-hexane/EtOAc, 10:1) to afford 1058 mg (3.27 mmol) of sulfonamide **4a** (72%).

$Co_2(CO)_8$ (3.8 mmol) was added to a solution of sulfonamide **4a** (1020 mg, 3.15 mmol) in DCE (30 mL) at room temperature (no inert atmosphere required). The reaction mixture was stirred for 2h until complete formation of the alkyne-hexacarbonyldicobalt complex was observed by TLC. At this moment, DMSO (9.5 mmol) was added and the reaction was heated to 65 ºC and stirred for another 24-48 hours at this temperature. The solvent was removed in vacuum and the crude reaction was purified by flash column chromatography using *n*-hexane/EtOAc (3:1) as eluent to afford compound **6a** (742 mg, 67% yield).

VII. Hydrogenation to 7.

A round-bottomed flask was charged with **6a** (50 mg, 0.14 mmol), palladium over activated charcoal (15 mg, 10 mol%) and ethyl acetate (4 mL). The flask was purged with hydrogen gas 3 times and fitted with a gas bag, and left to stir until the reaction was complete (TLC analysis, typically 1 hour). The reaction mixture was then passed through a plug of Celite to remove the catalyst and the remaining solution was concentrated to dryness. The crude mixture was purified by flash column chromatography using FluoroFlash® silica gel (*n*-hexane/EtOAc, 15:1 – 10:1) to yield 43 mg of **7**.

(3*S*,4a*S*,7a*R*)-2-(*tert*-Butylsulfonyl)-7a-fluoro-3-phenyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one (7)

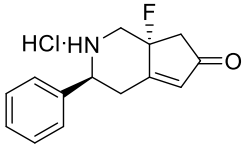


Colorless oil (87% yield); $[\alpha]^{25}_{D}$ = + 9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.27 (m, 5H), 5.19 (t, *J* = 5.6 Hz, 1H), 4.22 (t, *J* = 15.5 Hz, 1H), 3.48 (dd, *J* = 36.1, 15.8 Hz, 1H), 2.84-2.39 (m, 5H), 2.20 (m, 1H), 1.75 (dd, *J* = 19.0, 10.0 Hz, 1H), 1.43 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -149.75 ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 140.3, 129.1, 129.0, 127.4, 126.2, 125.6, 96.6 (d, J^1_{CF} = 192.9 Hz), 62.3, 61.8, 57.0, 56.2, 47.8 (d, J^2_{CF} = 22.3 Hz), 42.4, 40.1, 38.2 (d, J^2_{CF} = 22.1 Hz), 37.6, 24.4 ppm. HRMS (ESI): m/z calc for $C_{18}H_{24}FNO_3S$ [M + NH_4]: 371.1799; found: 371.1801.

VIII. Removal of the *tert*-butyl sulfonyl group to 8.

A solution of **6a** (100 mg, 0.28 mmol) in DCM (5.7 mL) was cooled to 0 °C. Anisole (0.62 mL, 5.69 mmol) and triflic acid (0.09 mL, 0.98 mmol) were added and the mixture was stirred for 2 hours. After completion, sat. aq. solution of K_2CO_3 was added. The organic layer was separated and the aqueous layer was further extracted with DCM (x2), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to yield the unprotected amine. The residue was taken up in DCM (2.5 mL) and HCl 4M in dioxane (2.5 mL) was added. The mixture was stirred for 2 hours at room temperature. Then, solvents were removed under reduced pressure and the resulting solid was washed with Et_2O to yield 70 mg of **8**.

(3*S*,7a*R*)-7a-Fluoro-3-phenyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one hydrochloride (8).



White solid (93%). Mp > 250 °C; $[\alpha]^{25}_{D}$ = – 17.5 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.56 – 7.48 (m, 2H), 7.48 – 7.39 (m, 3H), 6.45 (s, 1H), 5.13 (dd, *J* = 6.6, 2.9 Hz, 1H), 3.88 (dd, *J* = 14.3, 11.7 Hz, 1H), 3.54 – 3.30 (m, 3H), 2.85 – 2.61 (m, 2H); ^{19}F NMR (282 MHz, MeOD) δ -145.98 – -146.27 (m, 1F); ^{13}C NMR (75 MHz, MeOD) δ 202.6, 165.7 (d, *J* =

16.5 Hz), 135.2 (d, *J* = 4.5 Hz), 134.5, 130.9, 130.5, 129.6, 95.1 (d, *J* = 178.1 Hz), 56.0, 47.2 (d, *J* = 26.8 Hz), 44.1 (d, *J* = 23.2 Hz), 28.5; HRMS (ESI): m/z calcd for $C_{14}H_{14}FNO$ [M+H]: 232.1121; found: 232.1132.

IX. X-Ray structure of compound 6a. [15]

Single crystals of $C_{18}H_{22}FNO_3S$ were obtained using dichloromethane and *n*-hexane (1:3), with slow evaporation in glass vial.

Crystal Data for $C_{18}H_{22}FNO_3S$ (*M* =351.42 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 7.04243(6) Å, *b* = 11.01934(7) Å, *c* = 23.03499(18) Å, *β* = 89.9411(8)°, *V* = 1787.58(2) $Å_3$, *Z* = 4, *T* = 290.5(2) K, μ(CuKα) = 1.835 mm-1, *Dcalc* = 1.306 g/cm3, 32994 reflections measured (8.896° ≤ 2Θ ≤ 137.982°), 6655 unique (R_{int} = 0.0325, R_{sigma} = 0.0208) which were used in all calculations. The final R_1 was 0.0321 (I > 2σ(I)) and wR_2 was 0.0846 (all data).

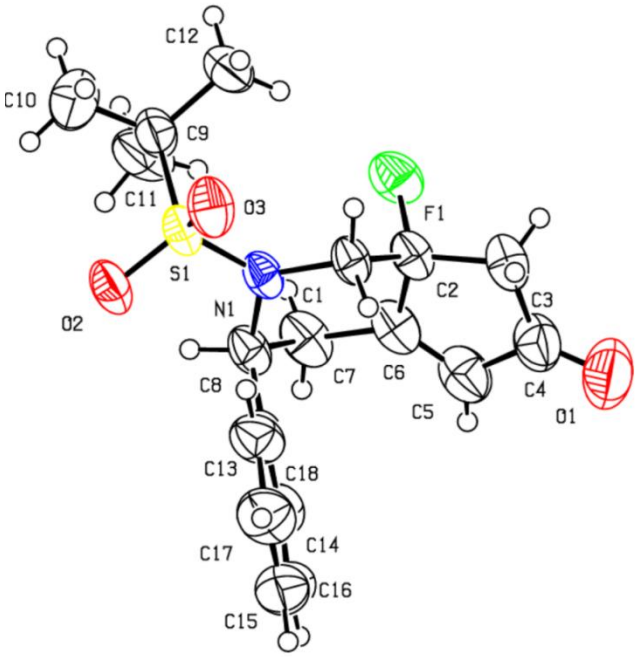


Figure S1. Ortep diagram for compound **6a**.

[1] Boultwood, T.; Affron, D. P.; Trowbridge, A. D.; Bull, J. A. *J. Org. Chem*. **2013**, *78*, 6632 1 − 6647.

[2] Kevin W. Kells, K. W.; Chong, J. M., *J. Am. Chem Soc*. **2004**, *126*, 15666 – 15667.

[3] Sanaboina, C.; Jana, S.; Eppakayala, L. *Synlett* **2014**, *25*, 1006 – 1008.

[4] Blomkvist, B.; Dinér, P. *Tetrahedron Lett*. **2018**, *59*, 1249 – 1253.

[5] Lim, J.; Taoka, B.; Otte, R. D.; Spencer, K.; Dinsmore, C. J.; Altman, M. D.; Chan, G.; Rosenstein, C.; Sharma, S.; Su, H-P.; Szewczak, A. A.; Xu, L.; Yin, H.; Zugay-Murphy, J.; Marshall, C. G.; Young, J. R. *J. Med. Chem*. **2011**, *54*, 7334 – 7349.

[6] García-Muñoz, M. J.; Dema, H. K.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2014**, *25*, 362 – 372.

[7] Procopiou, G.; Lewis, W.; Harbottle, G.; Stockman, R. A. *Org. Lett*. **2013**, *15*, 2030 – 2033.

[8] Chogii, I.; Njardarson, J. T. *Angew .Chem. Int. Ed.* **2015**, *54*, 13706 – 13710.

[9] Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999,** *64,* 12 – 13.

[10] Schenkel, L. B.; Ellman, J. A. *Org. Lett*. **2004**, *6*, 3621 – 3624.

[11] Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850 – 3851.

[12] Cui, L.; Li, C.; Zhang, L. A., *Angew. Chem. Int. Ed.* **2010**, *49*, 9178 – 9181.

[13] García-Muñoz, M. J.; Foubelo, F.; Yus, M. *J. Org. Chem*. **2016**, *81*, 10214 – 10226.

[14] Despite attempts to improve the 19F NMR spectra of these compounds, such as longer relaxation and acquisition times, compounds **6** have always given low-intensity signals in their 19F spectra.

[15] CCDC 1937096 contains the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Scientific Article 5:

Linear Chiral *N*-bridged Triynes as Key Frameworks for Expeditious Access to a Merged Tetrahydroisoquinoline Core

Linear Chiral *N*-bridged Triynes as Key Frameworks for Expeditious Access to a Merged Tetrahydroisoquinoline Core

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KEYWORDS cycloaddition; triynes; rhodium; central chirality; chiral homopropargyl amides

ABSTRACT: A route for the preparation of merged symmetrical tetrahydroisoquinolines with central chirality through a rhodium-catalyzed intramolecular [2+2+2]-cycloaddition involving enantiopure triynes as substrates is described. The *N*-tethered 1,7,13-triynes used in our approach were easily prepared from readily accessible chiral homopropargyl amides, the basic building blocks in our approach which were efficiently obtained by diastereoselective addition of propargyl magnesium bromide to Ellman imines. Additional substitution at the benzenes ring could be attained when substituted triynes at the terminal triple bonds were employed giving access to more complex tetrahydroisoquinolines after the rhodium-catalyzed intramolecular [2+2+2]-cycloaddition.

Introduction

The synthesis of compounds with structures inspired by those of natural products is a recurrent activity in chemical research providing the accredited efficiency shown by this strategy along time in the design and discovery of bioactive molecules.[1] Fused *N*-heterocyclic cores are among the most important scaffold segments present in the framework of many natural products with diverse biological activity. Among the family of nitrogen-containing heterocycles, tetrahydroisoquinolines are frequently identified as

privileged structural subunits that occur in a variety of biologically and therapeutically active molecules, playing also crucial roles in drug discovery (**Figure 1**).[2,3]

The quest for novel synthetic routes for nitrogen-containing polyheterocycles using atom-economical and efficient pathways remains an active field in synthetic organic chemistry. From a synthetic point of view, it is desirable that the preparation of complex target molecules could be achieved quickly, quantitatively, and selectively by simple operations from readily available starting materials. In this regard, cycloaddition reactions play a significant role in the synthesis of polycyclic compounds although, in most cases, an appropriate metallic catalyst is required.[4] Transition-metals have been shown to be efficient catalysts, over the past decades, in cycloaddition reactions allowing the reaction to take place with high yields and selectivities, and with a wide functional group tolerance.[5] Among these transformations, transition-metal catalyzed [2+2+2]-cycloadditions constitute a reliable method for the access to sophisticated ring structures[6-12] and useful intermediates in the synthesis of ubiquitous *N*-heterocyclic compounds.[6-10]

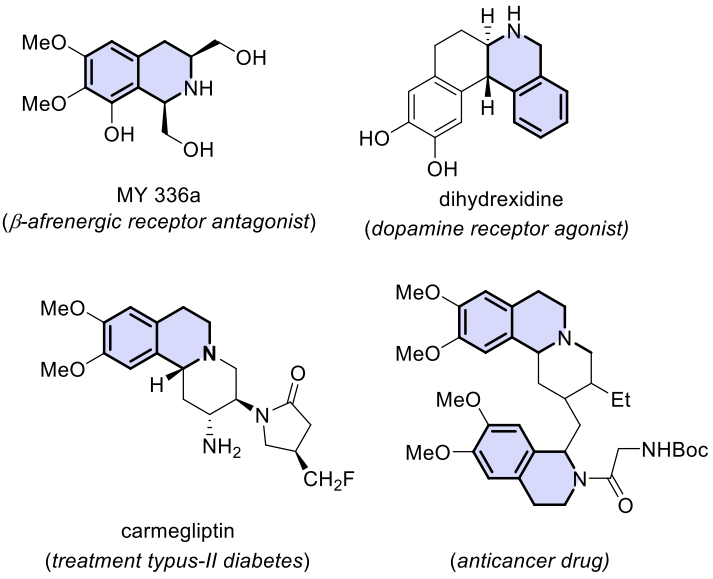


Figure 1. Representative examples of tetrahydroisoquinoline scaffolds present in bioactive compounds.

The partially intermolecular or semi-intramolecular version of these cycloadditions involve as partners nitrogen containing enynes,[6] diynes,[7] and alkenes/alkynes or, alternatively, diynes and nitriles/heterocumulenes.[8] The intramolecular versions involve nitrogen-tethered enediynes[9] or triynes[10] that specifically lead to the preparation of tricyclic derivatives have been investigated along the last decade. However, most of the above-mentioned reports involve the use of non-chiral substrates neglecting the frequent and important relationship between chirality in the heterocyclic subunits and the biological activity of the final compound. In fact, only punctual examples of semi-intramolecular [2+2+2] cycloadditions involving chiral diynes[13] have been described meanwhile there are, in the best of our knowledge, no examples of intramolecular [2+2+2]-cycloadditions involving chiral triynes.

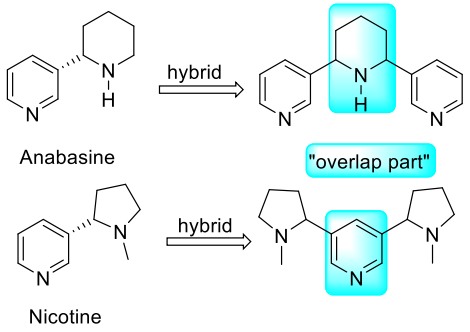


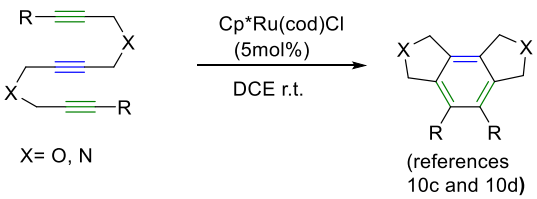
Figure 2. Structures of some natural 'twins' products.

It is worth mentioning that the intramolecular [2+2+2]-cycloaddition of chiral triynes can be envisaged as a direct method to the synthesis of asymmetric hybrid derivatives of fused heterocycles as result of combination and partial overlap of their corresponding structures. This kind of structures connects with the concept of synthesis of twin drugs following the overlap method.[14] The twin drugs design constitutes a common strategy in medicinal chemistry and is based in the association of two pharmacological entities in a hybrid structure.[14] Although twin drugs can be found among natural products[15] with marked bioactivity (**Figure 2**), the strategy has been extensively applied in drug design.[14] The aim behind the synthesis of these hybrids is producing more potent and selective pharmacological effects based in the duplication of the corresponding pharmacophores.

Given that alkaloids are recurrent references for inspire bioactive molecules,[1] a wide variety of hybrids based in the structure of alkaloids have been developed.[16]

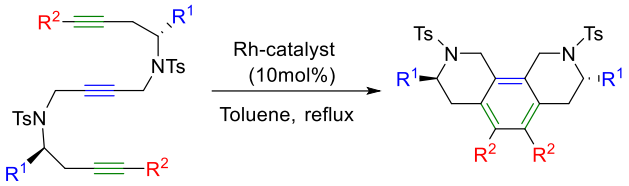
Previous work

Achiral triynes



This work

Triynes with central chirality

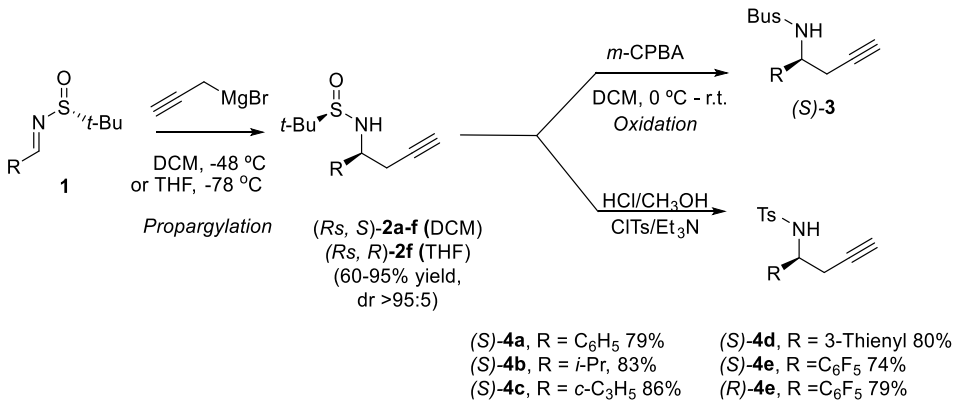


In this regard, we envisaged that chiral homopropargyl amides can be used as chiral building blocks for the preparation of new linear chiral *N*-tethered-1,7,13-trynes that can be converted, through an intramolecular [2+2+2]-cycloaddition reaction, in a merged compound of two chiral 3-substituted tetrahydroisoquinolines overlapped at the benzene ring. (Scheme 1).

Results and discussion

First, we prepared the chiral *N*-bridged 1,7,13-triynes following a concise approach based in simple starting materials such as chiral homopropargyl amides and commercially available 2-butyn-1,4-diol. For the preparation of the required chiral homopropargyl amides **2**, we followed an previously reported efficient approach based on the diastereoselective 1,2-addition of propargylmagnesium bromide to a variety of aryl, heteroaryl and alkyl substituted Ellman´s sulfinylimines (R_S)-**1** (Scheme 2).[17] Through this synthetic methodology, a representative set of chiral homopropargyl amides (R_S,*S*)-**2a-e** was easily prepared in good to high yields and high diastereoselectivities (dr >95:5). Furthermore, enantiopure homopropargyl amides (R_S,*R*)-**4e** and (R_S,*S*)-**4e** were also prepared following

the divergent diastereoselective variant of the above-mentioned route, which we have recently reported by selecting the appropriate solvent (Scheme 2).[17a] Subsequent oxidadion with *m*-CPBA of homopropargyl amides (R_S,*S*)-**2** afforded sulfonamides (*S*)-**3** in high yields.

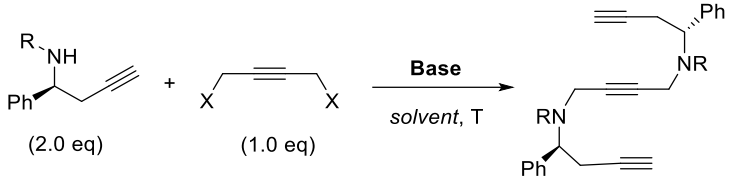


Scheme 2. Synthesis of chiral homopropargyl amides **2-4**.

To identify an efficient synthetic route aimed for the preparation of 1,7,13-triynes, we selected sulfonamide (*S*)-**3** as benchtop substrate. Based on our previous experience in *N*-alkylation reactions that proved that the direct alkylation of the sulfinylamides resulted in unsatisfactory yields (<20%), we selected sulfonamide (*S*)-**3** instead of sulfinylamide (R_S,*S*)-**2a**. First, sulfonamide (*S*)-**3** reacted with commercially available 2-butyn-1,4-diol under Mitsonobu conditions (Table 1). Despite the desired triyne was obtained, the product was difficult to separate from the customary secondary by-products formed in this type of reaction. Alternatively, sulfonamide (*S*)-**3** (2.0 equiv) was treated with NaH in DMF or THF and subsequently reacted with prepared 1,4-dibromo-2-butyne, but no conversion was observed (Table 1, entries 1-4). However, changing the base and the solvent to K_2CO_3 or Cs_2CO_3 in CH_3CN also showed to be ineffective (Table 1, entry 5). With an excess of 1,4-dibromo-2-butyne (3.0 equiv) in acetonitrile and K_2CO_3 as base, triyne (*S*,*S*)-**5** was obtained with 12% yield, which could be increased to 38% using Cs_2CO_3 as a base (Table 1, entries 6 and 7). Considering the decomposition of 1,4-dibromo-2-butyne after heating of the reaction mixture, we decided to change to 2-butyn-1,4-ditosylate but the transformation using sulfonamide (*S*)-**3** resulted also unsuccessful (Table 1, entry 8). Then, we changed to

p-tosylamide (*S*)-**4a,** which after deprotonation with Cs_2CO_3 in CH_3CN at room temperature reacted with the 2-butyn-1,4-ditosylate at 80 °C affording triyne (*S*,*S*)-**6a** with 57% yield (Table 1, entry 11). Interestingly, the reaction yield could be increased up 72% with slow addition of 2-butyn-1,4-ditosylate (Table 1, entry 12).

Table 1. Optimization of reaction conditions for the synthesis of triyne (*S*,*S*)-**5** and (*S*,*S*)-**6a**.

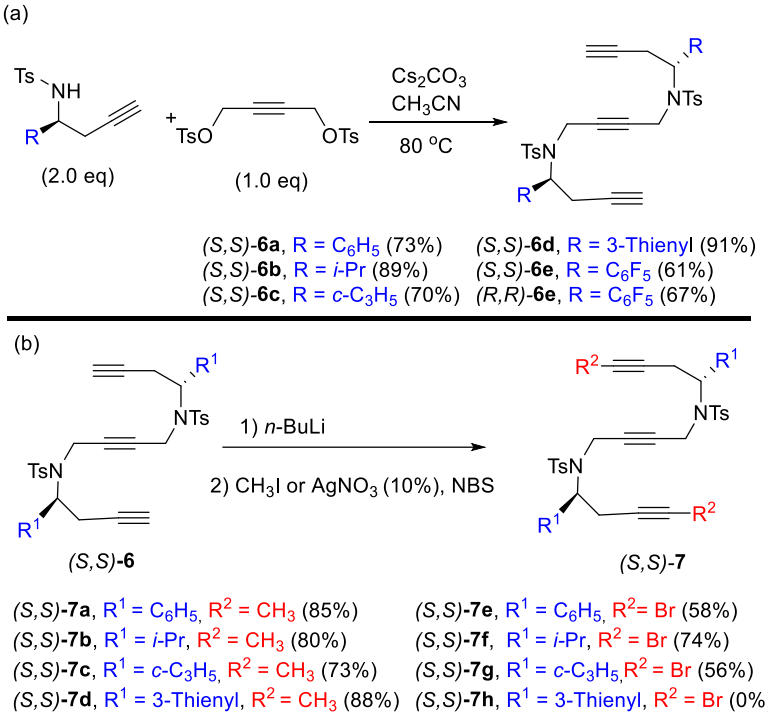


(*S*,*S*)-**5** (R = Bus)
(*S*,*S*)-**6a** (R = Ts)

Entry	R	X	Base	Solvent	T (°C)	t (h)	Yield (%)
1	Bus	Br	NaH	DMF	r.t.	2	n.r.
2	Bus	Br	NaH	THF	r.t.	2	n.r.
3	Bus	Br	NaH	DMF	50	24	n.r.
4	Bus	Br	NaH	THF	50	24	n.r.
5	Bus	Br	K_2CO_3	CH_3CN	reflux	24	n.r
6[b,c]	Bus	Br	K_2CO_3	CH_3CN	reflux	6	**5** (12)[f]
7[b,c]	Bus	Br	Cs_2CO_3	CH_3CN	reflux	24	**5** (38)[f]
8[d]	Bus	TsO	Cs_2CO_3	CH_3CN	reflux	48	n.r.
9[b]	Ts	TsO	Cs_2CO_3	DMF	r.t	24	n.r.
10	Ts	TsO	K_2CO_3	CH_3CN	r.t.	24	n.r.
11	Ts	TsO	Cs_2CO_3	CH_3CN	reflux	14	**6a** 57[g]
12[e]	Ts	TsO	Cs_2CO_3	CH_3CN	reflux	14	**6a** (72)[g]

[a] General reaction conditions: 1,4-dibromo-2-butyne or 2-butyn-1,4-ditosylate (1.0 equiv), base (2.0 equiv), solvent (0.1 M). [b] 5.0 equiv of base. [c] 3.0 equiv of 1,4-dibromo-2-butyne. [d] 3.0 equiv of base. [e] Slow addition of 2-butyn-1,4-ditosylate. [f] Yield of (*S*,*S*)-5. [g] Yield of (*S*,*S*)-**6a**.

With the optimized conditions for the synthesis of enantiopure 1,7,13-triynes (Cs_2CO_3 as a base in CH_3CN at 80 °C), we prepared a set of different unsubstituted 1,7-triynes (*S*,*S*)-**6a-d** from the corresponding tosylamides (*S*)-**4a-d** and 2-butyn-1,4-ditosylate (Scheme 3a). We also synthetized the enantiopoure triynes (*R*,*R*)-**6e** and (*S*,*S*)-**6e** starting from the corresponding homopropargyl amides (*R*)-**4e** and (*S*)-**4e**. The yields were moderate to good when applying the previously optimal conditions established for the preparation of sulfonamide (*S*)-**4a**.



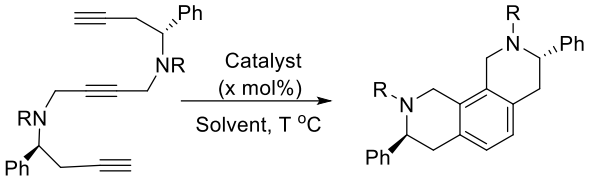
Scheme 3. Synthesis of (a) triynes (*S*,*S*)-**6a-e** and (*R*,*R*)-**6e** and (b) triynes (*S*,*S*)-**7a-h**.

Alternatively, triynes (*S*,*S*)-**7a-h** having substituents at the terminal triple bonds were prepared from triynes (*S*,*S*)-**6a-d** by reacting the corresponding acetylide anions with the appropriate electrophile. Methyl- and bromo- derivatives (*S*,*S*)-**7a-d** and (*S*,*S*)-**7e-g**, respectively, were prepared with good yields following procedures previously described, adapted to our purpose.[17b,18] Meanwhile, preparation of derivative (*S*,*S*)-**7h** resulted problematic because a competing bromination at the thiophene ring took place (Scheme 3b).

Initial examination of the intramolecular [2+2+2]-cycloaddition of triynes was performed by using triynes (*S*,*S*)-**5** and (*S*,*S*)-**6a** (0.1 mmol) as the substrates in the presence of the Wilkinson complex (10 mol %) in toluene at 85 °C, and we found that the benzene tricyclic derivatives (*S*,*S*)-**8** and (*S*,*S*)-**9a** were formed in 38 and 54% yield (Table 2 entries 1 and 2), respectively, as determined using ^{1}H NMR. After considering that triyne (*S*,*S*)-**6a** could be prepared with higher yield and reacted more efficiently than triyne (*S*,*S*)-**5**, the former was selected as model substrate to optimize the reaction conditions of the intramolecular [2+2+2]-cycloaddition. The examination of different transition-metal catalysts (10 mol%) was initially assayed. As shown in Table 2, Rh, Co, Ru and Ir complexes were tested as catalysts under different conditions and the experiments showed that the rhodium complexes $[RhCl(CO)_2]_2$ and $RhCl(PPh_3)_3$ were more effective as catalysts (Table 2, entries 3-9) than the Ir, Ru or Co complexes tested (Table 2 entries 10-12).

In the cases of the rhodium catalyst, DCE and toluene were equally appropriate solvents (Table 2, entries 3-6), but the higher temperatures reached under reflux of toluene slightly improved the yield (Table 2, entry 7). Reduction of both, the catalyst loading, from 10 mol % to 5 mol %, and the reaction time from 14 h to 6 h, eroded the yields (Table 2, entries 8 and 9). Then, we adopted the Wilkinson complex (10 mol %) in toluene at reflux as the optimal conditions to carry out the intramolecular [2+2+2]-cycloaddition of triyne (*S*,*S*)-**6a** leading to a chiral *N*-tethered tricyclic compound having a C_2-symmetry, with acceptable yield.

Table 2. Conditions for the [2+2+2]-cycloaddition of (*S*,*S*)-**5** and (*S*,*S*)-**6a**.



(*S*,*S*)-**5** (R = Bus)
(*S*,*S*)-**6a** (R = Ts)

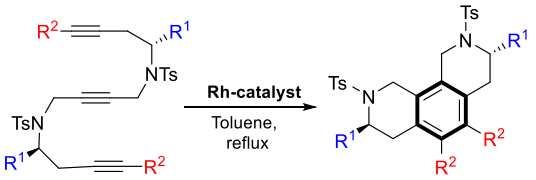
(*S*,*S*)-**8** (R = Bus)
(*S*,*S*)-**9a** (R = Ts)

Entry	Catalyst[a]	Solvent[b]	T (ºC)	t (h)	Yield (%)[c]
1	$RhCl(PPh_3)_3$	Toluene	85	14	(*S,S*)-**8** (38)
2	$RhCl(PPh_3)_3$	Toluene	85	14	(*S,S*)-**9a** (54)
3	$[RhCl(CO_2)_2]_2$	DCE	reflux	14	(*S,S*)-**9a** (55)
4	$[RhCl(CO)_2]_2$	Toluene	85	14	(*S,S*)-**9a** (57)
5	$[RhCl(CO)_2]_2$	Toluene	reflux	14	(*S,S*)-**9a** (64)
6	$RhCl(PPh_3)_3$	DCE	reflux	14	(*S,S*)-**9a** (52)
7	$RhCl(PPh_3)_3$	Toluene	reflux	14	(*S,S*)-**9a** (67)
8	$RhCl(PPh_3)_3$	Toluene	reflux	6	(*S,S*)-**9a** (33)
9	$RhCl(PPh_3)_3$[d]	Toluene	reflux	14	(*S,S*)-**9a** (41)
10	Grubbs 1stgen	DCE	reflux	14	n.r.
11	$[IrCl(cod)_2]_2$	Toluene	reflux	14	n.r.
12	$CoCl(PPh_3)_3$	THF	reflux	14	n.r.

[a] 10 mmol%. [b] Solvent 0.1 M. [c] Isolated yield. [d] 5 mol %.

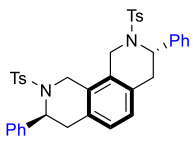
The scope of linear chiral *N*-bridged triynes was then investigated using a catalytic amount of Rh-catalyst and the results are summarized in Scheme 4. Linear 1,7,13-triynes (*S*,*S*)-**6a-d** and enantiomeric triynes (*R*,*R*)-**6e** and (*S*,*S*)-**6e**, all of them unsubstituted at the alkyne termini, underwent a rhodium-catalyzed intramolecular [2+2+2]-cycloaddition reaction, in which three sigma bonds were simultaneously formed affording the corresponding tricyclic compounds with moderate to good yields when applying the previously optimized conditions for triyne (*S*,*S*)-**6a** (10 mol % of $RhCl(PPh_3)_3$). In this way, we obtained the tricyclic compounds with a benzene embedded in two chiral piperazines, (*S*,*S*)-**9a-d**, and the enantiomeric pair (*R*,*R*)-**9e** and (*S*,*S*)-**9e** (Scheme 4). Crystals of (*R*,*R*)-**9e** suitable for single

crystal X-ray diffraction were grown from a Cl_2CH_2/*n*-hexane solution and its absolute structure unambiguously determined (Scheme 4). The case exemplified for compound **9e** in which each enantiomer is accessed by simply changing the configuration of the homopropargyl amide **4e** used to construct the triyne, is of relevance since the target molecules are potential bioactive compounds.

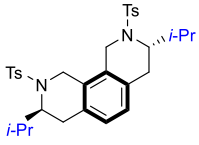


6/7
R^2= H, Me, Br

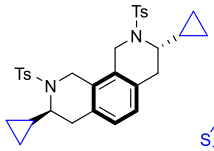
9



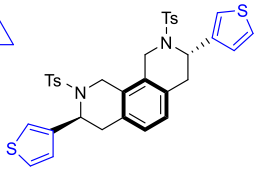
(*S*,*S*)-**9a** (67 %)[a]



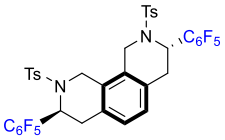
(*S*,*S*)-**9b** (69 %)[a]



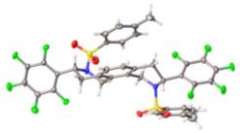
(*S*,*S*)-**9c** (63 %)[a]



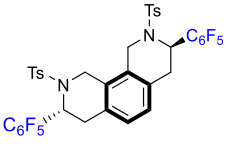
(*S*,*S*)-**9d** (60 %)[a]



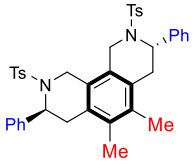
(*S*,*S*)-**9e** (74 %)[a]



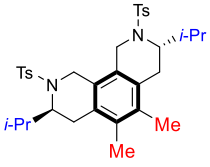
X-ray structure for (*R*,*R*)-**9e**
(40% probability level)



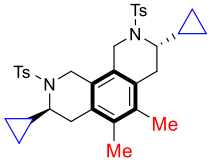
(*R*,*R*)-**9e** (76 %)[a]



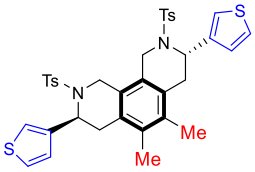
(*S*,*S*)-**9f** (72 %)[b]



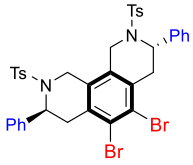
(*S*,*S*)-**9g** (67 %)[b]



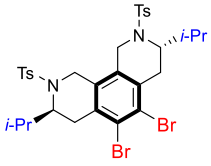
(*S*,*S*)-**9h** (75 %)[b]



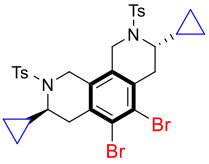
(*S*,*S*)-**9i** (71 %)[b]



(*S*,*S*)-**9j** (56 %)[c]



(*S*,*S*)-**9k** (82 %)[c]



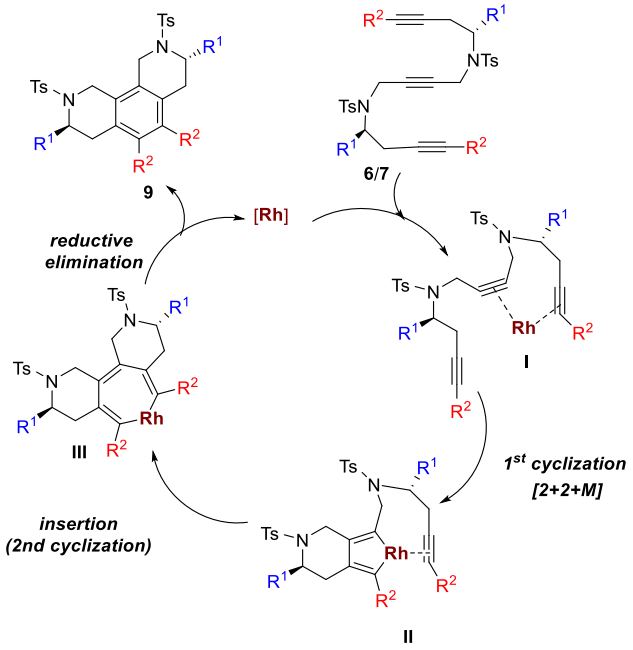
(*S*,*S*)-**9l** (57 %)[c]

[a] 10 mol % $RhCl(PPh_3)_3$; [b] 15 mol % $RhCl(PPh_3)_3$; [c] 15 mol % $[RhCl(CO)_2]_2$

Scheme 4. Substrate scope for the synthesis of cycloadducts (*S*,*S*)-**9a-l** and (*R*,*R*)-**9e**.

Linear triynes that incorporate methyl (*S*,*S*)-**7a-d** or bromine (*S*,*S*)-**7e-g** substituents at the terminal bonds were also appropriate substrates for the rhodium-catalyzed intramolecular cycloaddition leading to the corresponding cycloadducts **9f-l** in yields ranging from 56 to 82%. We found that the $RhCl(PPh_3)_3$ catalyst was also appropriate for the [2+2+2]-cycloaddition of triynes bearing a substituent at both terminal positions, but these substrates required higher catalyst loadings (15 mol %). The atoms or groups attached to the triple bond of triynes (*S*,*S*)-**7** become substituents of the benzene ring after the cyclization reaction; thus, fully substituted benzenes can be accessed via the [2+2+2]-cycloaddition of these terminal substituted triynes. Finally, for triynes bearing a Br substituent at the terminal positions, $[RhCl(CO)_2]_2$ (15 mol %) was found to be optimal for the [2+2+2]-cycloaddition.

Regarding the mechanism, formation of compounds **9** can be understood through a catalytic cycle analogous to others previously proposed for Rh-catalyzed [2+2+2]-cycloaddition of triynes.[19] The [2+2+2]-cycloaddition reaction proceeds through the initial formation of complex **I** via through the coordination of the Rh catalyst to the diyne moiety in triynes **6** or **7** through the internal triple bond and one of the terminal triple bonds, followed by C-C oxidative coupling (first cyclization) to generate rhodacyclopentadiene intermediate **II** ([2+2+M]). Coordination and insertion of the remaining triple bond (second cyclization) in the Rh–C(sp^2) bond with formation of 6-7-6 fused-tricyclic rhodacycloheptatriene **III**. Finally, reductive elimination and formation of the C(sp^2)–C(sp^2) bond affords the benzene ring of [2+2+2]-cycloaddition product **9** and the Rh catalyst is regenerated (Scheme 6).



Scheme 6. Proposed mechanism for the Rh-catalyzed [2+2+2] cycloaddition reaction of triynes **6-7**.

Conclusion

In summary, we have described a rhodium-catalyzed intramolecular [2+2+2]-cycloaddition of *N*-bridged 1,7,13-triynes 6/7 that provide a merged symmetrical tetrahydroisoquinoline **9** possesing central chirality. The developed approach allows the generation of chiral tricycles having stereogenic centers via a [2+2+2]-cycloaddition involving chiral triynes as substrates. Final products are, in some cases, fully substituted benzenes with uncommon substitution patterns. The versatility of the approach is further exemplified by the synthesis of each enantiomer of cycloadduct **9** by simply changing the configuration of the homopropargyl amides **4** used as basic building blocks. The developed protocol precludes the general need of recurring to the presence of sp2 hybridized moieties in the reactive system for generation, via [2+2+2]-cycloaddition, of cycloadducts having stereogenic centers, a condition that normally results in a less favorable transformation as alkenes are more reluctant to react in this type of transformations. The chiral *N*-bridged 1,7,13-triynes

used as substrates were easily prepared from chiral homopropargyl amides, which in turn, were obtained by diastereoselective addition of propargyl Grignard reagents to Ellman imines. This process has a high synthetic potential to provide efficient routes to various chiral polycyclic skeletons of biological interest.

Experimental section

General remarks. Reactions were carried out under nitrogen atmosphere unless otherwise indicated. CH_2Cl_2 (DCM) was used without further purification. The reactions were monitored with the aid of TLC on 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and solution of potassium permanganate and sodium hydroxide in water. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz Bruker Avance-III 300 spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points (M.p.) were measured on a Büchi B−540 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C.

General procedure I for the synthesis of tosylamides (*S*)-4b-e and (*R*)-4e. i) Desulfinylation: Compounds 2 (1 mmol) were dissolved in MeOH (0.1 M) and a solution of HCl in dioxane (4 M, 4 mmol) was added. The mixture was stirred at room temperature overnight (18 h). The reaction was monitored by TLC. Once the starting material was consumed, the solvent was evaporated, and the resulting crude was washed with cold Et_2O until the amine chlorhydrate appeared as a white solid. ii) *N*-Tosylation: The white solid obtained in the above stage was suspended in DCM (0.1 M) and the temperature was decreased to 0 °C with an ice bath. Then, Et_3N (3 mmol) was added and when the white solid was dissolved TsCl was added (1.5 mmol). The mixture was stirred overnight (18 h) at room

temperature. The reaction was monitored by TLC. Once the reaction was finished, it was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (5:1).

*(S)-4-Methyl-N-(2-methylhex-5-yn-3-yl)benzene sulfonamide [(S)-**4b**].* According to general procedure I, from 260 mg (1.21 mmol) of (R_S,*S*)-**2b**, 266 mg of (*S*)-**4b** were obtained as a white solid (83% yield) M.p. 72–74 °C; $[\alpha]_D^{25}$ = +67.1 (c 1.0,); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.93 (d, *J* = 9.2 Hz, 1H), 3.15–3.06 (m, 1H), 2.43 (s, 3H), 2.34 (dd, *J* = 17.1, 4.2, 2.6 Hz, 1H), 2.20 (dd, *J* = 17.1, 6.3, 2.6 Hz, 1H), 1.97–1.90 (m, 2H), 0.87 (d, *J* = 5.5 Hz, 3H), 0.84 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 138.0, 129.6 (2×CH), 127.1 (2×CH), 79.7, 71.3, 57.3, 30.7, 22.6, 21.5, 19.2, 18.0. HRMS (ESI): *m/z* Calcd for $C_{14}H_{20}NO_2S$ [M+H$^+$]: 266.1201; Found: 266.1209.

*(S)-N-(1-Cyclopropylbut-3-yn-1-yl)-4-methylbenzene sulfonamide [(S)-**4c**].* According to general procedure I, from 244 mg (1.15 mmol) of (R_S,*S*)-**2c**, 261 mg of (*S*)-**4c** were obtained as a colorless oil (86% yield); $[\alpha]_D^{25}$ = +47.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.59 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 7.6 Hz, 1H), 2.49–2.41 (m 1H), 2.23–2.20 (m, 5H), 1.79 (t, *J* = 2.6 Hz, 1H), 0.87–0.79 (m, 1H), 0.34–0.24 (m, 1H), 0.19–0.10 (m, 1H), 0.05–0.03 (m, 1H), -0.14 – -0.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.1, 129.6 (2×CH), 127.1 (2×CH), 80.0, 71.3, 56.9, 25.7, 21.5, 15.5, 4.2, 3.6. HRMS (ESI): *m/z* Calcd for $C_{14}H_{18}NO_2S$ [M+H$^+$]: 264.1043; Found: 264.1053.

*(S)-4-Methyl-N-(1-(thiophen-3-yl)but-3-yn-1-yl)benzene sulfonamide [(S)-**4d**].* According to general procedure I, from 700 mg (2.74 mmol) of (R_S,*S*)-**2d**, 670 mg of (*S*)-**4d** were obtained as a white solid (80% yield) M.p. 107–109 °C; $[\alpha]_D^{25}$ = -49.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.61 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.81 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.41 (d, *J* = 8.1 Hz, 1H), 4.61–4.54 (m, 1H), 2.60–2.57 (m, 2H), 2.34 (s, 3H), 1.93 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 140.4, 137.5, 129.6 (2×CH), 127.1 (2×CH), 126.2, 126.0, 122.3, 79.4, 72.2, 51.7, 26.7, 21.5. HRMS (ESI): *m/z* Calcd for $C_{15}H_{19}N_2O_2S_2$ [M+NH_4^+]: 323.0881; Found: 323.0882.

*(S)-4-Methyl-N-(1-(perfluorophenyl)but-3-yn-1-yl)benzene sulfonamide [(S)-**4e**].* According to general procedure I, from 444 mg (1.31 mmol) of (R_S,*S*)-**2e**, 377 mg of (*S*)-**4e** were obtained as a white solid (74% yield) M.p. 107–109 °C; $[\alpha]_D^{25}$ = -21.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.60 (d, *J* = 9.4 Hz, 1H), 4.95–4.87 (m, 1H), 2.81–2.64 (m, 2H), 2.37 (s, 3H), 1.94 (t, *J* = 2.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.41 – -142.52 (m, 2F), -153.98 – -154.13 (m, 1F), -161.47 – -161.65 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.3-142.6 (m, 2xC-F), 144.1, 142.5-149.1 (m, C-F), 139.2-135.3 (m, 2×C-F), 136.4, 129.5 (2×CH), 127.0 (2×CH), 113.1-112.6 (m, 1C), 77.6, 72.1, 47.8, 25.3, 21.3. HRMS (ESI): *m/z* Calcd for $C_{17}H_{13}F_5NO_2S$ [M+H$^+$]: 390.0569; Found: 390.0570.

*(R)-4-Methyl-N-(1-(perfluorophenyl)but-3-yn-1-yl)benzene sulfonamide [(R)-**4e**].* According to general procedure I, from 116 mg (0.34 mmol) of (R_S,*R*)-**2e**, 105 mg of (*R*)-**4e** were obtained as a white solid (79% yield) M.p. 109–111 °C; $[\alpha]_D^{25}$ = +27.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.65 (d, *J* = 9.3 Hz, 1H), 4.88–4.80 (m, 1H), 2.75–2.57 (m, 2H), 2.30 (s, 3H), 1.87 (t, *J* = 2.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.33 – -142.46 (m, 2F), -154.32 – -154.47 (m, 1F), -161.78 – -161.96 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.3 – 142.7 (m, 2xC-F), 144.1, 142.6 – 139.1 (m, C-F), 139.1 – 135.3 (m, 2×C-F), 136.4, 129.5 (2×CH), 127.0 (2×CH), 113.1 – 112.6 (m, 1C), 77.6, 72.1, 47.8, 25.3, 21.3. HRMS (ESI): *m/z* Calcd for $C_{17}H_{13}F_5NO_2S$ [M+H$^+$]: 390.0580; Found: 390.0582.

General procedure for the synthesis of triynes (*S*,*S*)-5; (*S*,*S*)-6a-e and (*R*,*R*)-6e. To a suspension of Cs_2CO_3 (2 mmol) in acetonitrile (6 mL) was added homopropargyl amide (*S*)-**4** or (*R*)-**4** (1 mmol) and the solution was stirred for 1h at room temperature. Then, a solution of 2-butyn-1,4-ditosylate (0.8 mmol) in acetonitrile (4 mL) was slowly added for 8 h at 80 °C. The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (6:1).

*2-Methyl-N-(4-((2-methyl-N-((S)-1-phenylbut-3-yn-1-yl)propan-2-yl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-phenylbut-3-yn-1-yl)propane-2-sulfonamide [(S,S)-**5**].* According to general procedure II, from 203 mg (0.76 mmol) of (*S*)-**3**, 80 mg of (*S*,*S*)-**5** were obtained as a white solid (39% yield) M.p. 95–97 °C; $[\alpha]_D^{25}$ = –23.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.54–7.51 (m, 4H), 7.42–7.33 (m, 6H), 5.29–5.24 (m, 2H), 4.12 (d, *J* = 17.8 Hz, 2H), 3.61 (d, *J* =17.8 Hz, 2H), 3.06–2.98 (m, 2H), 1.99 (t, *J* = 2.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.6, 128.6 (2×CH), 128.6 (2×CH), 128.4, 81.3, 80.7, 71.7, 62.1, 61.2, 34.7, 24.8, 23.3. HRMS (ESI): *m/z* Calcd for $C_{32}H_{44}N_3O_4S_2$ $[M+NH_4^+]$: 598.2755; Found: 598.2768.

*4-Methyl-N-(4-((4-methyl-N-((S)-1-phenylbut-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-phenylbut-3-yn-1-yl)benzenesulfonamide [(S,S)-**6a**].* According to general procedure II, from 140 mg (0.47 mmol) of (*S*)-**4a**, 110 mg of (*S*,*S*)-**6a** were obtained as a colorless oil (73% yield); $[\alpha]_D^{25}$ = –34.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.25–7.19 (m, 14H), 5.16–5.11 (m, 2H), 3.98 (d, *J* = 16.7 Hz, 2H), 3.36 (d, *J* =16.7 Hz, 2H), 2.86 (ddd, *J* = 16.9, 9.9, 2.6 Hz, 2H), 2.57 (d, *J* = 16.9, 5.4, 2.6 Hz, 2H), 2.35 (s, 6H), 1.83 (t, J = 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 137.7, 136.2, 129.7 (2×CH), 128.5 (2×CH), 128.4, 128.2 (2×CH), 127.5 (2×CH), 80.4, 80.0, 71.5, 59.4, 33.3, 21.8, 21.6. HRMS (ESI): *m/z* Calcd for $C_{38}H_{40}N_3O_4S_2$ $[M+NH_4^+]$: 666.2454; Found: 666.2455.

*4-Methyl-N-(4-((4-methyl-N-((S)-2-methylhex-5-yn-3-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-2-methylhex-5-yn-3-yl)benzenesulfonamide [(S,S)-**6b**].* According to general procedure II, from 209 mg (0.79 mmol) of (*S*)-**4b**, 203 mg of (*S*,*S*)-**6b** were obtained as a colorless oil (89% yield); $[\alpha]_D^{25}$ = +23.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 8.3 Hz, 4H), 7.22 (d, *J* = 8.0 Hz, 4H), 4.13 (d, *J* = 16.8 Hz, 2H), 3.97 (d, *J* = 16.8 Hz, 2H), 3.53–3.46 (m, 2H), 2.41–2.35 (m, 2H), 2.34 (s, 6H), 2.32–2.26 (m, 2H), 1.96–1.89 (m, 2H), 1.82 (t, *J* = 2.7 Hz, 2H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.79 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 137.9, 129.4 (2×CH), 127.7 (2×CH), 80.8, 79.7, 71.5, 62.2, 33.1, 30.3, 21.9, 21.5, 20.6, 19.9 . HRMS (ESI): *m/z* Calcd for $C_{32}H_{41}N_2O_4S_2$ $[M+H^+]$: 581.2484; Found: 581.2469.

*N-((S)-1-Cyclopropylbut-3-yn-1-yl)-N-(4-((N-((S)-1-cyclopropylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(S,S)-**6c**].*

According to general procedure II , from 261 mg (0.99 mmol) of (*S*)-**4c**, 198 mg of (*S*,*S*)-**6c** were obtained as a colorless oil (70% yield); $[\alpha]_D^{25}$ = –9.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 8.3 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 4H), 4.26 (d, *J* = 16.8 Hz, 2H), 4.11 (d, *J* = 16.8 Hz, 2H), 3.10 – 3.02 (m, 2H), 2.63–2.47 (m, 4H), 2.38 (s, 6H), 1.93 (t, *J* = 2.7 Hz, 2H), 1.09–1.01 (m,2H), 0.69–0.59 (m, 2H), 0.38–0.26 (m, 4H), 0.01– -0.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 137.7, 129.5 (2×CH), 127.4 (2×CH), 80.9, 80.2, 70.9, 62.3, 33.9, 24.7, 21.5, 13.9, 7.0, 4.1. HRMS (ESI): *m/z* Calcd for $C_{32}H_{40}N_3O_4S_2$ [M+NH_4^+]: 594.2447; Found: 594.2455.

*4-Methyl-N-(4-((4-methyl-N-((S)-1-(thiophen-3-yl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-(thiophen-3-yl)but-3-yn-1-yl)benzenesulfonamide [(S,S)-**6d**].* According to general procedure II, from 100 mg (0.33 mmol) of (*S*)-**4d**, 99 mg of (*S*,*S*)-**6d** were obtained as a white solid (91% yield) M.p. 46–48 °C; $[\alpha]_D^{25}$ = –39.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.24–7.18 (m, 4H), 6.84 (dd, J = 4.9, 1.4 Hz, 2H), 5.21–5.16 (m, 2H), 4.06 (d, *J* = 16.7 Hz, 2H), 3.49 (d, *J* = 16.7 Hz, 2H), 2.90 (ddd, *J* = 16.8, 9.1, 2.6 Hz, 2H), 2.69 (ddd, *J* = 16.8, 5.7, 2.6 Hz, 2H), 2.42 (s, 6H), 1.93 (t, *J* = 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 138.1, 137.6, 129.7 (2×CH), 127.7, 127.5 (2×CH), 126.1, 123.9, 80.4, 79.9, 71.6, 55.8, 33.3, 23.3, 21.6. HRMS (ESI): *m/z* Calcd for $C_{34}H_{36}N_3O_4S_4$ [M+NH_4^+]: 678.1575; Found: 678.1583.

*4-Methyl-N-(4-((4-methylN-((S)-1-(perfluorophenyl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(S,S)-**6e**].* According to general procedure II, from 103 mg (0.26 mmol) of (*S*)-**4e** , 67 mg of (*S*,*S*)-**6e** were obtained as a colorless oil (61% yield); $[\alpha]_D^{25}$ = –37.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 5.41 (dd, *J* = 10.7, 6.0 Hz, 2H), 4.17 (d, *J* = 17.3 Hz, 2H), 3.99 (d, *J* =17.3 Hz, 2H), 3.11–3.01 (m, 2H), 2.85–2.77 (m, 2H), 2.42 (s, 6H), 1.91 (t, *J* = 2.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -139.37 – -139.49 (m, 4F), -152.50 – -152.65 (m, 2F), -161.04 – -161.24 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.5 – 143.9 (m, 2×C-F), 144.3, 143.2 – 139.5 (m, C-F), 139.3 – 135.6 (m, 2×C-F), 136.0, 129.7 (2×CH), 127.4 (2×CH), 111.6 – 111.1 (m, C), 79.7, 78.3, 71.9, 51.5, 34.2, 22.2, 21.5. HRMS (ESI): *m/z* Calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1479; Found: 846.1479.

*4-Methyl-N-(4-((4-methyl-N-((R)-1-(perfluorophenyl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((R)-1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(R,R)-**6e**].* According to general procedure II, from 105 mg (0.27 mmol) of (*R*)-**4e**, 75 mg of (*R*,*R*)-**6e** were obtained as a colorless oil (67% yield); $[\alpha]_D^{25}$ = +36.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 5.41 (dd, *J* = 10.7, 6.0 Hz, 2H), 4.17 (d, *J* = 17.3 Hz, 2H), 3.99 (d, *J* =17.3 Hz, 2H), 3.11–3.01 (m, 2H), 2.85–2.77 (m, 2H), 2.42 (s, 6H), 1.91 (t, *J* = 2.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -139.38 – -139.50 (m, 4F), -152.53 – -152.70 (m, 2F), -161.06 – -161.26 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.5 – 143.9 (m, 2×C-F), 144.3, 143.2 – 139.5 (m, C-F), 139.3 – 135.6 (m, 2×C-F), 136.4, 129.7 (2×CH), 127.4 (2×CH), 111.6 – 111.1 (m, C), 79.7, 78.3, 71.9, 51.5, 34.2, 22.2, 21.5. HRMS (ESI): *m/z* Calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1518; Found: 846.1513.

General procedure III for the synthesis of triynes (*S*,*S*)-7a-d. The corresponding triyne (*S*,*S*)-**6a-d** (1 mmol) was dissolved in THF and the resulting solution was cooled at -78 °C. Then, HMDSLi (1M, 4 mmol) was added and the resulting solution was stirred 1 h at -78 °C. Finally, MeI was added (8 mmol) and the mixture was stirred at room temperature overnight (18 h). The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (6:1).

*4-Methyl-N-(4-((4-methyl-N-((S)-1-phenylpent-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-phenylpent-3-yn-1-yl)benzenesulfonamide [(S,S)-**7a**].* According to general procedure III, from 110 mg (0.17 mmol) of (*S*,*S*)-**6a**, 98 mg of (*S*,*S*)-**7a** were obtained as a white solid (85% yield) M.p. 42 – 44 °C; $[\alpha]_D^{25}$ = –48.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24–7.19 (m, 14H), 5.11–5.06 (m, 2H), 3.93 (d, *J* = 16.7 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 2H), 2.81–2.72 (m, 2H), 2.53–2.44 (m, 2H), 2.34 (s, 6H), 1.55 (t, *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.9, 137.0, 129.6 (2×CH), 128.4 (2×CH), 128.1, 127.5 (2×CH), 79.9, 78.8, 75.3, 59.8, 33.2, 22.0, 21.6, 3.6. HRMS (ESI): *m/z* Calcd for $C_{40}H_{44}N_3O_4S_2$ [M+NH_4^+]: 694,2773; Found: 694.2765.

*4-Methyl-N-(4-((4-methyl-N-((S)-2-methylhept-5-yn-3-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-2-methylhept-5-yn-3-yl)benzenesulfonamide [(S,S)-**7b**].* According to general procedure III, from 55 mg (0.09 mmol) of (*S*,*S*)-**6b**, 46 mg of (*S*,*S*)-**7b** were obtained as a colorless oil (80% yield); $[\alpha]_D^{25}$ = +44.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 4.18 (d, *J* = 17.2 Hz, 2H), 4.05 (d, *J* = 17.2 Hz, 2H), 3.57–3.49 (m, 2H), 2.40 (s, 6H), 2.38–2.30 (m, 4H), 2.01–1.94 (m, 2H), 1.65 (t, *J* = 2.5 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 141.7, 136.7, 128.0 (2×CH), 126.3 (2×CH), 78.2, 77.3, 74.2, 61.4, 31.8, 29.1, 20.6, 20.2, 19.3, 18.6, 2.2. HRMS (ESI): *m/z* Calcd for $C_{34}H_{44}N_2O_4S_2$ [M+H$^+$]: 626.3058; Found: 626.3071.

*N-((S)-1-Cyclopropylpent-3-yn-1-yl)-N-(4-((N-((S)-1-cyclopropylpent-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(S,S)-**7c**].* According to general procedure III, from 52 mg (0.09 mmol) of (*S*,*S*)-**6c**, 40 mg of (*S*,*S*)-**7c** were obtained as a colorless oil (73% yield); $[\alpha]_D^{25}$ = –5.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.75 (d, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 4.25 (d, *J* = 16.7 Hz, 2H), 4.13 (d, *J* = 16.7 Hz, 2H), 3.10–3.02 (m, 2H), 2.53–2.49 (m, 4H), 2.41 (s, 6H), 1.70 (t, *J* = 2.5 Hz, 6H), 1.09–1.00 (m, 2H), 0.69–0.62 (m, 2H), 0.38–0.30 (m, 4H), 0.08– -0.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.2, 138.0, 129.4 (2×CH), 127.5 (2×CH), 80.2, 78.0, 75.7, 62.8, 33.8, 24.7, 21.5, 14.1, 6.8, 4.1, 3.5. HRMS (ESI): *m/z* Calcd for $C_{34}H_{44}N_3O_4S_2$ [M+NH_4^+]: 622.2765; Found: 622.2768.

*4-Methyl-N-(4-((4-methyl-N-((S)-1-(thiophen-3-yl)pent-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-N-((S)-1-(thiophen-3-yl)pent-3-yn-1-yl)benzenesulfonamide [(S,S)-**7d**].* According to general procedure III, from 62 mg (0.09 mmol) of (*S*,*S*)-**6d**, 57 mg of (*S*,*S*)-**7d** were obtained as a colorless oil (88% yield); $[\alpha]_D^{25}$ = –38.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.23–7.19 (m, 4H), 6.87 (dd, *J* = 4.8, 1.5 Hz, 2H), 5.16–5.11 (m, 2H), 4.03 (d, *J* = 16.6 Hz, 2H), 3.48 (d, *J* = 16.6 Hz, 2H), 2.87–2.77 (m, 2H), 2.66–2.57 (m, 2H), 2.42 (s, 6H), 1.65 (t, *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 138.8, 137.8, 129.7 (2×CH), 127.9, 127.5 (2×CH), 125.8, 123.8, 79.8, 78.8, 75.3, 56.3, 33.2, 23.5, 21.6, 3.6. HRMS (ESI): *m/z* Calcd for $C_{36}H_{40}N_3O_4S_4$ [M+NH_4^+]: 706.1882; Found: 706.1896.

General procedure IV for the synthesis of triynes (*S*,*S*)-7e-g. The corresponding triyne (*S*,*S*)-**6** (1 mmol) was dissolved in acetone. Then, $AgNO_3$ (0.2 mmol) and N-bromosuccinimide (2.2 mmol) was added and the resulting solution was stirred 18 h at r.t. The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with water and extracted with Et_2O. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with n-hexane/EtOAc (8:1).

*N-((S)-4-Bromo-1-phenylbut-3-yn-1-yl)-N-(4-((N-((S)-4-bromo-1-phenylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(S,S)-**7e**].* According to general procedure IV, from 110 mg (0.17 mmol) of (*S*,*S*)-**6a**, 98 mg of (*S*,*S*)-**7e** were obtained as a white solid (58% yield) M.p. 42–44 °C; $[\alpha]_D^{25}$ = –48.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24–7.19 (m, 14H), 5.11–5.06 (m, 2H), 3.93 (d, *J* = 16.7 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 2H), 2.81–2.72 (m, 2H), 2.53–2.44 (m, 2H), 2.34 (s, 6H), 1.55 (t, *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.9, 137.0, 129.6 (2×CH), 128.4 (2×CH), 128.1, 127.5 (2×CH), 79.9, 78.8, 75.3, 59.8, 33.2, 22.0, 21.6, 3.6. HRMS (ESI): *m/*z Calcd for $C_{38}H_{38}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 822.0672; Found: 822.0665.

*N-((S)-6-Bromo-2-methylhex-5-yn-3-yl)-N-(4-((N-((S)-6-bromo-2-methylhex-5-yn-3-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(S,S)-**7f**].* According to general procedure IV, from 286 mg (0.49 mmol) of (*S*,*S*)-**6b**, 270 mg of (*S*,*S*)-**7f** were obtained as a colorless oil (74% yield); $[\alpha]_D^{25}$ = –6.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.05 (d, *J* = 16.8 Hz, 2H), 3.87 (d, *J* = 16.8 Hz, 2H), 3.55–3.48 (m, 2H), 2.44–2.36 (m, 2H), 2.35–2.28 (m, 2H), 2.34 (s, 6H), 1.89–1.82 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.80 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 137.7, 129.5 (2×CH), 127.6 (2×CH), 79.6, 77.1, 62.4, 41.0, 33.1, 30.6, 23.0, 21.6, 20.6, 20.0. HRMS (ESI): *m/z* Calcd for $C_{32}H_{42}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 756.0977; Found: 756.0982.

*N-((S)-4-Bromo-1-cyclopropylbut-3-yn-1-yl)-N-(4-((N-((S)-4-bromo-1-cyclopropylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(S,S)-**7g**].* According to general procedure IV, from 59 mg (0.10 mmol) of (*S*,*S*)-**6c**, 42 mg of (*S*,*S*)-**7g** were obtained as a colorless oil (56% yield); $[\alpha]_D^{25}$ = –8.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz,

$CDCl_3$): δ (ppm) 7.74 (d, *J* = 8.3 Hz, 4H), 7.29 (d, *J* = 8.0 Hz, 4H), 4.24 (d, *J* = 16.8 Hz, 2H), 4.09 (d, *J* = 16.8 Hz, 2H), 3.14–3.06 (m, 2H), 2.67–2.53 (m, 4H), 2.42 (s, 6H), 1.09–0.98 (m, 2H), 0.74–0.63 (m, 2H), 0.41–0.31 (m, 4H), 0.10– -0.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.6, 129.6 (2×CH), 127.4 (2×CH), 80.2, 62.3, 40.6, 33.8, 30.9, 25.8, 21.6, 14.0, 6.8, 4.1. HRMS (ESI): *m/z* Calcd for $C_{32}H_{35}Br_2N_2O_4S_2$ [M+NH_4^+]: 752.0631; Found: 752.0638.

General Procedure V for synthesis of tricyclic compounds (*S*,*S*)-8, (*S*,*S*)-9a-l and (*R*,*R*)-9a. In a flame-dried Schlenk sealed tube, the rhodium-catalyst (10-15 mol %) and the corresponding triyne (*S,S*)-**5**, **6** or **7** (1 mmol) were purged with argon. Then, toluene was added (100 mL/mmol triyne, 0.01 M). The resulting mixture was heated at 100 °C overnight (14 h). After complete reaction the solvent was removed, and the crude product was purified by flash chromatography with n-hexane/EtOAc (8:1).

*(3S,8S)-2,9-Bis(tert-butylsulfonyl)-3,8-diphenyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**8**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 80 mg (0.10 mmol) of (*S*,*S*)-**5**, 30 mg of (*S*,*S*)-**8** were obtained as a white solid (38% yield) M.p. 176–178 °C; $[\alpha]_D^{25}$ = +26.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51 (d, *J* = 8.3 Hz, 4H), 7.23–7.20 (m, 6H), 7.15–7.12 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 4H), 6.85 (s, 2H), 5.42–5.39 (m, 2H), 4.52 (d, *J* = 16.9 Hz, 2H), 3.93 (d, *J* = 16.9 Hz, 2H), 3.05 (d, *J* = 4.1 Hz, 4H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.9, 137.2, 130.5, 129.5 (2×CH), 128.5 (2×CH), 128.1, 127.6, 127.5, 127.2 (2×CH), 126.9 (2×CH), 53.6, 40.5, 31.4, 21.5. HRMS (ESI): *m/z* Calcd for $C_{32}H_{44}N_3O_4S_2$ [M+NH_4^+]: 598.2765; Found: 598.2768.

*(3S,8S)-3,8-Diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9a**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 44 mg (0.10 mmol) of (*S*,*S*)-**6a**, 30 mg of (*S*,*S*)-**9a** were obtained as a colorless oil (67% yield); $[\alpha]_D^{25}$ = +55.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51 (d, *J* = 8.3 Hz, 4H), 7.23–7.20 (m, 6H), 7.15–7.12 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 4H), 6.85 (s, 2H), 5.42–5.39 (m, 2H), 4.52 (d, *J* = 16.9 Hz, 2H), 3.93 (d, *J* = 16.9 Hz, 2H), 3.05 (d, *J* = 4.1 Hz, 4H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.9, 137.2, 130.5, 129.5 (2xCH), 128.5 (2×CH), 128.1, 127.6, 127.5, 127.2 (2×CH), 126.9 (2×CH), 53.6, 40.5, 31.4, 21.5. HRMS (ESI): *m/z* Calcd for $C_{38}H_{40}N_3O_4S_2$ [M+NH_4^+]: 846.1496; Found: 846.1501.

*(3S,8S)-3,8-Diisopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9b**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 106 mg (0.18 mmol) of (*S*,*S*)-**6b**, 73 mg of (*S*,*S*)-**9b** were obtained as a white solid (69% yield) M.p. 58–60 °C; $[\alpha]_D^{25}$ = +33.6 (c 1.0, CHCl3) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 8.3 Hz, 4H), 7.20 (d, *J* = 8.0 Hz, 4H), 6.77 (s, 2H), 4.59 (d, *J* = 17.4 Hz, 2H), 4.04 (d, *J* = 17.4 Hz, 2H), 3.84–3.78 (m, 2H), 2.77 – 2.64 (m, 4H), 2.36 (s, 6H), 1.66–1.54 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.88 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 137.8, 130.1, 129.6 (2×CH), 127.8, 127.7, 126.9 (2×CH), 57.6, 40.4, 29.9, 28.2, 21.5, 20.2, 19.7. HRMS (ESI): *m/z* Calcd for $C_{32}H_{41}N_2O_4S_2$ [M+H$^+$]: 581.2491; Found: 581.2502.

*(3S,8S)-3,8-Dicyclopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9c**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 54 mg (0.09 mmol) of (*S*,*S*)-**6c**, 34 mg of (*S*,*S*)-**9c** were obtained as a colorless oil (63% yield); $[\alpha]_D^{25}$ = +55.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24 (d, *J* = 8.0 Hz, 4H), 6.90 (s, 2H), 4.60 (d, *J* = 16.7 Hz, 2H), 4.33 (d, *J* = 16.7 Hz, 2H), 3.54–3.49 (m, 2H), 2.98 (dd, *J* = 15.7, 5.8 Hz, 2H), 2.71 (d, *J* = 16.3 Hz, 2H), 2.39 (s, 6H), 0.90–0.78 (m, 2H), 0.46–0.39 (m, 4H), 0.36–0.29 (m, 2H), 0.27–0.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.2, 137.8, 130.5, 129.6 (2×CH), 128.2, 127.8, 127.1 (2×CH), 56.5, 40.7, 33.3, 21.5, 12.7, 4.5, 4.3. HRMS (ESI): *m/z* Calcd for $C_{32}H_{37}N_2O_4S_2$ [M+H$^+$]: 577.2193; Found: 577.2189.

*(3S,8S)-3,8-Di(thiophen-3-yl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9d**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 67 mg (0.10 mmol) of (*S*,*S*)-**6d**, 40 mg of (*S*,*S*)-**9d** were obtained as a colorless oil (60% yield); $[\alpha]_D^{25}$ = +20.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.57 (d, *J* = 8.3 Hz, 4H), 7.18–7.14 (m, 6H), 6.90 (s, 2H), 6.78–6.76 (m, 4H), 5.47 (d, *J* = 5.6 Hz, 2H), 4.50 (d, *J* = 16.8 Hz, 2H), 3.88 (d, *J* = 16.8 Hz, 2H), 3.16 (dd, *J* = 16.3, 6.3 Hz, 2H), 3.00 (d, *J* = 16.3 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 139.6, 137.2, 130.3, 129.7 (2×CH), 127.9, 127.8, 127.3, 127.0 (2×CH), 125.9, 122.8, 50.0, 40.5, 32.5, 21.5. HRMS (ESI): *m/z* Calcd for $C_{34}H_{33}N_2O_4S_4$ [M+H$^+$]: 661.1309; Found: 661.1318.

*(3S,8S)-3,8-Bis(perfluorophenyl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9e**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 55 mg (0.07 mmol) of (*S*,*S*)-**6e**, 37 mg of (*S*,*S*)-**9e** were obtained as a white solid (74%

yield) M.p. 207–209 °C; $[\alpha]_D^{25}$ = +2.9 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.3 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 6.91 (s, 2H), 5.04 (dd, *J* = 11.5, 6.0 Hz, 2H), 4.84 (d, *J* = 16.0 Hz, 2H), 4.15 (d, *J* = 16.0 Hz, 2H), 2.95 (dd, *J* = 14.7, 6.0 Hz, 4H), 2.82 (dd, *J* = 14.7, 11.9 Hz, 2H), 2.30 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.29 – -142.39 (m, 4F), -154.80 – -154.95 (m, 2F), -161.41 – -161.59 (m, 4F); 13C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.0 – 143.8 (m, 2×C-F), 143.7, 141.9 – 139.7 (m, C-F), 138.8 – 136.6 (m, 2×C-F), 135.7, 133.0, 131.4, 129.2 (2×CH), 127.0 (2×CH), 126.2, 116.3 – 116.1 (m, C), 49.2, 42.0, 33.8, 21.3. HRMS (ESI): *m/z* Calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ $[M+NH_4^+]$: 846.1513; Found: 846.1496.

*(3R,8R)-3,8-Bis(perfluorophenyl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(R,R)-**9e**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (10 mol %), from 70 mg (0.09 mmol) of (*R*,*R*)-**6e**, 53 mg of (*R*,*R*)-**9e** were obtained as a white solid (76% yield) M.p. 208–210 °C; $[\alpha]_D^{25}$ = -3.4 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.3 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 6.91 (s, 2H), 5.04 (dd, *J* = 11.6, 6.0 Hz, 2H), 4.84 (d, *J* = 16.0 Hz, 2H), 4.15 (d, *J* = 16.0 Hz, 2H), 2.95 (dd, *J* = 14.7, 6.0 Hz, 4H), 2.82 (dd, *J* = 14.7, 11.9 Hz, 2H), 2.30 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.29 – -142.39 (m, 4F), -154.80 – -154.95 (m, 2F), -161.41 – -161.59 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.8 – 143.1 (m, 2C-F), 143.7, 140.2 – 136.7 (m, C-F), 139.5 – 136.0 (m, 2xC-F), 135.7, 133.0, 131.4, 129.2 (2×CH), 127.0 (2×CH), 126.2, 116.4 – 115.9 (m, C), 49.2, 42.0, 33.8, 21.3. HRMS (ESI): *m/z* Calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ $[M+NH_4^+]$: 846.1513; Found: 846.1514.

*(3S,8S)-5,6-Dimethyl-3,8-diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9f**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (15 mol %), from 98 mg (0.14 mmol) of (*S*,*S*)-**7a**, 71 mg of (*S*,*S*)-**9f** were obtained as a white solid (72% yield) M.p. 89–91 °C; $[\alpha]_D^{25}$ = +16.3 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 8.3 Hz, 4H), 7.23–7.20 (m, 6H), 7.11–7.06 (m, 8H), 5.45 (d, *J* = 5.8 Hz, 2H), 4.43 (d, *J* = 16.7 Hz, 2H), 3.85 (d, *J* = 16.7 Hz, 2H), 3.08 (d, *J* = 16.7 Hz, 2H), 3.08 (d, *J* = 16.9 Hz, 2H), 2.89 (dd, *J* = 16.9, 6.9 Hz, 2H), 2.35 (s, 6H), 2.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 139.0, 137.3, 133.0, 129.4 (2×CH), 128.6, 128.5 (2×CH), 127.7, 127.3 (2xCH), 127.0 (2×CH), 125.4, 53.6, 40.4, 29.1, 21.5, 15.2. HRMS (ESI): *m/z* Calcd for $C_{40}H_{41}N_2O_4S_2$ $[M+H^+]$: 677.2490; Found: 677.2502.

*(3S,8S)-3,8-Diisopropyl-5,6-dimethyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9g**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (15 mol %), from 46 mg (0.08 mmol) of (*S*,*S*)-**7b**, 31 mg of (*S*,*S*)-**9g** were obtained as a white solid (67% yield) M.p. 58–60 °C; $[\alpha]_D^{25}$ = +35.3 (c 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 8.3 Hz, 4H), 7.18 (d, *J* = 8.0 Hz, 4H), 4.55 (d, *J* 17.2 Hz, 2H), 4.03 (d, *J* = 17.2 Hz, 2H), 3.84–3.79 (m, 2H), 2.80–2.50 (m, 4H), 2.36 (s, 6H), 2.03 (s, 6H), 1.64–1.56 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.0, 137.9, 133.3, 129.5 (2xCH), 128.2, 126.9 (2xCH), 125.0, 57.5, 40.2, 28.3, 27.3, 21.5, 20.3, 20.1, 15.2. HRMS (ESI): *m/z* Calcd for $C_{34}H_{48}N_3O_4S_2$ [M+NH_4^+]: 626.3070; Found: 626.3081.

*(3S,8S)-3,8-Dicyclopropyl-5,6-dimethyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9h**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (15 mol %), from 20 mg (0.03 mmol) of (*S*,*S*)-**7c**, 15 mg of (*S*,*S*)-**9h** were obtained as a colorless oil (75% yield); $[\alpha]_D^{25}$ = +49.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.56 (d, *J* = 16.8 Hz, 2H), 4.33 (d, *J* = 16.8 Hz, 2H), 3.56–3.51 (m, 2H), 2.86–2.72 (m, 4H), 2.39 (s, 6H), 2.09 (s, 6H), 0.90–0.82 (m, 2H), 0.46–0.39 (m, 4H), 0.36–0.30 (m, 2H), 0.28–0.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 137.8, 133.8, 129.5 (2×CH), 128.6, 127.1 (2×CH), 125.1, 56.5, 40.6, 31.4, 21.5, 15.3, 13.0, 4.6, 4.3. HRMS (ESI): *m/z* Calcd for $C_{34}H_{44}N_3O_4S_2$ [M+NH_4^+]: 622.2776; Found: 622.2768.

*(3S,8S)-5,6-Dimethyl-3,8-di(thiophen-3-yl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9i**].* According to general procedure V, catalyst $RhCl(PPh_3)_3$ (15 mol %), from 55 mg (0.08 mmol) of (*S*,*S*)-**7d**, 38 mg of (*S*,*S*)-**9i** were obtained as a colorless oil (71% yield); $[\alpha]_D^{25}$ = +28.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.3 Hz, 4H), 7.19–7.14 (m, 6H), 6.78–6.74 (m, 4H), 5.51 (d, *J* = 5.2 Hz, 2H), 4.42 (d, *J* = 16.4 Hz, 2H), 3.82 (d, *J* = 16.4 Hz, 2H), 3.10–2.93 (m, 4H), 2.38 (s, 6H), 2.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 139.8, 137.2, 133.9, 129.5 (2×CH), 128.4, 127.3, 127.0 (2×CH), 125.9, 125.1, 122.7, 49.9, 40.4, 30.6, 21.5, 15.3. HRMS (ESI): *m/z* Calcd for $C_{36}H_{37}N_2O_4S_4$ [M+H^+]: 689.1617; Found: 689.1631.

*(3S,8S)-5,6-Dibromo-3,8-diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9j**].* According to general procedure V, catalyst $[RhCl(CO)_2)]_2$ (15 mol %), from 73 mg (0.09 mmol) of (S,S)-7e, 59 mg of (S,S)-9j were obtained as a white solid

(81% yield) M.p. 78 – 80 °C; $[\alpha]_D^{25}$ = +13.8 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.41 (d, *J* = 8.3 Hz, 4H), 7.22–7.19 (m, 6H), 7.05–7.02 (m, 4H), 7.00 (d, *J* = 8.0 Hz, 4H), 5.38 (d, *J* = 6.1 Hz, 2H), 4.35 (d, *J* = 17.4 Hz, 2H), 3.70 (d, *J* = 17.4 Hz, 2H), 3.32 (d, *J* = 18.1 Hz, 2H), 2.83 (dd, *J* = 18.1, 6.8 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 137.8, 136.9, 132.6, 129.6 (2×CH), 129.4, 128.8 (2×CH), 128.0, 127.1 (2×CH), 126.9, 126.8 (2xCH), 53.4, 40.0, 32.8. HRMS (ESI): *m/z* Calcd for $C_{38}H_{38}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 824.0620; Found: 824.0610.

*(3S,8S)-5,6-Dibromo-3,8-diisopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9k**].* According to general procedure V, catalyst $[RhCl(CO_2)]_2$ (15 mol %), from 100 mg (0.14 mmol) of (*S*,*S*)-**7f**, 82 mg of (*S*,*S*)-**9k** were obtained as a white solid (82% yield) M.p. 69–71 °C; $[\alpha]_D^{25}$ = +37.7 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60 (d, *J* = 8.3 Hz, 4H), 7.18 (d, *J* = 8.0 Hz, 4H), 4.19 (d, *J* = 17.7 Hz, 2H), 3.97 (d, J = 17.7 Hz, 2H), 3.80–3.75 (m, 2H), 3.00 (d, *J* = 17.1 Hz, 2H), 2.62 (d, *J* = 17.1, 6.4 Hz, 2H), 2.37 (s, 6H), 1.60–1.52 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.7, 132.4, 129.6 (2×CH), 129.1, 127.3, 126.9 (2×CH), 57.4, 39.9, 32.0, 28.6, 21.5, 20.0, 19.9. HRMS (ESI): *m/z* Calcd for $C_{32}H_{42}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 756.0966; Found: 756.0963.

*(3S,8S)-5,6-Dibromo-3,8-dicyclopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(S,S)-**9l**].* According to general procedure V, catalyst $[RhCl(CO_2)]_2$ (15 mol %), from 42 mg (0.06 mmol) of (*S*,*S*)-**7g**, 33 mg of (*S*,*S*)-**9l** were obtained as a white solid (79% yield) M.p. 71–73 °C; $[\alpha]_{25}^D$ = +27.6 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.66 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.61 (d, *J* = 17.0 Hz, 2H), 4.31 (d, *J* = 17.0 Hz, 2H), 3.55–3.49 (m, 2H), 2.97 (d, *J* = 17.1 Hz, 2H), 2.84 (dd, *J* = 17.1, 6.1 Hz, 2H), 2.40 (s, 6H), 0.87–0.77 (m, 2H), 0.52–0.42 (m, 4H), 0.34–0.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.6, 137.4, 132.7, 129.7 (2×CH), 129.3, 127.7, 127.0 (2×CH), 56.3, 40.3, 35.7, 21.5, 13.0, 4.8, 4.2. HRMS (ESI): *m/z* Calcd for $C_{32}H_{38}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 750.0660; Found: 750.0665.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org."

^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF).

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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REFERENCES

1. a) Goss, R. J. M.; Shankar, S.; Fayad, A. A. The generation of 'unnatural' products: Synthetic biology meets synthetic chemistry. *Nat. Prod. Rep*. **2012**, *29*, 870–889; b) Danishefsky, S. J. On the potential of natural products in the discovery of pharma leads: A case for reassessment. *Nat. Prod. Rep*. **2010**, *27*, 1114–1116; c) Wilson, R. M.; Danishefsky, S. J. Small Molecule Natural Products in the Discovery of Therapeutic Agents: The synthesis Connection. *J. Org. Chem*. **2006**, *71*, 8329-8351.
2. Faheem; Kumar, B. K.; Sekhar, K. V. G. C.; Chander, S.; Kunjiappan, S.; Murugesan, S. Medicinal chemistry perspectives of 1,2,3,4-tetrahydroisoquinoline analogs-biological activities and SAR studies. *RSC Adv*. **2021**, *11*, 12254-12287.
3 a) Das, B. G.; Shah, S.; Singh, V. K. Copper Catalyzed One-Pot Three-Component Imination-Alkynylation-aza-Michael Sequence: Enantio- and Diastereoselective Syntheses of 1,3-Disubstituted Isoindolines and Tetrahydroisoquinolines. *Org. Lett*. **2019**, *21*, 4981−4985; b) Custódio, D. L., da Veiga Jr., V. F. Lauraceae alkaloids. *RSC Adv*. **2014**, *4*, 21864-21890; c) Antkiewicz-Michaluk, L.; Wasik, A.; Michaluk, J. 1-Methyl-1,2,3,4-Tetrahydroisoquinoline, and Endogenous Amine with Unexpected Mechanism of Action: New Vistas of Therapeutic Application. *Neurotox. Res*. **2014**, 25, 1–12; d) D'Incalci, M.; Galmarini, C. M. A. Review of Trabectedin (ET-743): A Unique Mechanism of Action. *Mol. Cancer Ther*. **2010**, *9*, 2157-2163; f) Abe, K.; Saitoh, T.; Horiguchi, Y.;

Utsunomiya, I.; Taguchi, K. Synthesis and Neurotoxicity of Tetrahydroisoquinoline Derivatives for Studyind Parkinson's Disease. *Biol. Pharm. Bull.* **2005**, *28*, 1355-1362.

4 a) Fluegel, L. L.; Hoye, T. R. Hexahydro-Diels-Alder Reaction: Benzyne Generation via Cycloisomerization of Tethered Triynes. *Chem. Rev*. **2021**, *121*, 2413-2444; b) Aubert, C.; Buisine, O.; Malacria, M. The Behavior of 1,n-Enynes in the Presence of Transition Metals. *Chem. Rev*. **2002**, *102*, 813–834; c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. Transition Metal Catalyzed Carbocyclations in Organic Synthesis. *Chem. Rev*. **1996**, *96*, 635–662.

5. a) Matton, P.; Huvelle, S.; Haddad, M.; Phansavath, P.; Ratavalomana-Vidal V. Recent Progress in Metal-catalyzed [2+2+2] Cycloadditions reactions *Synthesis* **2021**. DOI: 10.1055/s-0040-1719831; b) Domínguez, G.; Pérez-Castells, J. Alkenes in [2+2+2] Cycloadditions. *Chem. Eur. J*. **2016**, *22*, 6720-6739; c) Galan, B. R.; Rovis, T. [2+2+2] Cycloadditions. *Angew. Chem. Int. Ed*. **2009**, *48*, 2830-2834; d) Hegedus, L. S. Transition Metals in Organic Synthesis: Highligths for the year 1996. *Coord. Chem. Rev.* **1998**, *168*, 49–175; e) Lautens, M.; Klute, W.; Tam, W. Transition Metal-Mediated Cycloadditions. *Chem. Rev*. **1996**, *96*, 49–92.

6 a) Suzuki, S.; Nishigaki, S.; Shibata, Y.; Tanaka, K. Rhodium-Catalyzed Enantioselective [2+2+1] Cycloaddition of 1,6- Enynes with Cyclopropylideneacetamide. *Org. Lett.* **2018**, *20*, 7461–7465; b) Yoshizaki, S.; Nakamura, Y.; Masutomi, K.; Yoshida, T.; Noguchi, K.; Shibata, Y.; Tanaka, K. Rhodium-Catalyzed Asymmetric [2+2+2] Cycloaddition of 1,6-Enynes with Cyclopropylideneacetamides. *Org. Lett*. **2016**, *18*, 388–391; c)Masutomi, K.; Sakiyama, N.; Noguchi, K.; Tanaka, K. Rhodium-Catalyzed Regio, Diastereo-, and Enantioselective [2+2+2] Cycloaddition of 1,6-Enynes with Acrylamides. *Ang. Chem., Int. Ed.* **2012**, *51*, 13031–1303; d) Tanaka, K.; Otake, Y.; Sagac, H.; Noguchi, K.; Hirano, M. Highly region-, diastereo-, and enantioselective [2+2+2] cycloaddition of 1,6-enynes with electron-deficient ketones catalyzed byRhI/H8-binap complex. *Ang. Chem., Int. Ed.* **2008**, *47*, 1312–1316.

7. Alvarez, S.; Medina, S.; Domínguez, G.; Pérez-Castells, J. Ruthenium Alkylidene-Catalyzed Reaction of 1,6-Heptadyines with Alkene. *J. Org. Chem.* **2015**, *80*, 2436−2442.

8. a) Onodera, G.; Suto, M.; Takeuchi, R. Iridium-Catalyzed [2+2+2] Cycloaddition of □,□-Dyines with Isocyanates. *J. Org. Chem*. **2012**, *77*, 908-920; b) Onodera, G.; Shimizu, Y.; Kimura, J., Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. Iridium-Catalyzed [2+2+2] Cycloaddition of □,□-Dyines with Nitriles. *J. Am. Chem. Soc.* **2012**, *134,* 10515-10531.

9. a) Ventre, S.; Simon, C.; Rekhroukh, F.; Malacria, M.; Amatore, M.; Aubert, C.; Petit, M. Catalytic Version of Enediyne Cobalt-Mediated Cycloaddition and Selective Access to Unsual Bicyclic Trienes. *Chem. Eur. J.* **2013**, *19*, 5830-5835; b) Dachs, A.; Pla-Quintana, A.; Parella, T.; Solà, M.; Roglans, A. Intramolecular [2+2+2] Cycloaddition Reactions of Yne-ene-yne and Yne-yne-ene Enediynes Catalysed by Rh^{I}: Experimental and Theoretical Mechanistic Studies. *Chem. Eur. J.* **2011**, *17*, 14493–14507; c) Dachs, A.; Roglans, A.; Solà, M. $RhCl(PPh_3)_3$-Catalyzed Intramolecular Cycloaddition of Enediynes: The nature of the Tether and Substituents Controls the Reaction Mechanism. *Organometallics* **2011**, 30, 3151–3159; d) Geny, A.; Gaudrel, S.; Slowinski, F.; Amatore, M.; Chouraqui, G.; Malacria, M.; Aubert, C-; Gandon, V. A Straightforward Procedure for the [2+2+2] Cycloaddition of Enediynes. *Adv. Synth. Catal.* **2009**, *351*, 271-275; e) Shibata, T.; Kurokawa, H.; Kanda, K. Enantioselective Intramolecular [2+2+2] Cycloaddition of Enediynes for the Synthesis of Chiral Cyclohexa-1,3-dienes. *J. Org. Chem*. **2007**, *72*, 6521-6525; f) Eckenberg, P.; Growth, U. Cobalt Mediated Intramolecular [2+2+2]-Cycloaddition of Enediynes Towards Linear Annelated Polycycles. *Synlett* **2003**, 2188-2192.

10 a) Shibata, T.; Fusamae, T.; Takano, H.; Sugimura, N., Kanyiva, K. S. Enantioselective Synthesis of Nine to Eleven-Membered Cyclic Polyphenylenes Containing Heteroatoms by Catalytic Intramolecular [2+2+2] Cycloaddition. *Asian J. Org. Chem*. **2019**, 8, 970-977; b) Karmakar, R.; Mamidipalli, P.; Salzman, R.M.; Hong, S.; Yun, S. Y.; Guo, W.; Xia, Y.; Lee, D. Benzannulation of Triynes Initiated by an Alder Ene Reaction and Subsequent Trifluoromethylthiolate Addition. *Org. Lett.* **2016**, *18,* 3530–3533. c) Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. $CoCl(PPh_3)_3$ as Cyclotrimerization Catalyst for Functionalized Trynes under Mild Conditions. *J. Org. Chem*. **2015**, *80*, 9781−9793. d) Shibata, T.; Tsuchikama, K.; Otsuka, M. Enantioselective intramolecular [2+2+2] cycloaddition of triynes for the

synthesis of atropisomeric chiral *ortho*-diarylbenzenes derivatives*Tetrahedron: Asymmetry* **2006**, *17*, 614–619

11 a) Karras, M.; Holec, J.; Bednárová, L.; Pohl, R.; Schmidt, B.; Stará, I. G.; Starý, I. Asymmetric Synthesis of Nonracemic 2-Amino[6]helicenes and Their Self-Assembly into Langmuir Films. *J. Org. Chem*. **2018**, *83*, 5523–5538; b) Yamano, R.; Shibata, Y.; Tanaka, K. Substituent-Controlled and Rhodium-Catalyzed Intramolecular [2+2+2] and [2+2+2+1] Cycloadditions of Electron Deficient Triynes *Chem. Eur. J*. **2018**, *24*, 6364–6370; c) Yamano R.; Hara, J.; Murayama, K., Sugiyama, H.; Teraoka, K.; Uekusa, H.; Kawauchi, S.; Shibata, Y.; Tanaka, K. Rh-Mediated Enantioselective Synthesis, Crystal Structures, and Photophysical/Chiroptical Properties of Phenanthrenols Based [9]Helicene-like Molecules *Org. Lett*. **2017**, *19*, 42–45.

12 a) Cassú, D.; Parella, T.; Solà, M.; Pla-Quintana, A.; Roglans, A. Rhodium-Catalyzed [2+2+2] Cycloaddition Reactions of Linear Allene-Ene-Ynes to afford Fused Tricyclic Scaffols: Insights into the Mechanism. *Chem. Eur. J*. **2017**, *23*, 14889–14899; b) Haraburda, E.; Torres, O.; Parella, T.; Solà, M.; Pla-Quintana, A.; Roglans, A. Stereoselective Rhodium-Catalysed [2+2+2] Cycloaddition of Linear Allene-Ene/Yne-Allene Substrates: Reactivity and Theoretical Mechanistic Studies. *Chem. Eur. J*. **2014**, *20*, 5034–5045. c) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. Ruthenium (II)-Catalyzed Selective Intramolecular [2+2+2] Alkyne Cyclotrimerizations. *J. Am. Chem. Soc*. **2003**, *125*, 12143-12160.

13 a) Sirvent, A., García-Muñoz, M. J.; Yus, M.; Foubelo, F. Stereoselective Synthesis of Tetrahydroisoquinolines from Chiral 4-Azaocta-1,7-diynes and 4-Azaocta-1,7-enynes. *Eur. J. Org. Chem*. **2020**, 113-126.b) Bauer, R. A.; Diblasi, C.M.; Tan, D. S. The tert-Butylsulfinylamide Lynchpin in Transition-Metal-Mediated Multiscaffold Library Syhthesis. *Org. Lett*. **2010**, *12*, 2084-2087.

14 Contreras, J.-M.; Sippl, W. The Practice of Medicinal Chemistry. Wermuth, C.G. Ed., 3rd Edition; Elsevier Ltd. 2008, pp 380-414.

15 Tomassoli, I.; Gündish, D. The twin drug approach for novel nicotinic receptor ligands. *Bioorg. Med. Chem*. **2015**, *23*, 4375-4389.

16 Feng, S.; Yunqiang, B.; Jing, L.; Zhenghua, L.; Li, Z.; Junman, F.; Yonghong, L.; Meng, Z. Indole Alkaloids, Synthetic Dimers and Hybrids with Potential in vivo Anticancer Activity. *Curr. Top. Med. Chem.* **2021**, *21*, 377-403.

17. a) Llobat, A.; Escorihuela, J.; Fustero, S.; Medio-Simon, M. Diastereoselectivity of the Addition of Propargylic MagnesiumReagents to Fluorinated Aromatic Sulfinyl Imines. *Org. Lett*. **2021**, *23*, 3691-3695; b) Llobat, A.; Sedgwick, D. M.; Cabré, A.; Román, R.; Mateu, N.; Escorihuela, J.; Medio-Simón, M.; Soloshonok, V. A.; Han, J.; Riera, A.; Fustero, S. Asymmetric Synthesis of Fluorinated Monoterpenic Alkaloid Derivatives from Chiral Fluoroalkyl Aldimines via the Pauson-Khand Reaction. *Adv. Synth. Catal*. **2020**, *362*, 1378-1384; c) Llobat, A.; Escorihuela, J.; Sedgwick, D. M.; Rodenes, M.; Román, R.; Soloshonok, V. A.; Han, J.; Medio-Simón, M.; Fustero, S. The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocyles. *Eur. J. Org. Chem*. **2020**, 4193–4207; d) Llobat, A.; Román, R.; Mateu, N.; Sedgwick, D. M.; Barrio, P.; Medio-Simón, M.; Fustero, S. The Fluoro-Pauson–Khand Reaction in the Synthesis of Enantioenriched Nitrogenated Bicycles Bearing a Quaternary C–F Stereogenic Center. *Org. Lett.* **2019**, *21*,7294-7297.

18 Xie, L.; Wu, Y.; Yi, W.; Zhy, L.; Xiang, J.; He, W. Gold Catalyzed Hydratation of Haloalkynes to □-Halomethyl Ketones. *J. Org. Chem*. **2013**, *78*, 9190-9195.

19 Roglans, A.; Pla-Quintana, A.; Parella, T. Mechanistic Studies of Transition-Metal-Catalyzed [2+2+2] Cycloadditions Reactions. *Chem. Rev*. **2021**, *121*, 1894-1979.

Supporting Information for

Linear Chiral-N-bridged Triynes as Key frameworks for Expeditious Access to a Merged Tetrahydroisoquinoline Core

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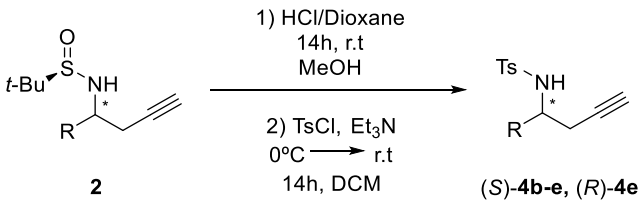
I. General Information.

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. CH_2Cl_2 (DCM) was used without further purification. The reactions were monitored with the aid of TLC on 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and solution of potassium permanganate and sodium hydroxide in water. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz Bruker AvanceIII 300 spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points were measured on a Büchi B−540 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C.

Imines (*R*)-**1**, homopropargyl amides (*S,Rs*)-**2a-e**, (*R,Rs*)-**2e**, (*S*)-**3** and *(S)*-**4a** were prepared according with previous described procedures[1,2]

II. General procedure I for the synthesis of tosylamides (*S*)-4b-e and (*R*)-4e.



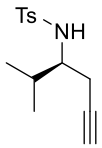
2 (*S*)-**4b-e**, (*R*)-**4e**

1) *Desulfinylation*: Compounds **2** (1 mmol) were dissolved in MeOH (0.1M) and a solution of HCl in dioxane (4M, 4 mmol) was added. The mixture was stirred at room temperature overnight (18h). The reaction was monitorized by TLC. Once the starting material was consumed, the solvent was evaporated and the resulting crude was washed with cold Et_2O until the amine clorhydrate appeared as a white solid.

2) *N-Tosylation*: The white solid obtained in the above stage was suspended in DCM (0.1M) and the temperature was decreased to 0°C with an ice bath. Then, Et_3N (3 mmol) was added and when the white solid was dissolved TsCl was added (1.5 mmol). The mixture was stirred

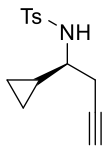
overnight (18h) at room temperature. The reaction was monitorized by TLC. Once the reaction was finished, it was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (5:1).

(*S*)-4-Methyl-*N*-(2-methylhex-5-yn-3-yl)benzenesulfonamide [(*S*)-4b].



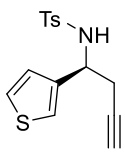
According to general procedure I, from 260 mg (1.21 mmol) of (*R*$_S$, *S*)-**2b**, 266 mg of (*S*)-**4b** were obtained as a white solid (83% yield) m.p. 72–74 °C; $[\alpha]^{25}_D$ = +67.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.93 (d, *J* = 9.2 Hz, 1H), 3.15-3.06 (m, 1H), 2.43 (s, 3H), 2.34 (dd, *J* = 17.1, 4.2, 2.6 Hz, 1H), 2.20 (dd, *J* = 17.1, 6.3, 2.6 Hz, 1H), 1.97-1.90 (m, 2H), 0.87 (d, *J* = 5.5 Hz, 3H) 0.84 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 138.0, 129.6 (2xCH), 127.1 (2xCH), 79.7, 71.3, 57.3, 30.7, 22.6, 21.5, 19.2, 18.0. HRMS (ESI): m/z calcd for $C_{14}H_{20}NO_2S$ [M+H$^+$]: 266.1201; found: 266.1209.

(*S*)-*N*-(1-Cyclopropylbut-3-yn-1-yl)-4-methylbenzenesulfonamide [(*S*)-4c].



According to general procedure I, from 244 mg (1.15 mmol) of (*R*$_S$, *S*)-**2c**, 261 mg of (*S*)-**4c** were obtained as a colorless oil (86% yield); $[\alpha]^{25}_D$ = +47.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.59 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 7.6 Hz, 1H), 2.49-2.41 (m 1H), 2.23-2.20 (m, 5H), 1.79 (t, *J* = 2.6 Hz, 1H), 0.87-0.79 (m, 1H), 0.34-0.24 (m, 1H), 0.19-0.10 (m, 1H), 0.05-0.03 (m, 1H), -014 – -0.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.1, 129.6 (2xCH), 127.1 (2xCH), 80.0, 71.3, 56.9, 25.7, 21.5, 15.5, 4.2, 3.6. HRMS (ESI): m/z calcd for $C_{14}H_{18}NO_2S$ [M+H$^+$]: 264.1043; found: 264.1053.

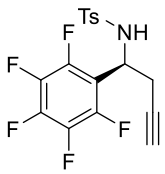
(*S*)-4-Methyl-*N*-(1-(thiophen-3-yl)but-3-yn-1-yl)benzenesulfonamide [(*S*)-4d].



According to general procedure I, from 700 mg (2.74 mmol) of (*R*$_S$, *S*)-**2d**, 670 mg of (*S*)-**4d** were obtained as a white solid (80% yield) m.p. 107–109 °C; $[\alpha]^{25}_D$ = -49.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.61 (d, *J* =

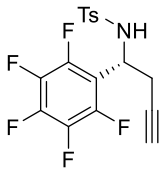
8.3 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.81 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.41 (d, *J* = 8.1 Hz, 1H), 4.61-4.54 (m, 1H), 2.60-2.57 (m, 2H), 2.34 (s, 3H), 1.93 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 140.4, 137.5, 129.6 (2xCH), 127.1 (2xCH), 126.2, 126.0, 122.3, 79.4, 72.2, 51.7, 26.7, 21.5. HRMS (ESI): m/z calcd for $C_{15}H_{19}N_2O_2S_2$ [M+NH_4^+]: 323.0881; found: 323.0882.

***(S)*-4-Methyl-*N*-(1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(*S*)-4e].**



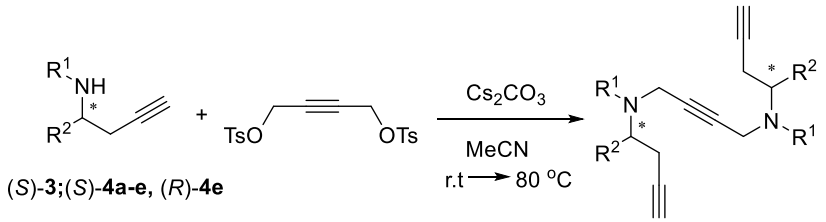
According to general procedure I, from 444 mg (1.31 mmol) of (R_s, *S*)-**2e**, 377 mg of (*S*)-**4e** were obtained as a white solid (74% yield) m.p. 107–109 °C; $[\alpha]^{25}_D$ = -21.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.60 (d, *J* = 9.4 Hz, 1H), 4.95-4.87 (m, 1H), 2.81-2.64 (m, 2H), 2.37 (s, 3H), 1.94 (t, *J* = 2.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.41 – -142.52 (m, 2F), -153.98 – -154.13 (m, 1F), -161.47 – -161.65 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.3-142.6 (m, 2xC-F), 144.1, 142.5-149.1 (m, C-F), 139.2-135.3 (m, 2xC-F), 136.4, 129.5 (2xCH), 127.0 (2xCH), 113.1-112.6 (m, 1C), 77.6, 72.1, 47.8, 25.3, 21.3 . HRMS (ESI): m/z calcd for $C_{17}H_{13}F_5NO_2S$ [M+H^+]: 390.0569; found: 390.0570.

(*R*)-4-Methyl-*N*-(1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(*R*)-4e].



According to general procedure I, from 116 mg (0.34 mmol) of (R_s, *R*)-**2e**, 105 mg of (*R*)-**4e** were obtained as a white solid (79% yield) m.p. 109–111 °C; $[\alpha]^{25}_D$ = +27.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.65 (d, *J* = 9.3 Hz, 1H), 4.88-4.80 (m, 1H), 2.75-2.57 (m, 2H), 2.30 (s, 3H), 1.87 (t, *J* = 2.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.33 – -142.46 (m, 2F), -154.32 – -154.47 (m, 1F), -161.78 – -161.96 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.3 – 142.7 (m, 2xC-F), 144.1, 142.6 – 139.1 (m, C-F), 139.1 – 135.3 (m, 2xC-F), 136.4, 129.5 (2xCH), 127.0 (2xCH), 113.1 – 112.6 (m, 1C), 77.6, 72.1, 47.8, 25.3, 21.3. HRMS (ESI): m/z calcd for $C_{17}H_{13}F_5NO_2S$ [M+H^+]: 390.0580; found: 390.0582.

III. General procedure II for the synthesis of triynes (*S,S)*-5; (*S, S*)-6a-e and (*R, R*)-6e.



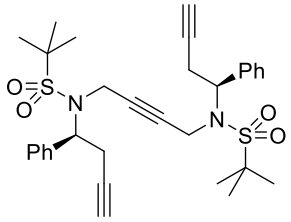
(*S*)-**3**;(*S*)-**4a-e**, (*R*)-**4e**

(*S, S*)-**5**;(*S, S*)-**6a-e**, (*R, R*)-**6e**

To a suspension of Cs_2CO_3 (2 mmol) in acetonitrile (6 mL) was added homopropargyl amide *(S)*-**4** or *(R)*-**4** (1 mmol) and the solution was stirred for 1h at room temperature. Then, a solution of 2-butyn-1,4-ditosylate (0.8 mmol) in acetonitrile (4 mL) was slowly added for 8 h at 80°C. The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (6:1).

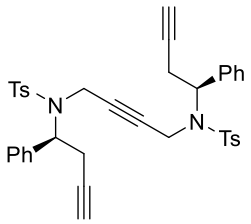
2-Methyl-*N*-(4-((2-methyl-*N*-((*S*)-1-phenylbut-3-yn-1-yl)propan-2-yl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-phenylbut-3-yn-1-yl)propane-2-sulfonamide [*(S, S)*-5].

According to general procedure II, from 203 mg (0.76 mmol) of (*S*)-**3**, 80 mg of (*S, S*)-**5** were



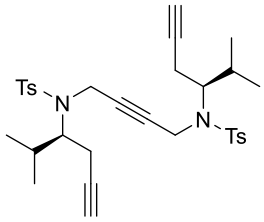
obtained as a white solid (39% yield) m.p. 95 – 97 °C; $[\alpha]^{25}_D$ = –23.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm 7.54 – 7.51 (m, 4H), 7.42 – 7.33 (m, 6H), 5.29 – 5.24 (m, 2H), 4.12 (d, *J* = 17.8 Hz, 2H), 3.61 (d, *J* =17.8 Hz, 2H), 3.06 – 2.98 (m, 2H), 1.99 (t, *J* = 2.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.6, 128.6 (2xCH), 128.6 (2xCH), 128.4, 81.3, 80.7, 71.7, 62.1, 61.2, 34.7, 24.8, 23.3. HRMS (ESI): m/z calcd for $C_{32}H_{44}N_3O_4S_2$ [M+NH_4^+]: 598.2755; found: 598.2768.

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-1-phenylbut-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-phenylbut-3-yn-1-yl)benzenesulfonamide [(*S, S*)-6a].



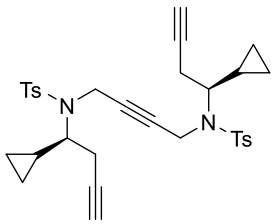
According to general procedure II, from 140 mg (0.47 mmol) of (*S*)-**4a**, 110 mg of (*S*, *S*)-**6a** were obtained as a colorless oil (73% yield); $[\alpha]^{25}_{D}$ = –34.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.25 – 7.19 (m, 14H), 5.16 – 5.11 (m, 2H), 3.98 (d, *J* = 16.7 Hz, 2H), 3.36 (d, *J* =16.7 Hz, 2H), 2.86 (ddd, *J* = 16.9, 9.9, 2.6 Hz, 2H), 2.57 (d, *J* = 16.9, 5.4, 2.6 Hz, 2H), 2.35 (s, 6H), 1.83 (t, *J* = 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 137.7, 136.2, 129.7 (2xCH), 128.5 (2xCH), 128.4, 128.2 (2xCH), 127.5 (2xCH), 80.4, 80.0, 71.5, 59.4, 33.3, 21.8, 21.6. HRMS (ESI): m/z calcd for $C_{38}H_{40}N_3O_4S_2$ [M+NH_4^+]: 666.2454; found: 666.2455.

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-2-methylhex-5-yn-3-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-2-methylhex-5-yn-3-yl)benzenesulfonamide [(*S, S*)-6b].



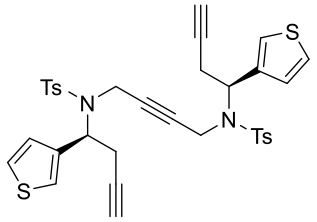
According to general procedure II, from 209 mg (0.79 mmol) of (*S*)-**4b**, 203 mg of (*S, S*)-**6b** were obtained as a colorless oil (89% yield); $[\alpha]^{25}_{D}$ = +23.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 8.3 Hz, 4H), 7.22 (d, *J* = 8.0 Hz, 4H), 4.13 (d, *J* = 16.8 Hz, 2H), 3.97 (d, *J* = 16.8 Hz, 2H), 3.53–3.46 (m, 2H), 2.41 – 2.35 (m, 2H), 2.34 (s, 6H), 2.32 – 2.26 (m, 2H), 1.96–1.89 (m, 2H), 1.82 (t, *J* = 2.7 Hz, 2H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.79 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 137.9, 129.4 (2xCH), 127.7 (2xCH), 80.8, 79.7, 71.5, 62.2, 33.1, 30.3, 21.9, 21.5, 20.6, 19.9 . HRMS (ESI): m/z calcd for $C_{32}H_{41}N_2O_4S_2$ [M+H^+]: 581.2484; found: 581.2469.

***N*-((*S*)-1-Cyclopropylbut-3-yn-1-yl)-*N*-(4-((N-((*S*)-1-cyclopropylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(*S, S*)-6c].**



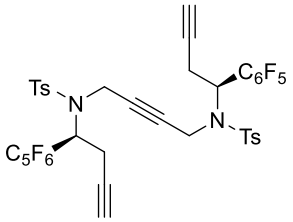
According to general procedure II , from 261 mg (0.99 mmol) of (*S*)-**4c**, 198 mg of (*S, S*)-**6c** were obtained as a colorless oil (70% yield); $[\alpha]^{25}_{D}$ = –9.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 8.3 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 4H), 4.26 (d, *J* = 16.8 Hz, 2H), 4.11 (d, *J* = 16.8 Hz, 2H), 3.10 – 3.02 (m, 2H), 2.63 – 2.47 (m, 4H), 2.38 (s, 6H), 1.93 (t, *J* = 2.7 Hz, 2H), 1.09 – 1.01 (m,2H), 0.69 – 0.59 (m, 2H), 0.38 – 0.26 (m, 4H), 0.01 – -0.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 137.7, 129.5 (2xCH), 127.4 (2xCH), 80.9, 80.2, 70.9, 62.3, 33.9, 24.7, 21.5, 13.9, 7.0, 4.1. HRMS (ESI): m/z calcd for $C_{32}H_{40}N_3O_4S_2$ $[M+NH_4^+]$: 594.2447; found: 594.2455.

4-Methyl-*N*-(4-((4-methyl-N-((*S*)-1-(thiophen-3-yl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-(thiophen-3-yl)but-3-yn-1-yl)benzenesulfonamide [(*S, S*)-6d].



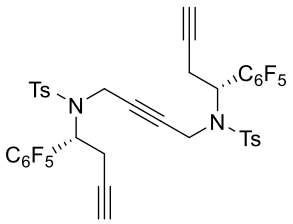
According to general procedure II, from 100 mg (0.33 mmol) of (*S*)-**4d**, 99 mg of (*S, S*)-**6d** were obtained as a white solid (91% yield) m.p. 46 – 48 °C; $[\alpha]^{25}_{D}$ = –39.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.24 – 7.18 (m, 4H), 6.84 (dd, *J* = 4.9, 1.4 Hz, 2H), 5.21 – 5.16 (m, 2H), 4.06 (d, *J* = 16.7 Hz, 2H), 3.49 (d, *J* = 16.7 Hz, 2H), 2.90 (ddd, *J* = 16.8, 9.1, 2.6 Hz, 2H), 2.69 (ddd, *J* = 16.8, 5.7, 2.6 Hz, 2H), 2.42 (s, 6H), 1.93 (t, *J* = 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 138.1, 137.6, 129.7 (2xCH), 127.7, 127.5 (2xCH), 126.1, 123.9, 80.4, 79.9, 71.6, 55.8, 33.3, 23.3, 21.6. HRMS (ESI): m/z calcd for $C_{34}H_{36}N_3O_4S_4$ $[M+NH_4^+]$: 678.1575; found: 678.1583.

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-1-(perfluorophenyl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(*S, S*)-6e].



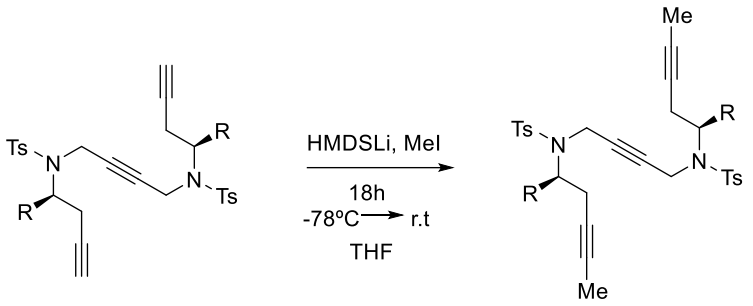
According to general procedure II, from 103 mg (0.26 mmol) of (*S*)-**4e** , 67 mg of (*S, S*)-**6e** were obtained as a colorless oil (61% yield); $[\alpha]^{25}_{D}$ = –37.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 5.41 (dd, *J* = 10.7, 6.0 Hz, 2H), 4.17 (d, *J* = 17.3 Hz, 2H), 3.99 (d, *J* =17.3 Hz, 2H), 3.11 – 3.01 (m, 2H), 2.85 – 2.77 (m, 2H), 2.42 (s, 6H), 1.91 (t, *J* = 2.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -139.37 – -139.49 (m, 4F), -152.50 – -152.65 (m, 2F), -161.04 – -161.24 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.5 – 143.9 (m, 2xC-F), 144.3, 143.2 – 139.5 (m, C-F), 139.3 – 135.6 (m, 2xC-F), 136.0, 129.7 (2xCH), 127.4 (2xCH), 111.6 – 111.1 (m, C), 79.7, 78.3, 71.9, 51.5, 34.2, 22.2, 21.5. HRMS (ESI): m/z calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1479; found: 846.1479.

4-Methyl-*N*-(4-((4-methyl-*N*-((*R*)-1-(perfluorophenyl)but-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*R*)-1-(perfluorophenyl)but-3-yn-1-yl)benzenesulfonamide [(*R, R*)-6e].



According to general procedure II, from 105 mg (0.27 mmol) of (*R*)-**4e**, 75 mg of (*R, R*)-**6e** were obtained as a colorless oil (67% yield); $[\alpha]^{25}_{D}$ = +36.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 5.41 (dd, *J* = 10.7, 6.0 Hz, 2H), 4.17 (d, *J* = 17.3 Hz, 2H), 3.99 (d, *J* =17.3 Hz, 2H), 3.11 – 3.01 (m, 2H), 2.85 – 2.77 (m, 2H), 2.42 (s, 6H), 1.91 (t, *J* = 2.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -139.38 – -139.50 (m, 4F), -152.53 – -152.70 (m, 2F), -161.06 – -161.26 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.5 – 143.9 (m, 2xC-F), 144.3, 143.2 – 139.5 (m, C-F), 139.3 – 135.6 (m, 2xC-F), 136.4, 129.7 (2xCH), 127.4 (2xCH), 111.6 – 111.1 (m, C), 79.7, 78.3, 71.9, 51.5, 34.2, 22.2, 21.5. HRMS (ESI): m/z calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1518; found: 846.1513.

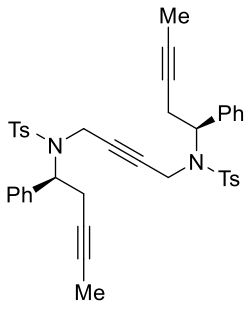
IV. General procedure III for the synthesis of triynes (*S, S*)-7a-d.



(*S, S*)-**6a-d** (*S, S*)-**7a-d**

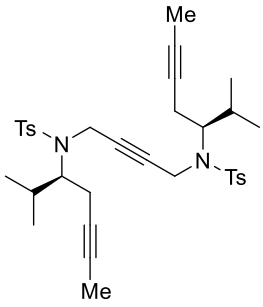
The corresponding triyne (*S, S*)-**6a-d** (1 mmol) was dissolved in THF and the resulting solution was cooled at -78°C. Then, HMDSLi (1M, 4 mmol) was added and the resulting solution was stirred 1h at -78°C. Finally, MeI was added (8 mmol) and the mixture was stirred at room temperature overnight (18h). The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with DCM. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (6:1).

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-1-phenylpent-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-phenylpent-3-yn-1-yl)benzenesulfonamide [(*S, S*)-7a].



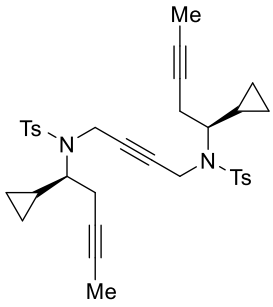
According to general procedure III, from 110 mg (0.17 mmol) of (*S, S*)-**6a**, 98 mg of (*S, S*)-**7a** were obtained as a white solid (85% yield) m.p. 42 – 44 °C; $[\alpha]^{25}_{D}$ = –48.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24 – 7.19 (m, 14H), 5.11 – 5.06 (m, 2H), 3.93 (d, *J* = 16.7 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 2H), 2.81 – 2.72 (m, 2H), 2.53 – 2.44 (m, 2H), 2.34 (s, 6H), 1.55 (t *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.9, 137.0, 129.6 (2xCH), 128.4 (2xCH), 128.1, 127.5 (2xCH), 79.9, 78.8, 75.3, 59.8, 33.2, 22.0, 21.6, 3.6. HRMS (ESI): m/z calcd for $C_{40}H_{44}N_3O_4S_2$ [M+NH_4^+]: 694,2773; found: 694.2765.

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-2-methylhept-5-yn-3-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-2-methylhept-5-yn-3-yl)benzenesulfonamide [(*S, S*)-7b].



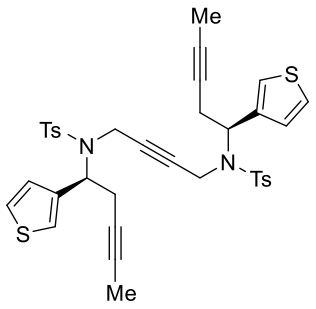
According to general procedure III, from 55 mg (0.09 mmol) of (*S, S*)-**6b**, 46 mg of (*S, S*)-**7b** were obtained as a colorless oil (80% yield); $[\alpha]^{25}_{D}$ = +44.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.77 (d, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 4.18 (d, *J* = 17.2 Hz, 2H), 4.05 (d, *J* 17.2 Hz, 2H), 3.57 – 3.49 (m, 2H), 2.40 (s, 6H), 2.38 – 2.30 (m, 4H), 2.01 – 1.94 (m, 2H), 1.65 (t, *J* = 2.5 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 141.7, 136.7, 128.0 (2xCH), 126.3 (2xCH), 78.2, 77.3, 74.2, 61.4, 31.8, 29.1, 20.6, 20.2, 19.3, 18.6, 2.2. HRMS (ESI): m/z calcd for $C_{34}H_{44}N_2O_4S_2$ [M+H$^+$]: 626.3058; found: 626.3071.

***N*-((*S*)-1-Cyclopropylpent-3-yn-1-yl)-*N*-(4-((*N*-((*S*)-1-cyclopropylpent-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(*S, S*)-7c].**



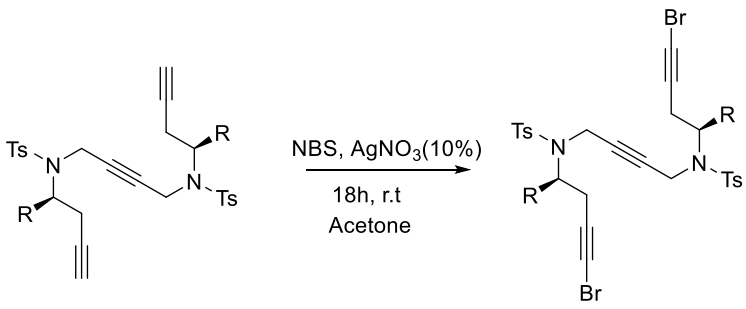
According to general procedure III, from 52 mg (0.09 mmol) of (*S, S*)-**6c**, 40 mg of (*S, S*)-**7c** were obtained as a colorless oil (73% yield); $[\alpha]^{25}_{D}$ = –5.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.75 (d, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 4.25 (d, *J* 16.7 Hz, 2H), 4.13 (d, *J* = 16.7 Hz, 2H), 3.10 – 3.02 (m, 2H), 2.53 – 2.49 (m, 4H), 2.41 (s, 6H), 1.70 (t, *J* = 2.5 Hz, 6H), 1.09 – 1.00 (m, 2H), 0.69 – 0.62 (m, 2H), 0.38 – 0.30 (m, 4H), 0.08 – -0.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.2, 138.0, 129.4 (2xCH), 127.5 (2xCH), 80.2, 78.0, 75.7, 62.8, 33.8, 24.7, 21.5, 14.1, 6.8, 4.1, 3.5. HRMS (ESI): m/z calcd for $C_{34}H_{44}N_3O_4S_2$ [M+NH$_4^+$]: 622.2765; found: 622.2768.

4-Methyl-*N*-(4-((4-methyl-*N*-((*S*)-1-(thiophen-3-yl)pent-3-yn-1-yl)phenyl)sulfonamido)but-2-yn-1-yl)-*N*-((*S*)-1-(thiophen-3-yl)pent-3-yn-1-yl)benzenesulfonamide [(*S, S*)-7d].



According to general procedure III, from 62 mg (0.09 mmol) of (*S, S*)-**6d**, 57 mg of (*S, S*)-**7d** were obtained as a colorless oil (88% yield); $[\alpha]^{25}_{D}$ = –38.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 4H), 7.23 – 7.19 (m, 4H), 6.87 (dd, *J* = 4.8, 1.5 Hz, 2H), 5.16 – 5.11 (m, 2H), 4.03 (d, *J* = 16.6 Hz, 2H), 3.48 (d, *J* = 16.6 Hz, 2H), 2.87 – 2.77 (m, 2H), 2.66 – 2.57 (m, 2H), 2.42 (s, 6H), 1.65 (t, *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 138.8, 137.8, 129.7 (2xCH), 127.9, 127.5 (2xCH), 125.8, 123.8, 79.8, 78.8, 75.3, 56.3, 33.2, 23.5, 21.6, 3.6. HRMS (ESI): m/z calcd for $C_{36}H_{40}N_3O_4S_4$ [M+NH_4^+]: 706.1882; found: 706.1896.

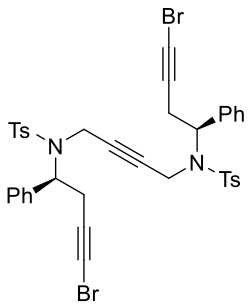
V. General procedure IV for the synthesis of triynes (*S, S*)-7e-g.



(*S, S*)-**6a-c** (*S, S*)-**7e-g**

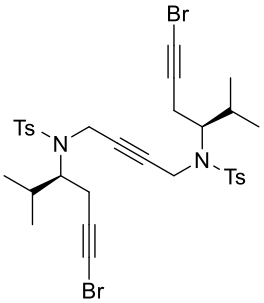
The corresponding triyne (*S,S*)-**6** (1 mmol) was dissolved in acetone. Then, $AgNO_3$ (0.2 mmol) and N-Bromosuccinimide (2.2 mmol) was added and the resulting solution was stirred 18h at r.t. The reaction was monitored by TLC. After no more observable changes, the reaction was quenched with water and extracted with Et_2O. The organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane/EtOAc (8:1).

***N*-((*S*)-4-Bromo-1-phenylbut-3-yn-1-yl)-N-(4-((*N*-((*S*)-4-bromo-1-phenylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(*S, S*)-7e].**



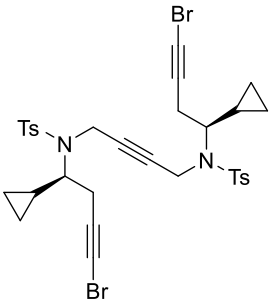
According to general procedure IV, from 110 mg (0.17 mmol) of (*S, S*)-**6a**, 98 mg of (*S, S*)-**7e** were obtained as a white solid (58% yield) m.p. 42 – 44 °C; $[\alpha]^{25}_{D}$ = –48.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24 – 7.19 (m, 14H), 5.11 – 5.06 (m, 2H), 3.93 (d, *J* = 16.7 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 2H), 2.81 – 2.72 (m, 2H), 2.53 – 2.44 (m, 2H), 2.34 (s, 6H), 1.55 (t *J* = 2.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.9, 137.0, 129.6 (2xCH), 128.4 (2xCH), 128.1, 127.5 (2xCH), 79.9, 78.8, 75.3, 59.8, 33.2, 22.0, 21.6, 3.6. HRMS (ESI): m/z calcd for $C_{38}H_{38}Br_2N_3O_4S_2$ [M+NH_4^+]: 822.0672; found: 822.0665.

***N*-((*S*)-6-Bromo-2-methylhex-5-yn-3-yl)-*N*-(4-((*N*-((*S*)-6-bromo-2-methylhex-5-yn-3-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(*S, S*)-7f].**



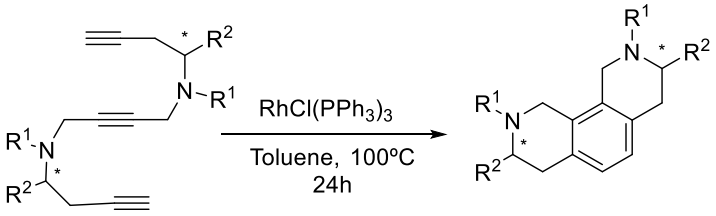
According to general procedure IV, from 286 mg (0.49 mmol) of (*S, S*)-**6b**, 270 mg of (*S, S*)-**7f** were obtained as a colorless oil (74% yield); $[\alpha]^{25}_{D}$ = –6.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.05 (d, *J* 16.8 Hz, 2H), 3.87 (d, *J* = 16.8 Hz, 2H), 3.55 – 3.48 (m, 2H), 2.44 – 2.36 (m, 2H), 2.35 – 2.28 (m, 2H), 2.34 (s, 6H), 1.89 – 1.82 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.80 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 137.7, 129.5 (2xCH), 127.6 (2xCH), 79.6, 77.1, 62.4, 41.0, 33.1, 30.6, 23.0, 21.6, 20.6, 20.0. HRMS (ESI): m/z calcd for $C_{32}H_{42}Br_2N_3O_4S_2$ [M+NH_4^+]: 756.0977; found: 756.0982.

***N*-((*S*)-4-Bromo-1-cyclopropylbut-3-yn-1-yl)-*N*-(4-((*N*-((*S*)-4-bromo-1-cyclopropylbut-3-yn-1-yl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)-4-methylbenzenesulfonamide [(*S, S*)-7g].**



According to general procedure IV, from 59 mg (0.10 mmol) of (*S, S*)-**6c**, 42 mg of (*S, S*)-**7g** were obtained as a colorless oil (56% yield); $[\alpha]^{25}_{D}$ = –8.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.74 (d, *J* = 8.3 Hz, 4H), 7.29 (d, *J* = 8.0 Hz, 4H), 4.24 (d, *J* 16.8 Hz, 2H), 4.09 (d, *J* = 16.8 Hz, 2H), 3.14 – 3.06 (m, 2H), 2.67 – 2.53 (m, 4H), 2.42 (s, 6H), 1.09 – 0.98 (m, 2H), 0.74 – 0.63 (m, 2H), 0.41 – 0.31 (m, 4H), 0.10 – -0.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.6, 129.6 (2xCH), 127.4 (2xCH), 80.2, 62.3, 40.6, 33.8, 30.9, 25.8, 21.6, 14.0, 6.8, 4.1. HRMS (ESI): m/z calcd for $C_{32}H_{35}Br_2N_2O_4S_2$ [M+NH_4^+]: 752.0631; found: 752.0638.

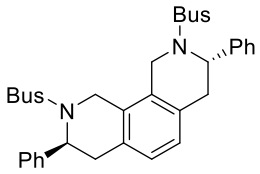
VI. General Procedure V for synthesis of tricyclic compounds *(S,S)*-**8**, *(S,S)*-**9a-l** and*(R,R)*-**9a**



(*S, S*)-**5/ 6 or 7** (*S, S*)-**8, 9a-e**

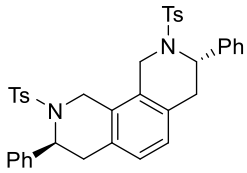
In a flame-dried Schlenk sealed tube, the rhodium-catalyst (10-15 mol %) and the corresponding triyne (*S, S*)-**5**, **6** or **7** (1 mmol) were purged with argon. Then, toluene was added (100 mL/mmol triyne, 0.01M). The resulting mixture was heated at 100°C overnight (14h). After complete reaction the solvent was removed, and the crude product was purified by flash chromatography with *n*-hexane/EtOAc (8:1).

(3*S*,8*S*)-2,9-Bis(tert-butylsulfonyl)-3,8-diphenyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-8].



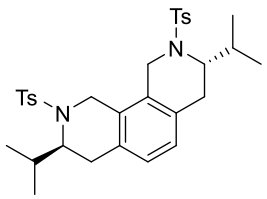
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 80 mg (0.10 mmol) of (*S, S*)-**5**, 30 mg of (*S, S*)-**8** were obtained as a white solid (38% yield) m.p. 176 – 178 °C; $[\alpha]^{25}_D$ = +26.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51 (d, *J* = 8.3 Hz, 4H), 7.23 – 7.20 (m, 6H), 7.15 – 7.12 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 4H), 6.85 (s, 2H), 5.42 – 5.39 (m, 2H), 4.52 (d, *J* = 16.9 Hz, 2H), 3.93 (d, *J* = 16.9 Hz, 2H), 3.05 (d, *J* = 4.1 Hz, 4H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.9, 137.2, 130.5, 129.5 (2xCH), 128.5 (2xCH), 128.1, 127.6, 127.5, 127.2 (2xCH), 126.9 (2xCH), 53.6, 40.5, 31.4, 21.5. HRMS (ESI): m/z calcd for $C_{32}H_{44}N_3O_4S_2$ [M+NH_4^+]: 598.2765; found: 598.2768.

(3*S*,8*S*)-3,8-Diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9a].



According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 44 mg (0.10 mmol) of (*S, S*)-**6a**, 30 mg of (*S, S*)-**9a** were obtained as a colorless oil (67% yield); $[\alpha]^{25}_D$ = +55.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.51 (d, *J* = 8.3 Hz, 4H), 7.23 – 7.20 (m, 6H), 7.15 – 7.12 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 4H), 6.85 (s, 2H), 5.42 – 5.39 (m, 2H), 4.52 (d, *J* = 16.9 Hz, 2H), 3.93 (d, *J* = 16.9 Hz, 2H), 3.05 (d, *J* = 4.1 Hz, 4H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 138.9, 137.2, 130.5, 129.5 (2xCH), 128.5 (2xCH), 128.1, 127.6, 127.5, 127.2 (2xCH), 126.9 (2xCH), 53.6, 40.5, 31.4, 21.5. HRMS (ESI): m/z calcd for $C_{38}H_{40}N_3O_4S_2$ [M+NH_4^+]: 846.1496; found: 846.1501.

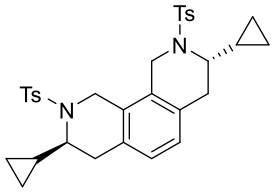
(3*S*,8*S*)-3,8-Diisopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9b].



According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 106 mg (0.18 mmol) of (*S, S*)-**6b**, 73 mg of (*S, S*)-**9b** were obtained as a white solid (69% yield) m.p. 58 – 60 °C; $[\alpha]^{25}_D$ = +33.6 (c 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J*

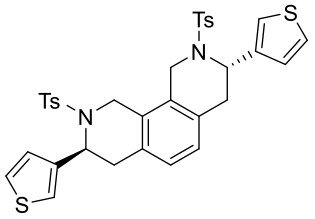
= 8.3 Hz, 4H), 7.20 (d, *J* = 8.0 Hz, 4H), 6.77 (s, 2H), 4.59 (d, *J* = 17.4 Hz, 2H), 4.04 (d, *J* = 17.4 Hz, 2H), 3.84 – 3.78 (m, 2H), 2.77 – 2.64 (m, 4H), 2.36 (s, 6H), 1.66 – 1.54 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.88 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 137.8, 130.1, 129.6 (2xCH), 127.8, 127.7, 126.9 (2xCH), 57.6, 40.4, 29.9, 28.2, 21.5, 20.2, 19.7. HRMS (ESI): m/z calcd for $C_{32}H_{41}N_2O_4S_2$ [M+H$^+$]: 581.2491; found: 581.2502.

(3*S*,8*S*)-3,8-Dicyclopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9c].



According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 54 mg (0.09 mmol) of (*S, S*)-**6c**, 34 mg of (*S, S*)-**9c** were obtained as a colorless oil (63% yield); $[\alpha]^{25}_D$ = +55.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, *J* = 8.3 Hz, 4H), 7.24 (d, *J* = 8.0 Hz, 4H), 6.90 (s, 2H), 4.60 (d, *J* = 16.7 Hz, 2H), 4.33 (d, *J* = 16.7 Hz, 2H), 3.54 – 3.49 (m, 2H), 2.98 (dd, *J* = 15.7, 5.8 Hz, 2H), 2.71 (d, *J* = 16.3 Hz, 2H), 2.39 (s, 6H), 0.90 – 0.78 (m, 2H), 0.46 – 0.39 (m, 4H), 0.36 – 0.29 (m, 2H), 0.27 – 0.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.2, 137.8, 130.5, 129.6 (2xCH), 128.2, 127.8, 127.1 (2xCH), 56.5, 40.7, 33.3, 21.5, 12.7, 4.5, 4.3. HRMS (ESI): m/z calcd for $C_{32}H_{37}N_2O_4S_2$ [M+H$^+$]: 577.2193; found: 577.2189.

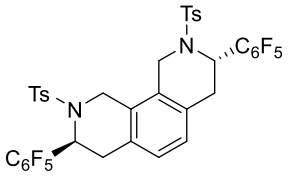
(3*S*,8*S*)-3,8-Di(thiophen-3-yl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9d].



According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 67 mg (0.10 mmol) of (*S, S*)-**6d**, 40 mg of (*S, S*)-**9d** were obtained as a colorless oil (60% yield); $[\alpha]^{25}_D$ = +20.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.57 (d, *J* = 8.3 Hz, 4H), 7.18 – 7.14 (m, 6H), 6.90 (s, 2H), 6.78 – 6.76 (m, 4H), 5.47 (d, *J* = 5.6 Hz, 2H), 4.50 (d, *J* = 16.8 Hz, 2H), 3.88 (d, *J* = 16.8 Hz, 2H), 3.16 (dd, *J* = 16.3, 6.3 Hz, 2H), 3.00 (d, *J* = 16.3 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.4, 139.6, 137.2, 130.3, 129.7 (2xCH), 127.9, 127.8, 127.3, 127.0 (2xCH), 125.9, 122.8,

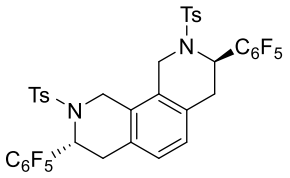
50.0, 40.5, 32.5, 21.5. HRMS (ESI): m/z calcd for $C_{34}H_{33}N_2O_4S_4$ [M+H$^+$]: 661.1309; found: 661.1318.

(3*S*,8*S*)-3,8-Bis(perfluorophenyl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9e].



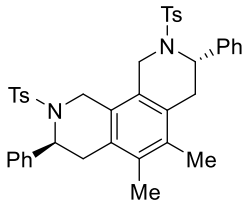
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 55 mg (0.07 mmol) of (*S, S*)-**6e**, 37 mg of (*S, S*)-**9e** were obtained as a white solid (74% yield) m.p. 207 – 209 °C; $[\alpha]^{25}_D$ = +2.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.3 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 6.91 (s, 2H), 5.04 (dd, *J* = 11.5, 6.0 Hz, 2H), 4.84 (d, *J* = 16.0 Hz, 2H), 4.15 (d, *J* = 16.0 Hz, 2H), 2.95 (dd, *J* = 14.7, 6.0 Hz, 4H), 2.82 (dd, *J* = 14.7, 11.9 Hz, 2H), 2.30 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.29 – -142.39 (m, 4F), -154.80 – -154.95 (m, 2F), -161.41 – -161.59 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.0 – 143.8 (m, 2C-F), 143.7, 141.9 – 139.7 (m, C-F), 138.8 – 136.6 (m, 2xC-F), 135.7, 133.0, 131.4, 129.2 (2xCH), 127.0 (2xCH), 126.2, 116.3 – 116.1 (m, C), 49.2, 42.0, 33.8, 21.3. HRMS (ESI): m/z calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1513; found: 846.1496.

(3*R*,8*R*)-3,8-Bis(perfluorophenyl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*R, R*)-9e].



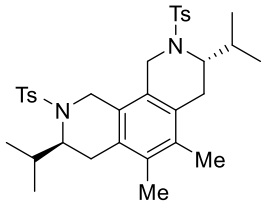
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (10 mol %), from 70 mg (0.09 mmol) of (*R, R*)-**6e**, 53 mg of (*R, R*)-**9e** were obtained as a white solid (76% yield) m.p. 208 – 210 °C; $[\alpha]^{25}_D$ = -3.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.3 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 6.91 (s, 2H), 5.04 (dd, *J* = 11.6, 6.0 Hz, 2H), 4.84 (d, *J* = 16.0 Hz, 2H), 4.15 (d, *J* = 16.0 Hz, 2H), 2.95 (dd, *J* = 14.7, 6.0 Hz, 4H), 2.82 (dd, *J* = 14.7, 11.9 Hz, 2H), 2.30 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) -142.29 – -142.39 (m, 4F), -154.80 – -154.95 (m, 2F), -161.41 – -161.59 (m, 4F); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 146.8 – 143.1 (m, 2C-F), 143.7, 140.2 – 136.7 (m, C-F), 139.5 – 136.0 (m, 2xC-F), 135.7, 133.0, 131.4, 129.2 (2xCH), 127.0 (2xCH), 126.2, 116.4 – 115.9 (m, C), 49.2, 42.0, 33.8, 21.3. HRMS (ESI): m/z calcd for $C_{38}H_{30}F_{10}N_3O_4S_2$ [M+NH_4^+]: 846.1513; found: 846.1514.

(3*S*,8*S*)-5,6-Dimethyl-3,8-diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9f].



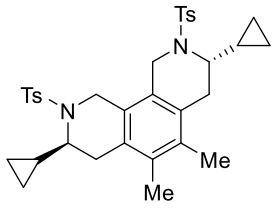
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (15 mol %), from 98 mg (0.14 mmol) of (*S, S*)-**7a**, 71 mg of (*S, S*)-**9f** were obtained as a white solid (72% yield) m.p. 89 – 91 °C; $[\alpha]^{25}_D$ = +16.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 8.3 Hz, 4H), 7.23 – 7.20 (m, 6H), 7.11 – 7.06 (m, 8H), 5.45 (d, *J* = 5.8 Hz, 2H), 4.43 (d, *J* = 16.7 Hz, 2H), 3.85 (d, *J* = 16.7 Hz, 2H), 3.08 (d, *J* = 16.7 Hz, 2H), 3.08 (d, *J* = 16.9 Hz, 2H), 2.89 (dd, *J* = 16.9, 6.9 Hz, 2H), 2.35 (s, 6H), 2.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 139.0, 137.3, 133.0, 129.4 (2xCH), 128.6, 128.5 (2xCH), 127.7, 127.3 (2xCH), 127.0 (2xCH), 125.4, 53.6, 40.4, 29.1, 21.5, 15.2. HRMS (ESI): m/z calcd for $C_{40}H_{41}N_2O_4S_2$ [M+H$^+$]: 677.2490; found: 677.2502.

(3*S*,8*S*)-3,8-Diisopropyl-5,6-dimethyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9g].



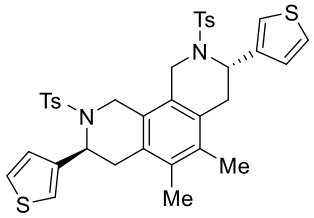
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (15 mol %), from 46 mg (0.08 mmol) of (*S, S*)-**7b**, 31 mg of (*S, S*)-**9g** were obtained as a white solid (67% yield) m.p. 58 – 60 °C; $[\alpha]^{25}_D$ = +35.3 (c 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 8.3 Hz, 4H), 7.18 (d, *J* = 8.0 Hz, 4H), 4.55 (d, *J* 17.2 Hz, 2H), 4.03 (d, *J* = 17.2 Hz, 2H), 3.84 – 3.79 (m, 2H), 2.80 – 2.50 (m, 4H), 2.36 (s, 6H), 2.03 (s, 6H), 1.64 – 1.56 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.0, 137.9, 133.3, 129.5 (2xCH), 128.2, 126.9 (2xCH), 125.0, 57.5, 40.2, 28.3, 27.3, 21.5, 20.3, 20.1, 15.2. HRMS (ESI): m/z calcd for $C_{34}H_{48}N_3O_4S_2$ [M+NH_4^+]: 626.3070; found: 626.3081.

(3*S*,8*S*)-3,8-Dicyclopropyl-5,6-dimethyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9h].



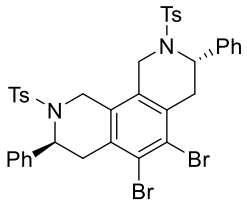
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (15 mol %), from 20 mg (0.03 mmol) of (*S, S*)-**7c**, 15 mg of (*S, S*)-**9h** were obtained as a colorless oil (75% yield); $[\alpha]^{25}_D$ = +49.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.56 (d, *J* = 16.8 Hz, 2H), 4.33 (d, *J* = 16.8 Hz, 2H), 3.56 – 3.51 (m, 2H), 2.86 – 2.72 (m, 4H), 2.39 (s, 6H), 2.09 (s, 6H), 0.90 – 0.82 (m, 2H), 0.46 – 0.39 (m, 4H), 0.36 – 0.30 (m, 2H), 0.28 – 0.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.1, 137.8, 133.8, 129.5 (2xCH), 128.6, 127.1 (2xCH), 125.1, 56.5, 40.6, 31.4, 21.5, 15.3, 13.0, 4.6, 4.3. HRMS (ESI): m/z calcd for $C_{34}H_{44}N_3O_4S_2$ [$M+NH_4^+$]: 622.2776; found: 622.2768.

(3*S*,8*S*)-5,6-Dimethyl-3,8-di(thiophen-3-yl)-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9i].



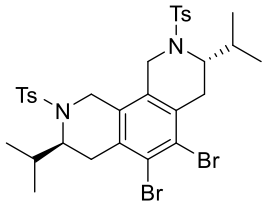
According to general procedure V , catalyst $RhCl(PPh_3)_3$ (15 mol %), from 55 mg (0.08 mmol) of (*S, S*)-**7d**, 38 mg of (*S, S*)-**9i** were obtained as a colorless oil (71% yield); $[\alpha]^{25}_D$ = +28.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.3 Hz, 4H), 7.19 – 7.14 (m, 6H), 6.78 – 6.74 (m, 4H), 5.51 (d, *J* = 5.2 Hz, 2H), 4.42 (d, *J* = 16.4 Hz, 2H), 3.82 (d, *J* = 16.4 Hz, 2H), 3.10 – 2.93 (m, 4H), 2.38 (s, 6H), 2.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.3, 139.8, 137.2, 133.9, 129.5 (2xCH), 128.4, 127.3, 127.0 (2xCH), 125.9, 125.1, 122.7, 49.9, 40.4, 30.6, 21.5, 15.3. HRMS (ESI): m/z calcd for $C_{36}H_{37}N_2O_4S_4$ [$M+H^+$]: 689.1617; found: 689.1631.

(3*S*,8*S*)-5,6-Dibromo-3,8-diphenyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9j].



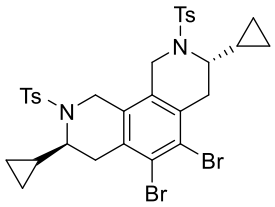
According to general procedure V , catalyst $[RhCl(CO_2)]_2$ (15 mol %), from 73 mg (0.09 mmol) of (*S, S*)-**7e**, 59 mg of (*S, S*)-**9j** were obtained as a white solid (81% yield) m.p. 78 – 80 °C; $[\alpha]^{25}_D$ = +13.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.41 (d, *J* = 8.3 Hz, 4H), 7.22 – 7.19 (m, 6H), 7.05 – 7.02 (m, 4H), 7.00 (d, *J* = 8.0 Hz, 4H), 5.38 (d, *J* = 6.1 Hz, 2H), 4.35 (d, *J* = 17.4 Hz, 2H), 3.70 (d, *J* = 17.4 Hz, 2H), 3.32 (d, *J* = 18.1 Hz, 2H), 2.83 (dd, *J* = 18.1, 6.8 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 137.8, 136.9, 132.6, 129.6 (2xCH), 129.4, 128.8 (2xCH), 128.0, 127.1 (2xCH), 126.9, 126.8 (2xCH), 53.4, 40.0, 32.8. HRMS (ESI): m/z calcd for $C_{38}H_{38}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 824.0620; found: 824.0610.

(3*S*,8*S*)-5,6-Dibromo-3,8-diisopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9k].



According to general procedure V , catalyst $[RhCl(CO_2)]_2$ (15 mol %), from 100 mg (0.14 mmol) of (*S, S*)-**7f**, 82 mg of (*S, S*)-**9k** were obtained as a white solid (82% yield) m.p. 69 – 71 °C; $[\alpha]^{25}_D$ = +37.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60 (d, *J* = 8.3 Hz, 4H), 7.18 (d, *J* = 8.0 Hz, 4H), 4.19 (d, *J* = 17.7 Hz, 2H), 3.97 (d, *J* = 17.7 Hz, 2H), 3.80 – 3.75 (m, 2H), 3.00 (d, *J* = 17.1 Hz, 2H), 2.62 (d, *J* = 17.1, 6.4 Hz, 2H), 2.37 (s, 6H), 1.60 – 1.52 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.5, 137.7, 132.4, 129.6 (2xCH), 129.1, 127.3, 126.9 (2xCH), 57.4, 39.9, 32.0, 28.6, 21.5, 20.0, 19.9. HRMS (ESI): m/z calcd for $C_{32}H_{42}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 756.0966; found: 756.0963.

(3*S*,8*S*)-5,6-Dibromo-3,8-dicyclopropyl-2,9-ditosyl-1,2,3,4,7,8,9,10-octahydro-2,9-phenanthroline [(*S, S*)-9l].



According to general procedure V , catalyst $[RhCl(CO_2)]_2$ (15 mol %), from 42 mg (0.06 mmol) of (S, *S*)-**7g**, 33 mg of (*S, S*)-**9l** were obtained as a white solid (79% yield) m.p. 71 – 73 °C; $[\alpha]^{25}_D$ = +27.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.66 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 4.61 (d, *J* = 17.0 Hz, 2H), 4.31 (d, *J* = 17.0 Hz, 2H), 3.55 – 3.49 (m, 2H), 2.97 (d, *J* = 17.1 Hz, 2H), 2.84 (dd, *J* = 17.1, 6.1 Hz, 2H), 2.40 (s, 6H), 0.87 – 0.77 (m, 2H), 0.52 – 0.42 (m, 4H), 0.34 – 0.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.6, 137.4, 132.7, 129.7 (2xCH), 129.3, 127.7, 127.0 (2xCH), 56.3, 40.3, 35.7, 21.5, 13.0, 4.8, 4.2. HRMS (ESI): m/z calcd for $C_{32}H_{38}Br_2N_3O_4S_2$ $[M+NH_4^+]$: 750.0660; found: 750.0665.

VIII. References

1. A. Llobat, R. Román, N. Mateu, D. M. Sedgwick, P. Barrio, M. Medio-Simón, S. Fustero *Org. Lett*. **2019**, *21*,7294–7297.

2. C. Shu, M.-Q. Liu; S.-S. Wang, L. Li, L.-W. Ye *J. Org. Chem*. **2013**, *78*, 3292-3299.

Conclusions

To sum up this Thesis report, the conclusions extracted from the different scientific articles are shown below:

- Propargylation/allenylation reactions of aryl fluorinated sulfinyl imines with propargyl and propargylic magnesium reagents were performed with excellent regio- and diastereoselectivities. We observed that diastereoselectivity depends on both solvent and basicity of the sulfinyl imine. Coordinating solvents such as THF were compatible only with less basic sulfinyl imines meanwhile non-coordinating solvents such as DCM allowed good diastereoselection in all cases.

- DFT calculations were performed in order to rationalize the experimental findings and helped to elucidate the possible mechanism. These calculations proved that coordination of N and O atoms (from the sulfinyl group or form the solvent if is coordinating) to the metal, plays a crucial role in determining the diastereoselectivity of the propargylation/allenylation reaction.

- Diastereoselective propargylation of sulfinyl imines turns out to be a key step in the preparation of chiral 4-aza-1,7-enynes and 4-aza-1,7-triynes. These interesting compounds play a crucial role in the synthesis of different enantioenriched heterocyclic scaffolds.

- Chiral 4-aza-1,7-enynes used as starting materials in RCEYM and domino CEYM/RCM reactions allowed the preparation of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes. These structures could have a special interest in medicinal or biological studies due to the prevalence of tetrahydropyridine moiety in pharmaceutical contexts.

- Chiral 1,3-dienes were optimum substrates for Diels-Alder reactions with tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione. Tricyclic scaffolds with major complexity were prepared in high diastereoselectivities (*dr* > 20:1). Furthermore, a gram scale synthesis was carried out with no loss of yield demonstrating the effectiveness of the proposed synthetic route.

- The preparation of chiral fluorinated *6H*-cyclopenta[*c*]pyridine-ones was achieved using fluoroalkyl substituted chiral 4-aza-1,7-enynes as substrates in Pauson-Khand cycloadditions. It has been proved that substitution of both the reacting

alkene and alkyne groups allowed further functionalization of the heterobyciclic core of the final products.

- The synthesis of a derivative bearing a fluorine atom at a fully bridgehead carbon stereogenic center was an interesting result given the difficulty in obtaining this kind of structures by alternative methods. Also, a catalytic version of Pauson-Khand cycloaddition was developed with good yields and diastereoseletivities and gram scale synthesis maintained high yields and diastereoselectivities.

- Intramolecular Pauson-Khand cycloaddition has proven to be a powerful synthetic tool in the construction of enantioenriched bicyclic cyclopentenones. Also, several synthetic transformations have been carried out on this bicyclic scaffolds. Hydrogenation of the unsaturated bicyclic system was carried out in order to generate a new stereocenter in the saturated derivative. Also, the removal of the Bus protecting group was successfully achieved in order to obtain the clorhydrate salts of the amines obtained.

- *N*-bridged-*1*,7,13-triynes were prepared in three steps from sulfinyl imines with excellent yields and diastereoselectivities. These compounds were suitable substrates for metal-catalyzed cycloadditions in order to obtain enantioenriched tricyclic scaffolds. After optimization of this reaction, enantioenriched phenanthroline derivatives were obtained with good yields and diastereoselectivities.

References

[1] Carruthers, W. (**1990**). *Cycloaddition Reactions in Organic Synthesis*. Pergamon Press.

[2] Grubbs, R. H. (**2003**). *Handbook of Metathesis Vol. 1 y 2*. Wiley-VCH.

[3] Uneyama, K. (**2006**)**.** *Organofluorine Chemistry*. Blackwell Publishing Ltd. Oxford. b) Chambers, R. D. *Fluorine in Organic Chemistry*. Blackwell Publishing Ltd. Oxford. **2004**. c) Hiyama, H. (**2000**). *Organofluorine Compounds: Chemistry and Applications Springer*. Berlín.

[4] Kobayashi, S.; Jorgensen, K. A. (**2001**). *Cycloaddition Reactions in Organic Synthesis*. Wiley-VCH.

[5] Woodward, R. B. Hoffmamm, R. (**1970**). *The Conservation of the Orbital Symmetry*. Verlag chemie.

[6] Trost, B. M.; Zuo, Z.; Schutlz, J. E. *Chem. Eur. J*. **2020**, *26*, 15354 – 15377.

[7] Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49-92.

[8] a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans*. I. **1973**, *9*. 997-981. b) Chung, Y. K.; *Coord. Chem. Rev*. **1999**, *188*, 297-314. c) Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1800-1810.

[9] a) Tanaka, K. (**2019)**. *Rhodium Catalysis in Organic Synthesis: Methods and Reactions.* Wiley-CVH. b) Tanaka, K.; Shibata, Y. (Tanaka, K. (Ed.)). (**2013)**. *[2+2+2] and Related Cycloadditions Mediated by Other Transition Metals* John Wiley & Sons. Inc. c) Tanaka, K. *Chem. Asian J*. **2009**, *4*, 508 – 518

[10] Villemin, D. *Tetrahedron Lett*. **1980**, *21*, 1715-1718.

[11] Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett*. **1980**, *21*, 2955-2958.

[12] Constantino, L.; Raimondi, L.; Pirisino, R.; Brunetti, T.; Pessotto, P.; Giannessi, F.; Lins, A.P.; Barlocco, D.; Antolini, L.; El-Abady, S. A. *Il Farmaco.* **2003**, 781-785.

[13] Tashrifi, Z.; Khanaposhtani, M. M.; Biglar, M.; Larijani, B.; Mahdavi, M. *Asian J. Org. Chem.* **2020**, *9*, 969-991

[14] Fandrick, D. R.; Roschangar, F.; Kim, C.; Hahm, B. J.; Cha, M. H.; Kim, H. Y.; Yoo, G.; Kim, T.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Haddad, N.; Shen, S.; Grinberg, N.; Lee, H.; Yee, N.; Senanayake, C. H. *Org. Process Res. Dev*. **2012**, *16*, 1131-1140.

References

[15] Thaima, T.; Pyne, S. G. *Org. Lett*. **2015**, *17*, 778-781.

[16] Kagoshima, H.; Uzawa, T.; Akiyama, T. *Chem. Lett*. **2002**, 298-299.

[17] Vieira, E. M.; Haeffner, F.; Snapper, M. L.; Hoveyda, A. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 6618-6621.

[18] Fandrick, D. R.; Hart, C. A.; Okafor,I. S. ; Mercadante, M. A.; Sanyal, S.; Masters, J. T.; Sarvestani, M.; Fandrick, K. R.; Stockdill, J. L. ; Grinberg, N.; Gonnella, N.; Lee, H.; Senanayake, C. H. *Org. Lett.* **2016**, *18*, 6192-6195.

[19] Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett*. **2010**, *12*, 748-751.

[20] Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci*. **2011**, *2*, 807-810.

[21] a) Cui, L.; Li, C.; Zhang, L. *Angew. Chem. Int. Ed*. **2010**, *49*, 9178-9181; b) Shu, C.; Liu, M-Q.; Wang, S-S.; Li, L.; Ye. L-W. *J. Org*. *Chem*. **2013**, *78*, 3292-3299.

[22] Liu, K.; Zhu, C.; Min, J.; Peng, S.; Xu, G.; Sun, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 12962-12967.

[23] a) García-Muñoz, M. J.; Foubelo, F.; Yus, M. *J. Org. Chem*. **2016**, *81*, 10214-10226; b) García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem*. **2013**, 1287-1295.

[24] Jin, S.; Xu, M. *Adv. Synth. Catal.* **2010**, *352*, 3136-3140.

[25] Yanagisawa, A.; Suzuki, T.; Koide, T.; Okitsu, S.; Arai, T. *Chem. Asian J*. **2008**, *3*, 1793-1800.

[26] Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron*, **2003**, *59*, 5377-5381.

[27] Günter, M.; Gais, H.-J. *J. Org. Chem*. **2003**, *68*, 8037-8041.

[28] Kavanagh, Y.; O'Brien, M.; Evans, P. *Tetrahedron*. **2009**, *65*, 8259-8268.

[29] Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem.* **2015**, 9781-9793.

[30] Shibata, T.; Tsuchikama, K.; Otsuka, M. *Tetrahedron: Asymmetry.* **2006**, 614-619.

[31] Karras, M.; Holec, J.; Bednárová, L.; Radek, P.; Schmidt, B.; Stará, I. G.; Stary, I. *J. Org Chem.* **2018**, 5523-5538.

[32] a) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, j. G. *Angew. Chem.* **2005**, *117*, 7608-7613; *Angew. Chem. Int. Ed*. **2005**, *44*, 7442-7447; b) Wu, C.-J.; Madhushaw, R. J.; Liu, R.-S. *J. Org*. *Chem*. **2003**, *68*, 7889-7892; c) Tonogaki, K.; Mori, M. *Tetrahedron Lett*. **2002**, *43*, 2235-2238; d) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc*. **1997**, *119*, 12388-12389.

[33] Katz, T. J.; Sivavec, T. M, *J. Am. Chem. Soc*. **1985**, *107*, 737-738.

[34] a) Mori, M.; Watanuki, S. *J. Chem. Soc. Chem. Comm*. **1992**, 1082-1084. b) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129-4130.

[35] a) Trost, B. M.; Yanoury, G. J. *J. Am. Chem. Soc.* **1988,** *110*, 1636-1638. b) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824-832.

[36] a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2039-2041. b) Grubbs, R. H.; Chang, S.; *Tetrahedron* **1998**, *54*, 4413-4450. c) Kim, S. H; Bowden, N. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. d) Kim, S. H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem*. **1996**, *61*, 1073-1081.

[37] a) Kinoshita, A.; Mori, M. *Synlett*. **1994**, 1020-1022. b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron.* **1999**, *55*, 8155-8167. c) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett*. **2000**, *2*, 543-545. e) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis.* **2001**, 654-664.

[38] Mori, M; Sakakibara, N.; Kinoshita, A. *J. Org. Chem*. **1998**, *63*, 6082-6083.

[39] Clark, J. S.; Trevitt, P.; Botali, D.; Stammen, B. *Chem. Comm*. **1998**, 2629-2633.

[40] a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1998**, *37,* 2490-2493. b) Huang, J., Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 2674-2678. c) Scholl, M.; Trnka, T.M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron. Lett*. **1999**, *40*, 2247-2250.

[41] Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4274-4277.

[42] Saito, N.; Sato, Y.; Mori, M. *Org. Lett*. **2002**, *4*, 803-805.

[43] a) Prada Gori, D. N.; Permingeat Squizatto, C.; Cornier, P. G.; Delpiccolo, C. M. L. *J. Org. Chem*. **2018**, *83*, 12798-12805; b) Arimitsu, S.; Hammond, G. B. *Beilstein J. Org. Chem*. **2010**, *6*, doi:10.3762/bjoc.6.48; c) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 2805-2808; d) Royer, F.; Vilain, C.; Elkaïm, L.; Grimaud, L. *Org. Lett*. **2003**, *5*, 2007-2009.

[44] a) Becker, M. R.; Watson, R. B.; Schindler, C. S. *Chem. Soc. Rev*. **2018**, *47*, 7867-7881; b) Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev*. **2015**, *115*, 871-930; c) Diver, S. T.; Griffiths, J. R.; in *Olefin Metathesis: Theory And Practice*, (Ed.: K. Grela), John Willey & Sons, Inc., Hoboken, NJ, **2014**, pp; 153-185; d) Vougioukalakis, G. C.; Grubbs, R.H. *Chem. Rev*. **2010**, *110*, 1746-1787; e) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199-2238; f) Diver, S. T.; Giessert, A. J.; *Chem. Rev*. **2004**, *104*, 1317-1382.

[45] a) Letort, A.; Long, D. L.; Prunet, J. *J. Org. Chem*. **2016**, *81*, 1231-1233; b) Ma, C.; Letort, A.; Aouzal, R.; Wilkes, A.; Maiti, G.; Farrugia, L. J.; Ricard, J.; Prunet, J. *Chem. Eur. J*. **2016**, *22*, 6891-6899; c) Miró, J.; Sánchez-Roselló, M.; Sanz, A.; Rabasa, F.; del Pozo, C.; Fustero, S. *Beilstein J. Org. Chem*. **2015**, *11*, 1486–1493; d) Mukherjee, S.; Lee, D. *Org. Lett*. **2009**, *11*, 2916-2919.

[46] a) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev*. **2009**, *38*, 2065-2092; b) K. C. Shital, B. Titas, N. Kaushik, *Chem. Lett*. **2006**, *35*, 376-77; c) Y.-K. Yang, J.-H. Choi, J. Tae, *J. Org. Chem*. **2005**, *70*, 6995-6998; d) B. G. Kim, M. L. Snapper, *J. Am. Chem. Soc*. **2006**, *128*, 52-53; e) M. Eckert, F. Monnier, G. T. Shchetnikov, I. D. Titanyuk, S. N. Osipov, L. Toupet, S. Dérien, P. H. Dixneuf, *Org. Lett.* **2005**, *7*, 3741-3743.

[47] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc*. **1997**, *119*, 12388-12389.

[48] Chachignon, H.; Scalacci, N.; Petricci, E.; Castagholo, D. *J. Org. Chem*. **2015**, *80*, 5287-5295.

[49] Sayyad, A. A.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2017**, 5055-5065.

[50] Yang, Q.; Alper, H.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 769-771.

[51] García-Muñoz, M. J.; Sirvent, A.; Foubelo, F.; Yus. M. *An. Acad. Bras. Cienc.* **2018**, 1059-1072.

[52] Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506-2514.

[53] Ricker, J. D.; Geary, L. M. *Top. Catal.* **2017**, *60*, 609-619.

[54] The Pauson Khand Reaction. Scope, Variations and Applications; Ríos Torres, R., Ed; Wiley: Chichester, UK, **2012**.

[55] Lee, H.; Kwong, F. *Eur. J. Org. Chem.* **2010**, 789-811.

[56] Park, J. H.; Chang, K.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461-2480.

[57] Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32-42.

[58] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E., *J. Chem. Soc. D.* **1971**, 36a-36a.

[59] Khand, IU.; Knox, GR.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. Perkin Trans.* **1973**, *1*, 975-977.

[60] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans.* **1973**, *1*, 977-981.

[61] García-Lacuna, J.; Domínguez, G.; Blanco-Urgoiti, J.; Pérez-Castells, J. *Org. Biomol. Chem.* **2019**, *17*, 9489-9501.

[62] Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 8431-8435.

[63] Zhao, N.; Xie, S.; Tian, P.; Tong, R.; Ning, C.; Xu, J. *Org. Chem. Front.* **2019**, *6*, 2014-2022.

[64] Hu, N.; Dong, C.; Zhang, C.; Liang, G. *Angew. Chem. Int. Ed.* **2019**, *58*, 6659-6662.

[65] Kaneko, H.; Takahashi, S.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2019**, *84*, 5645-5654.

[66] Cabré, A.; Khaizourane, H.; Garcon, M.; Verdaguer, X.; Riera, A. *Org. Lett.* **2018**, *20*, 3953-3957.

[67] Huang, Z.; Huang, J.; Qu, Y.; Zhang, W.; Gong, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2018**, *57*, 8744-8748.

[68] Magnus, P.; Principe, L. M. *Tetrahedron* **1985**, *26*, 4851-4854.

[69] An alkene–pentacarbonyldicobalt–alkyne complex of type III has also been isolated; however, it was shown not to evolve toward the final cyclopentenone product and, hence, it cannot be considered an intermediate in the PKR: Banide, E. V.; Müller-Bunz, H.; Manning, A. R.; Evans, P.; McGlinchey, M. J. *Angew. Chem. Int. Ed*. 2007, 46, 2907-2910.

[70] Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett*. **2002**, *43*, 7859-7862.

[71] Rodríguez, A. M.; Prieto; P. *Tetrahedron* **2016**, *72*, 7443-7448.

[72] Son, S. U.; Lee, S. I.; Chung, Y. K.; Kim,S.-W.; Hyeon, T. *Org. Lett*. **2002**, *4*, 277-279.

[73] Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S.; Yoo, S.-E. *Synlett.* **1991**, 204-206.

[74] Lam, F. L.; Lee, H. W.; Wang, J.; Kwong F. Y. In Recent Advancement of Catalytic Pauson-Khand-type Reactions. The Pauson Khand Reaction. Scope, Variations and Applications; Ríos Torres, R., Ed; Wiley: Chichester, UK, 2012, pp181-210.

[75] Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377-5381.

[76] Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett*. **2006**, *8*, 83-86.

[77] Miller, K. A.; Shanahan, C. S.; Martin, S. F. *Tetrahedron* **2008**, *64*, 6884-6900.

[78] Ishizaki, M.; Suzuki, D.; Hoshino, O. *J. Fluorine Chem*. **2001**, *111*, 81-90.

[79] Ferry, A.; Billard, T.; Langlois, B. R. *Synlett* **2005**, *6*, 1027-1029.

[80] Harthong, S.; Billard, T.; Langlois, B. R. *Synthesis* **2005**, 13, 2253-2263.

[81] Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem*. **2005**, 1258-1265.

[82] Nadano, R.; Ichikawa, J. *Chem. Lett*. **2007**, *36*, 22-23.

[83] Arimitsu, S.; Bottom, R. L.; Hammond, G. B. *J. Fluorine Chem*. **2008**, *129,* 1047-1051.

[84] Vorobyeva, D. V.; Mailyan, A. K.; Peregudov, A. S.; Karimova, N. M.; Vasilyeva, T. P.; Bushmarinov, I. S.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Tetrahedron* **2011**, *67*, 3524-3532.

[85] Konno, T.; Kida, T.; Tani, A.; Ishihara, T. *J. Fluorine Chem*. **2012**, *144*, 147-156.

[86] Fustero, S.; Lázaro, R.; Aiguabella, N.; Riera, A.; Simón-Fuentes, A.; Barrio, P. *Org. Lett*. **2014**, *16*, 1224-1227.

[87] Gallagher, A. G.; Tian, H.; Torres-Herrera, O. A.; Yin, S.; Xie, A. X.; Lange, D. M.; Wilson, J. K.; Mueller, L. G.; Gau, M. R.; Carroll, P. J.; Martínez-Solorio, D. *Org. Lett*. **2019**, *21*, 8646-8651.

[88] Dobbs, A. P.; Miller, I. J.; Martinovic, S. *Beilstein J. Org. Chem*. **2007**, *3*, No. 21, doi:10.1186/1860-5397-3-21.

[89] Ishaq, S.; Porter, M. J. *Synth. Commun*. **2006**, *36*, 547-557.

[90] Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2014**, *136*, 14381-14384.

[91] Román, R.; Mateu, N.; López, I.; Medio-Simón, M.; Fustero, S.; Barrio, P. *Org. Lett.* **2019**, *21*, 2569-2573.

[92] a) Schore, N. E. In Comprehensive Organometallic Chemistry II; Hegedus, L. S., Ed.; Pergamon Press: Oxford, **1999**, *Vol. 12*, 703-739; b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92; c) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901-2916.

[93] Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Ann. Chem*. **1948**, *560*, 1-92.

[94] a) Yamazaki, H.; Hagihara, N. *J. Organomet. Chem.* **1967**, *7*, 22-23; b) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549-4552.

[95] Suzuki, S.; Nishigaki, S.; Shibata, Y.; Tanaka, K. *Org. Lett*. **2018**, *20*, 7461-7465; b) Yoshizaki, S.; Nakamura, Y.; Masutomi, K.; Yoshida, T.; Noguchi, K.; Shibata, Y.; Tanaka, K. *Org. Lett*. **2016**, *18*, 388-391; c) Masutomi, K.; Sakiyama, N.; Noguchi, K.; Tanaka, K. *Angew.*

Chem. Int. Ed. **2012**, *51*, 13031-1303; d) Tanaka, K.; Otake, Y.; Sagac, H.; Noguchi, K.; Hirano, M. *Ang. Chem. Int. Ed*. **2008**, *47*, 1312-1316.

[96] Alvarez, S.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem*. **2015**, *80*, 2436-2442.

[97] Onodera, G.; Shimizu, Y.; Kimura, J.; Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 10515-10531.

[98] Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem*. **2012**, *77*, 908-920.

[99] a) Bauer, R. A.; DiBiasi, C. M.; Tan, D. S. *Org. Lett.* **2010**, *12*, 2084-2087; b) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-D.; Hou, X.-L. *Synlett*, **2006**, 1272-1274.

[100] a) Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem*. **2015**, *80*, 9781-9793; b) Ventre, S.; Simon, C.; Rekhroukh, F.; Malacria, M.; Amatore, M.; Aubert, C.; Petit, M. *Chem. Eur. J*. **2013**, *19*, 5830-5835; c) Dachs, A.; Pla-Quintana, A.; Parella, T.; Solà, M.; Roglans, A. *Chem. Eur. J*. **2011**, *17*, 14493-14507; d) Dachs, A.; Roglans, A.; Solà, M. *Organometallics* **2011**, *30*, 3151-3159; e) Geny, A.; Gaudrel, S.; Slowinski, F.; Amatore, M.; Chouraqui, G.; Malacria, M.; Aubert, C.; Gandon, V. *Adv. Synth. Catal*. **2009**, *351*, 271-275; f) Shibata, T.; Kurokawa, H.; Kanda, K. *J. Org*. *Chem*. **2007**, 72, 6521-6525; g) Eckenberg, P.; Growth, U. *Synlett.* **2003**, 2188-2192.

[101] a) Shibata, T.; Fusamae, T.; Takano, H.; Sugimura, N.; Kanyiva, K. S. *Asian J. Org. Chem*. **2019**, *8*, 970-977; b) Karmakar, R.; Mamidipalli, P.; Salzman, R. M.; Hong, S.; Yun, S. Y.; Guo, W.; Xia, Y.; Lee, D. *Org. Lett*. **2016**, *18*, 3530-3533.