STEREOSELECTIVE SYNTHESIS OF SULFONES AND AMINO ACIDS FROM FUNCTIONALIZED HETEROCYCLES

José Enrique Gómez Pulido

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DOCTORAL THESIS
José Enrique Gómez Pulido

Stereoselective Synthesis of Sulfones and
Amino Acids from Functionalized Heterocycles

2019

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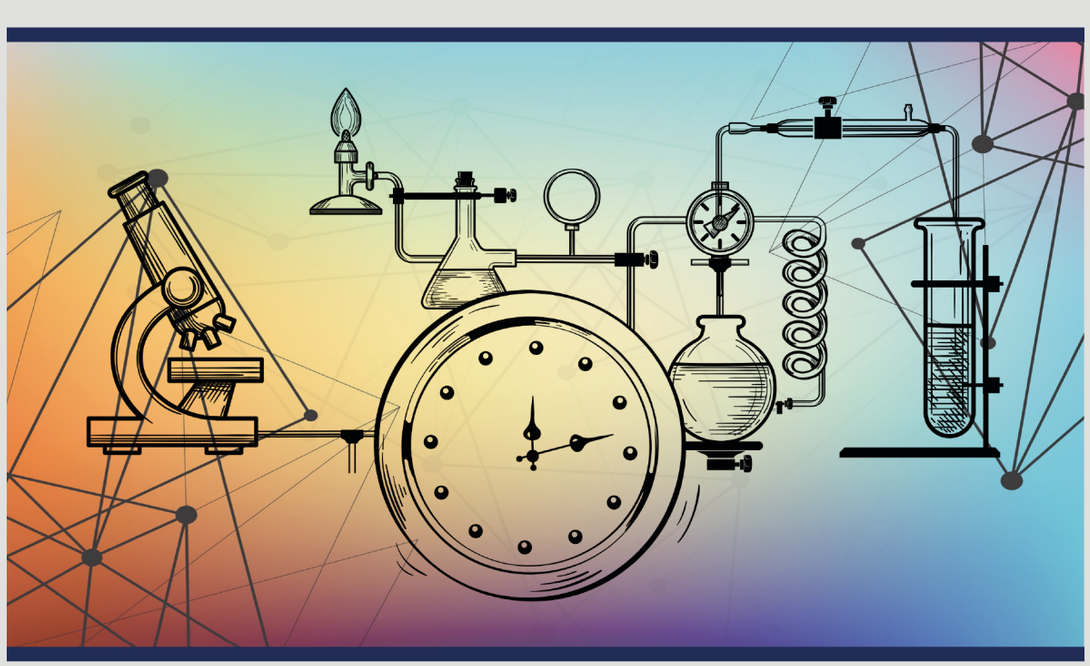

DOCTORAL THESIS
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PhD Thesis

Stereoselective Synthesis of Sulfones and Amino Acids from Functionalized Heterocycles

José Enrique Gómez Pulido

Supervised by Prof. Dr. Arjan W. Kleij

Tarragona

September 2019

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Prof. Dr. Arjan W. Kleij, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

I STATE that the present Doctoral Thesis, entitled "**Stereoselective Synthesis of Sulfones and Amino Acids from Functionalized Heterocycles**" presented by José Enrique Gómez Pulido to receive the degree of Doctor, has been carried out under my supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, September 2019

Doctoral Thesis Supervisor
Prof. Dr. Arjan W. Kleij

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"Use what talents you possess; the woods would be very silent if no birds sang there except those that sang best"

Henry Van Dyke

"Cuando los demás se iban de juerga después de entrenar, yo seguía golpeando a la pelota"

Pelé

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First, I would like to thank my supervisor **Arjan Kleij** for giving me the opportunity to work side by side with him and for his tremendous support. Thank you for your positivism and your kindness. You hold the most important qualities that a person should have to lead, but also to mentor and motivate young researchers. There are uncountable things that I have learnt from you along the way and, whatever the future holds for me, I hope that I can always be at the level of the person in who I have become under your supervision.

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me llevo de vosotras es ese positivismo que os invade y sin duda contagiáis. I would also like to thank the "Chinese clan" of the Lab 2.6: **Rui**, **Aijie**, **Jianing**, **Sijing**, **Chang** and **Kun** you all have contributed to my Chinese culture and I will never forget all the hilarious moments with all of you (Xièxiè). I do not want to forget, of course, the members that arrived towards the end of my PhD, but I am sure that they will make a difference in the future: **Alèria**, **Nicola**, **Josefine**, **Bart** and **Francesco**; many thanks for all the breakfasts over these last months and for all your help with the last bit of the thesis.

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During the first half of 2018, I was lucky to enjoy one of the most enriching experiences of my life, both personally and professionally. I had the chance to spend four months at Eli Lilly (UK), working side by side with a fantastic group of people that made me feel like at home. For this outstanding opportunity, I would like to warmly thank **Jeffery Richardson** and **Gary Sharman**, the mentors from whom I have learned everything there. Recordaré con simpatía también estos meses por haber conocido, a mi compañero de aventuras y un gran amigo desde entonces: **Santi** (o como suelo llamarle: ¡Que pasa fiera!). Gracias por transmitirme toda esa fuerza necesaria al final de esta etapa.

Estos años en Tarragona han marcado mi vida, y en especial esto se lo debo en gran parte a un grupo espectacular de personas, de diversas partes de la geografía española, que merecen toda mi admiración y agradecimiento pues me han arropado, enseñado y querido, convirtiéndose en mi familia: **PAVIPOLLOS**. Sois muchos y os quiero a todos, GRACIAS CHICOS, sólo el haberos conocido hace que valga la pena haber venido hasta Tarragona. Me gustaría empezar por agradecer a mis niños: **Chuchi** y **Andreu**. Ha sido un absoluto placer vivir con vosotros y un "privilegio" poder llevar vuestra paciencia a límites insospechados. Gracias por todos y cada uno de los días que hemos compartido juntos, pero sobre todo por convertir el 26, 4º de la calle Reding en un hogar. Se me hará duro no veros cada día, aunque ¡espero dejar en vosotros una huella tan grande como la que vosotros habéis dejado en mí! Siempre os llevaré en el corazón. Y ahora por orden en el grupo de WhatsApp: **Raúl**, ¡mi "Bro" de otra madre! eres un tío genial. (En realidad por iniciales "R" te tocaría ser el último, pero algún privilegio tiene que

tener ser el administrador, aparte de llenar el grupo de “stickers” sin que te echemos). Gracias por compartir todas esas horas en el Viding enseñándome a ser un “deportista nato” y no morir en HIIT y sobre todo por tu positivismo y tus bromas a la hora de comer. ¡Te echaré de menos!, aunque siempre nos quedará Madrid y su agua de calidad HPLC. **Alba**, “Criolla”, muchas gracias por tu simpatía, aunque hayas llegado la última lo has hecho con mucha fuerza y se te quiere mucho. Ese aire manchego “reshulón” no se olvidará fácilmente. Ni tampoco el de **Alicia Martínez**. Eres “muchismo bonica”; mil gracias por tu naturalidad y tus consejos. Esto que hemos vivido en Tarragona es un periodo duro, pero estoy convencido de que llegarás muy lejos, por tu trabajo, fortaleza y ¡porque te lo mereces! Muchísimo ánimo con la recta final. **Alicia Monleón**, ¡tía 10 -un todoterreno-! siempre de buen humor y dispuesta a ayudar. Me gustaría agradecerte sinceramente por haberme enseñado tú maravillosa forma de ver la vida: relativizando y siempre en positivo. Gracias por todas esas charlas y ánimos que desinteresadamente has compartido conmigo, especialmente durante este último año. **Cristina**, ha sido un placer conocer a una vallisoletana de pro en tierras Tarraconenses. Muchas gracias por esos viajes a casa, tu alegría y por haber compartido con nosotros a esa cosa tan bonita, **Victoria**; ¡que siempre será del Pucela! **Ester**, una tía molt auténtica y molt agradable. Mil gràcies per ser la noia més boja d'aquest grup i per tots els moments de rialles i bogeria. Segueix així i no canviïs. Eres el alma de la fiesta. **Jesús**, de ti he aprendido mucho. Creo que nunca conoceré a una persona que ame tanto la química como tú. “Mr. Cobalto” sé que llegarás muy lejos y espero estar ahí para verlo. Pero, sin duda, cervecear ya no será los mismo sin ti, sin todas esas discusiones y charlas filosóficas, intentando cambiar el mundo caña en mano. **Miguel**, ¡guaje! siempre he tenido la sensación de que lo mejor de esa “terrina” asturiana son sus gentes, y no hay más que conocerte para confirmarlo. “Por ti daba la vuelta al mundu encima el rabu un gochu”. Gracias por siempre estar dispuesto a tomar una caña/jarra o “fartarnos” a comer. Pero sobre todo mil gracias por ser como eres, “ye un máquina amigo” siempre feliz y con ganas de reírle las gracias a un “babayu” como yo. **Nuria**, es de traca que haya sido Tarragona donde nos hayamos vuelto a reencontrar, aunque he de reconocer que ha merecido la pena, y te echaré mucho de menos. Muchas gracias por los momentos que hemos compartido y también por todos esos mails organizativos de cumpleaños y quedadas, que siempre han terminado con una sonrisa. Siempre te estaré agradecido porque ¡si no es por ti no sé qué hubiese sido de este grupo! pues creo que has sido el pegamento que siempre nos ha mantenido unidos.

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Finalmente, me gustaría dedicar esta tesis a toda mi familia por su cariño eterno: tíos, primos y abuelos, tanto a los que siguen con fuerza andando el camino: **Saturnino**, **Rufino** y **Tomasa**; como a los que por desgracia nos abandonaron: *Te quiero abuela*, **Jesusa**. Pero por encima de todo, quiero agradecer con mis últimas palabras a mi hermano **Pablo**: *deja que el mundo sepa que estas aquí…y hazlo con pasión*. Y a mis padres, **José Luis** y **Pilar**, por la educación que nos han brindado tanto a mi hermano como a mí, inculcándonos que la vida se trata de afrontar los retos con esfuerzo y sacrificio, encajar las decepciones con alegría y celebrar los éxitos con humildad.

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Curriculum Vitae

José Enrique Gómez Pulido was born on December 17, **1991** in Madrid (Spain). He studied chemistry at the University of Valladolid (UVa) obtaining his BSc degree in June **2014**. During his undergraduate studies, he joined in the organic chemistry department to investigate the synthesis of non-natural steroidal scaffolds. After obtaining his BSc degree in the summer of **2014**, he spent an internship at the spin-off *Technical Proteins Nanobiotechnology S.L.* to work in the synthesis of protein polymers as an undergraduate researcher. Hereafter, he started his MSc degree in "Synthetic and Industrial Chemistry" at the University of Valladolid under the supervision of Professor Alfonso Pérez Encabo. During his MSc studies, his research focused on the synthesis of fluorinated pentose derivatives. He obtained his MSc degree in September **2015** and decided to move to Tarragona to start his PhD studies under the supervision of Professor Arjan W. Kleij at the Institute of Chemical Research of Catalonia (ICIQ), where he performed the research described in this thesis. His research was financially supported with an FPI Severo Ochoa Fellowship from the Spanish "Ministerio de Economía y Competitividad", MINECO. During his PhD studies, he spent four months at Eli Lilly (United Kingdom, UK) working at the Discovery Chemistry and Synthesis Group, under the supervision of Dr. Jeffery Richardson and Dr. Gary Sharman. The work carried out during this period focused on the development of an automated platform for the synthesis and structure elucidation of drug-like molecules. Finally, as a recognition of his doctoral studies he was awarded with one of the **2019** RSEQ-Lilly Awards for PhD students. The PhD results have been communicated at different national and international conferences, such as the Consolider INTECAT meeting in Huelva (**2016**), the 5th CARISMA Meeting held in Lisbon (**2017**), the XXXVI Reunión Bienal (RSEQ) in Sitges (**2017**), the German-Spanish Symposium and ICIQ-Summer School in Tarragona (**2017**), the 2nd Trans Pyrenean Meeting in Catalysis (TrapCat2) in Tarragona (**2018**), the ICIQ-INTECAT School in Montbrió (**2018**) and the XXXVII Reunión Bienal (RSEQ) in San Sebastián (**2019**).

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List of Publications

The following publications are based on the work described in this thesis:

- "*Catalytic Transformations of Functionalized Cyclic Organic Carbonates*" Guo, W.; **Gómez, J. E**.; Cristòfol, À.; Xie, J.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2018**, *57*, 13735-13747. (Review article)

- "*Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones*" **Gómez, J. E.**; Guo, W.; Kleij, A. W. *Org. Lett*. **2016**, *18*, 6042-6045.

- "*Copper-Catalyzed Enantioselective Construction of Tertiary Propargylic Sulfones*" **Gómez, J. E**.; Cristòfol, Á.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2019**, *58*, 3903-3907.

- "*Copper-Catalyzed Synthesis of γ-Amino Acids Featuring Quaternary Stereocenters"* **Gómez, J. E.**; Guo, W., Gaspa, S.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2017**, *56*, 15035-15038.

The following publications relate to other activities during this thesis. A brief summary of these projects is shown in the Annex.

- "*A Domino Process toward Functionally Dense Quaternary Carbons through Pd-Catalyzed Decarboxylative C(sp^3)–C(sp^3) Bond Formation*" Guo, W.; Kuniyil, R.; **Gómez, J. E**.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc*. **2018**, *140*, 3981-3987.

- "*Copper-Mediated S_N2' Allyl–Alkyl and Allyl–Boryl Couplings of Vinyl Cyclic Carbonates*" Miralles, N.; **Gómez, J. E**.; Kleij, A. W.; Fernández, E. *Org. Lett*. **2017**, *19*, 6096-6099.

- "*Metal-Free Synthesis of N-Aryl Amides using Organocatalytic Ring-Opening Aminolysis of Lactones*" Guo, W.; **Gómez, J. E**.; Martínez-Rodríguez, L.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *ChemSusChem* **2017**, *10*, 1969-1975.

Review articles:

- "*Recent Progress in Stereoselective Synthesis of Cyclic Organic Carbonates and Beyond*" **Gómez, J. E**.; Kleij, A. W. *Curr. Opin. Green Sust. Chem*. **2017**, *3*, 55-60.

- "*Catalytic Nonreductive Valorization of Carbon Dioxide into Fine Chemicals*" **Gómez, J. E**.; Kleij, A. W. *Adv. Organometal. Chem.* **2019**, *71*, 175-226.

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Preface

The work presented in this dissertation has been performed at the Institute of Chemical Research of Catalonia (ICIQ), during the period of November 2015 until September 2019 under the supervision of Professor Arjan W. Kleij. This thesis is divided into six sections: a general introduction containing the aims and outline of the thesis, three research chapters, a chapter in which the overall conclusions of the work are presented and an annex containing a brief description of other collaborative projects developed during this thesis. Each of the research chapters includes a brief introduction on the topic, followed by the collected results and their discussion, the main conclusions, and finally a detailed experimental section. References and their numbering are independently organized by chapters.

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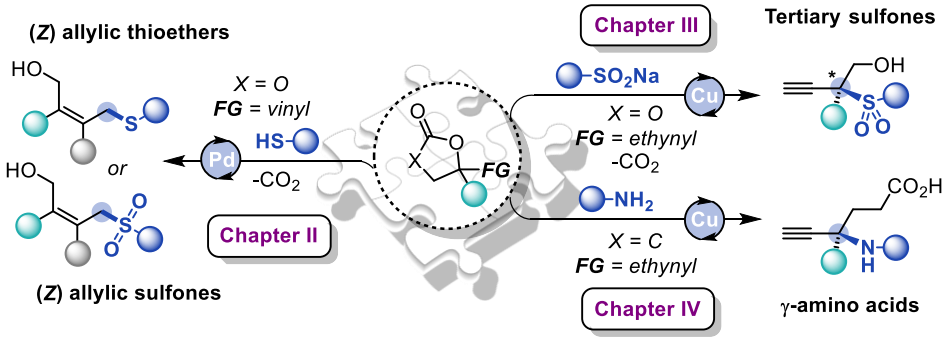
Summary

Heterocycles are usually valued as synthetic targets, however, particular attention is also given to heterocyclic compounds that hold promise in organic synthesis as precursors to construct more complex, valuable products.

In the past decade, the main interest of Kleij group at ICIQ (Tarragona) has been the development of novel catalytic nonreductive methodologies for recycling carbon dioxide into fine chemicals. In this regard, the group has developed a portfolio of new methods for the synthesis of functionalized cyclic organic carbonates (COCs). Given the fact that a library of high-functionalized synthons is available nowadays, our group has recently become interested in taking advantage of the intrinsic reactivity of these heterocycles and to use them as starting materials for the preparation of more complex organic compounds.

Therefore, with this paradigm shift in our group, these doctoral studies were focused on the development of new stereo- and enantio-selective catalytic methodologies taking advantage of the intrinsic reactivity of functionalized COCs and related heterocycles (*e.g.*, nonstrained lactones) and use these as starting materials for more complex chiral organic targets by means of transition-metal (TM) catalysis (specifically Pd and Cu).



In **Chapter I**, a general introduction on stereoselective TM-catalysis is presented alongside the synthetic utility of heterocycles serving as intermediates in TM-catalyzed organic transformations. Our current work has a major focus on catalytic transformations of COCs. Hence, a brief overview of the latest advances made in cyclic organic carbonate synthesis is presented first, followed by the state of the art in the emerging field of TM-catalyzed transformations of COCs (and some related heterocyclic scaffolds) in organic synthesis.

Chapter II, "*Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones*" presents the development of a new stereoselective synthetic protocol for a wide range of highly substituted (*Z*)-configured allylic thioethers through a Pd-catalyzed decarboxylative allylic thiolation of vinyl cyclic carbonates (VCCs). Furthermore, a one-pot two-step strategy was also designed allowing the stereoselective formation of pharmaceutically relevant allylic sulfones from their *in situ* prepared thioether precursors. This work has been published in: *Org. Lett*. **2016**, *18*, 6042-6045.

Chapter III, "*Copper-Catalyzed Enantioselective Construction of Tertiary Propargylic Sulfones*" discusses the discovery and optimization of a new synthetic approach targeting the construction of propargylic sulfones containing tetrasubstituted carbon stereocenters. A general asymmetric, decarboxylative methodology was achieved by means of a copper-catalyzed asymmetric sulfonylation of modular alkyne-substituted cyclic carbonates, using sulfinate salts as nucleophiles. A plausible mechanistic rationale was proposed considering the involvement of copper-allenylidene species as key reactive intermediates in this transformation. The results described in this chapter have been published in: *Angew. Chem. Int. Ed.* **2019**, *58*, 3903-3907.

Chapter IV, "*Copper-Catalyzed Synthesis of γ-Amino Acids Featuring Quaternary Stereocenters*" presents the first general asymmetric synthesis of γ,γ-disubstituted γ-amino acids. In parallel to Chapter III, we envisaged that the asymmetric synthesis of these building blocks would be feasible through a copper-allenylidene mediated ring opening of nonstrained five-membered lactones by amines. In addition, the newly prepared amino acids served as versatile precursors to a variety of other biologically relevant products. This work has been published in: *Angew. Chem. Int. Ed*. **2017**, *20*, 15035-15038, and highlighted in *Synfacts* **2018**, *14(01)*, 0043.

Chapter V, "*General Conclusions*" summarizes the most important conclusions based on the gathered results presented in this thesis, and lastly **Chapter VI** discloses additional publications related to other activities during this thesis.

List of abbreviations

In this doctoral thesis, the abbreviations and acronyms most commonly used in organic chemistry are based on the recommendations of the ACS "Guidelines for authors" which can be found at *http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf*

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Chapter I

General Introduction

Sections of this chapter have been adapted from:

Guo, W.; Gómez, J. E.; Cristòfol, À.; Xie, J.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2018**, *57*, 13735-13747

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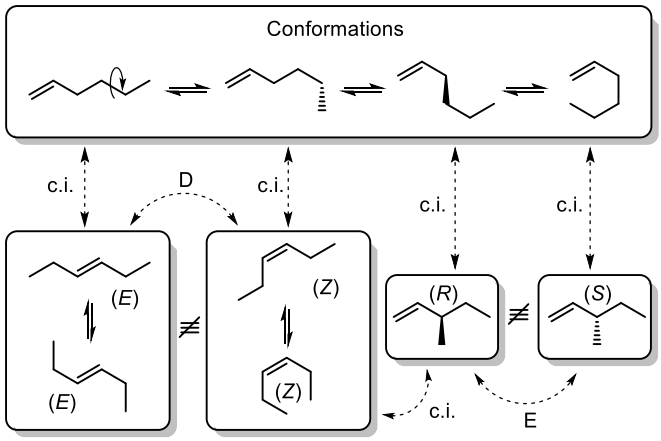
I.1. Stereoselective transition metal catalysis

Creating new chemical bonds and scaffolds are appealing characteristics of synthetic chemistry. In this context, stereoselective synthesis, *i.e.*, the capacity to selectively prepare one of the possible stereoisomeric structures is, without a doubt, a major challenge.[1] Scheme I-1 illustrates the different types of isomeric relationships taking olefins as an exemplary case. Control over the stereoselectivity of a reaction is important as the properties of a given substance are "macroscopic" manifestations directly correlated with the way the atoms are interconnected on a "microscopic level"; in this respect, different enantiomers or diastereomers of a molecule often have different biological activity.



Scheme I-1. Conformational, configurational and various other types of isomerism. (The molecules shown all have the same molecular formula (C_6H_{12}). Abbreviations: c.i. = constitutional isomers, D = diastereomers, E = enantiomers).

Chirality effects play a key role in everyday life. For example, (*S*)-asparagine is a tasteless compound while (*R*)-asparagine has a sweet taste. Similarly, chirality also plays an important role in pharmacology.[2] The drug thalidomide provides another example illustrating the importance of configurational identity: (*R*)-thalidomide is a sedative, whereas (*S*)-thalidomide has teratogenic effects on developing fetus (Figure I-1).[3] Therefore, there is a clear need for

1 Nógrádi, M.; Poppe, L.; Nagy, J.; Hornyánszky, G.; Boros, Z. *Stereochemistry and Stereoselective Synthesis: An Introduction*. Wiley-VCH, Germany, **2016**.
2 Lehmann, P. A. F. *Life Sciences*. **1978**, *22*, 1631-1635.
3 Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964-1973.

synthetic approaches that allow for stereocontrolled chemical transformations. Importantly, the relevance and general impact of stereoselective synthesis has been recognized by awarding in 2001 the Nobel Prize in chemistry to Knowles, Noyori and Sharpless. Stereoselective synthesis has manifested itself as a mature area of science being of fundamental importance in pharmaceutical, agrochemical and cosmetic development.[4]

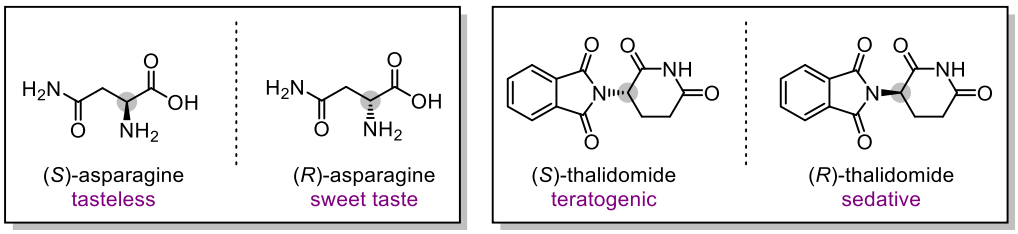


Figure I-1. Enantiomers of asparagine and thalidomide.

The reactions and classes of reactions which have found the broadest applicability in organic chemistry are those that address the issues of stereo- and enantiocontrol, while being compatible with a variety of functional groups. In this regard, catalysis, and especially the rich chemistry provided by the easy accessible d-orbitals of complexes derived from transition metals (TM), has contributed significantly over the last decades to the synthesis of complex chiral organic structures that previously were considered to be impossible to prepare in the laboratory.[5] As a testament of the importance of transition metal chemistry, several Nobel prizes in chemistry were awarded to TM-catalyzed reactions in the last two decades. The major advantage of using transition metal complexes as catalysts is that their catalytic activity can be readily modulated by (ancillary) ligands. A delicate balance between electronic and steric factors not only determines the efficiency and stability of a metal catalyst, but also has the potential to stir the stereoselective outcome of a transformation by a judicious choice of chiral (mostly organic) ligands coordinating to the metal center.[6]

A particular field to which TM-catalysis has contributed with a great deal of success is the ring-opening of heterocyclic substrates towards the stereoselective synthesis of complex

4 Carreira, E. M.; L. Kvaerno. *Classics in Stereoselective Synthesis*. Wiley-VCH, Germany, **2009**.
5 (a) Hartwig, J. F. *Organotransition Metal Chemistry*. Sausalito, CA, **2010**. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*. John Wiley & Sons, Chichester, **2004**.
6 Sandoval, C. A.; Noyori, R. *An Overview of Recent Developments in Metal-Catalyzed Asymmetric Transformations*. Wiley-VCH, Weinheim, **2012**.

heteroatom-containing cyclic or acyclic compounds.[7] Transition metals play a key role to render these ring-opening reactions viable under mild conditions and in high selectivity. In the past years, several reviews and research articles in the literature have highlighted an ever-increasing potential of a range of functionalized heterocycles in TM-mediated synthesis.[8] Such transformations may occur in three,[9] four,[10] five,[11] six[12] and "medium-sized"[13] heterocycles mainly containing nitrogen, oxygen and sulfur atoms, among others. Over time, the study and the fundamental knowledge gained within this field has also inspired chemists to develop new TM-catalyzed reactions using heterocycles that previously remained unexplored. Cyclic organic carbonates (COCs) have recently been introduced as a new class of modular and easily accessible reaction partners to develop highly chemo- and stereoselective methods for the preparation of a range of valuable heteroatom-containing molecules.

I.2. Cyclic carbonates

Organic carbonates (OCs), also known as carbonic acid esters, are a class of compounds with a carbonyl flanked by two alkoxy or aryloxy groups. However, if this functionality is embedded in a cyclic architecture they are generally referred to as cyclic organic carbonates.[14] Typically these COCs are liquid and highly stable compounds and represent substructures that can be found in various natural compounds (Figure I-2a, **I.1-I.3**).[15] Further properties of COCs include an aprotic nature and high polarity having also high level of modularity, hence playing an important role in modern life with rapidly increasing applications in both industry and academic laboratories.[16]

7 Kotschy, A.; Timári, G. *Heterocycles from Transition Metal Catalysis: Formation and Functionalization. Catalysis by Metal Complexes*. Springer, Dordrecht, **2005**.

8 (a) van der Plas, H. C. *Ring Transformations of Heterocycles*. Academic Press Inc, New York, **1973**. (b) Allen, B. D. W.; Lakeland, C. P.; Harrity, J. P. A. *Chem. Eur. J.* **2017**, *23*, 13830-13857.

9 (a) Huang, C.-Y.; Doyle, A. G. *Chem. Rev*. **2014**, *114*, 8153-8198. (b) Wang, C.; Luo, L.; Yamamoto, H. *Acc. Chem. Res*. **2016**, *49*, 193-204. (c) Ohno, H. *Chem. Rev*. **2014**, *114*, 7784-7814.

10 Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev*. **2016**, *116*, 12150-12233.

11 Lipshutz, B. H. *Chem. Rev*. **1986**, *86*, 795-819.

12 Li, T.-R.; Wang, Y.-N.; Xiao, W.-J.; Lu, L.-Q. *Tetrahedron Lett*. **2018**, *59*, 1521-1530.

13 Yet, L. *Chem. Rev*. **2000**, *100*, 2963-3008.

14 Shaikh, A.-A. G.; Sivaram, S. *Chem. Rev*. **1996**, *96*, 951-976.

15 Zhang, H.; Liu, H.-B.; Yue, J.-M. *Chem. Rev*. **2014**, *114*, 883-898.

16 For reviews, see: (a) Sakakura, T.; Kohno, K. *Chem. Commun*. **2009**, 1312-1330. (b) Schäffner, B.; Schäffner, F.; Verevkin, S. P.; Börner, A. *Chem. Rev*. **2010**, *110*, 4554-4581. (c) Lu, X. B.; Darensbourg D. J. *Chem. Soc. Rev*. **2012**, *41*, 1462-1484. For recent examples, see: (d) Cheng, X. B.; Yan, C.; Chen, X.; Guan, C.; Huang, J. Q.; Peng, H. J.; Zhang, R.; Yang, S. T.; Zhang, Q. *Chem*, **2017**, *2*, 258-270.

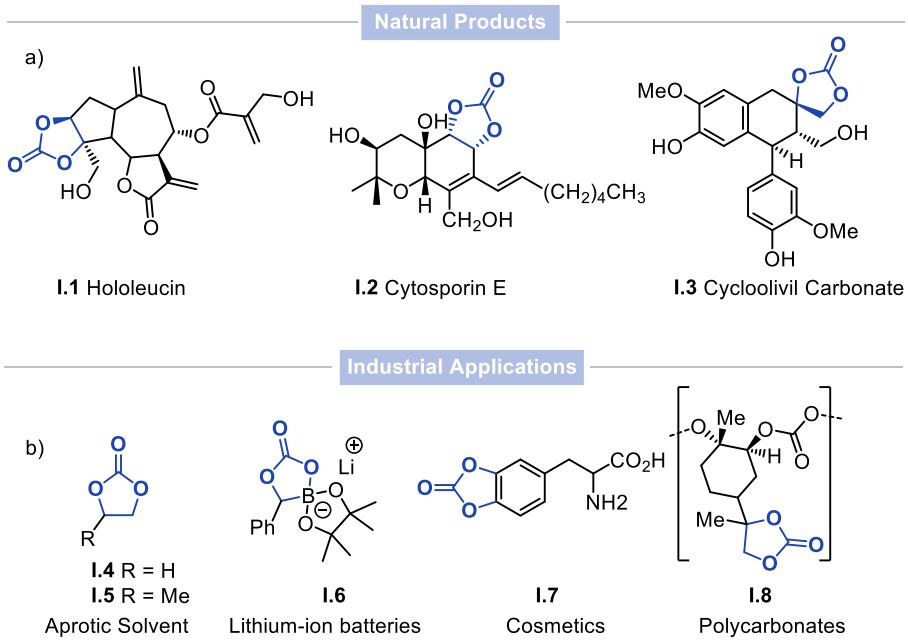


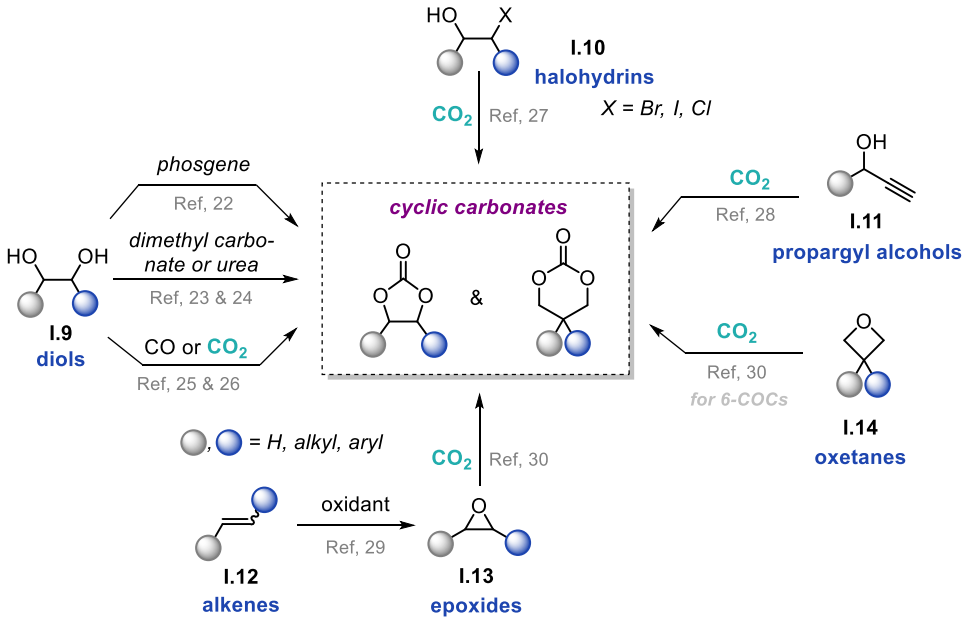
Figure I-2. a) Selected examples of naturally occurring COCs, and b) applications of cyclic carbonates.

Concerning their application in industry, simple cyclic organic carbonates such as ethylene and propylene carbonate are used in coatings,[16] paint,[16] electrolytes for lithium ion batteries[17] or applied as polar aprotic solvents (Figure I-2b, **I.4**-**I.6**).[18] On the other hand, they have also found applications in the production of cosmetics (Figure I-2b, **I.7**),[16] herbicides[19] and polymers (Figure I-2b, **I.8**).[20] Nonetheless, their value as synthetic intermediates is of particular interest. COCs are valuable precursors due to their diverse reactivity behavior. Strategies for utilizing COCs as synthetic intermediates principally include: (a) ring expansion reactions to give access to diverse oxygen-containing (macro)cyclic compounds, and (b) ring opening reactions to afford mostly acyclic products, among others. These transformations are typically imposing regio- and

17 Zhao, S.-J. P. H.; Shi, F. I.; Fu, Y.; Battaglia, V.; Ross Jr. P. N.; Liu, G. *J. Electrochem. Soc.* **2014**, *161*, A194-A200.
18 Parker, H. L.; Sherwood, J.; Hunt, A. J.; Clark, J. H. *ACS Sustain. Chem. Eng*. **2014**, *2*, 1739-1742.
19 Rukachaisirikul, V.; Rungsaiwattana, N.; Klaiklay, S.; Phongpaichit, S.; Borwornwiriyapan, K.; Sakayaroj, J. *J. Nat. Prod.* **2014**, *77*, 2375-2382.
20 Kindermann, N.; Cristòfol, A.; Kleij, A. W. *ACS Catal*. **2017**, *7*, 3860-3863.

stereoselectivity challenges, which can be overcome by using proper (transition metal) catalysts and reaction conditions.[21]

To date, the synthesis of cyclic carbonates is well-established, providing easy access to more sophisticated scaffolds, which can ultimately lead to the creation of more complex products. Scheme I-2 summarizes the most important methods for COC formation.



Scheme I-2. Synthetic approaches towards COC formation.

For a long time, the reaction between 1,2-diols (**I.9**) and a carbonylating agent in the presence of a suitable base was the main method to obtain cyclic carbonates.[22] Despite its utility, this approach encounters major drawbacks such as the toxicity of phosgene derivatives, as well as hazardous byproduct formation (*i.e.*, 2 molar equiv of HCl). Current alternative and greener methods to yield COCs from diols are the use of other C1 building blocks such as dimethyl

21 Guo, W.; Gómez, J. E.; Cristòfol, À.; Xie, J.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2018**, *57*, 13735-13747.

22 Burk, R. M.; Roof, M. B. *Tetrahedron Lett*. **1993**, *34*, 395-398.

carbonate,[23] urea,[24] carbon monoxide (CO)[25] or carbon dioxide (CO_2).[26] In the latter case, halohydrins (**I.10**),[27] propargyl alcohols (**I.11**),[28] and even alkenes (**I.12**)[29] can be used as starting materials. However, in the case of alkenes the original substrate requires to be first oxidized or converted into a halohydrin prior to reaction with CO_2. The most sustainable and prevalent route in both industry and academia is the atom-economic and redox neutral cycloaddition reaction of CO_2 with strained cyclic ethers such as epoxides (**I.13**, *cf.* 5-membered COCs) and oxetanes (**I.14**, *cf.* 6-membered COCs).[30]

The cheap, accessible and renewable nature of CO_2, and in particular the easy preparation of epoxides from ubiquitous olefin precursors has boosted this strategy during the last years. Thus far, the synthesis of cyclic organic carbonates by cycloaddition to epoxides represents one of few processes employing CO_2 that can be carried out under mild conditions if highly active catalysts are employed. This cycloaddition reaction is thermodynamically favored due to the release of the ring-strain energy contained in the epoxide substrate.[30]

Both heterogeneous and homogeneous catalysts have been developed to catalyze the cycloaddition reaction. Heterogeneous catalysts (*e.g.* metal organic frameworks, nanoparticles or supported catalysts) are relevant for industrial processes due to advantageous properties such as easy recoverability and recyclability, whereas homogeneous catalysts (*e.g.* metal-based catalysts and organocatalysts) can operate at lower catalyst loadings and milder conditions. Figure I-3 shows some of the most active homogeneous catalysts reported to date (**I.15**-**I.25**). For a more extensive discussion on other catalysts developed for this reaction (including metal-free catalysts) the reader is kindly referred to recently appeared accounts on this topic.[30]

23 Selva, M.; Caretto, A.; Noè, M.; Perosa, A. *Org. Biomol. Chem.* **2014**, *12*, 4143-4155.
24 Peña-López, M.; Neumann, H.; Beller, M.; *Eur. J. Org. Chem*. **2016**, 3721-3727.
25 Doro, F. Winnertz, P. Leitner, W. Prokofieva, A. Müller, T. E. *Green Chem*. **2011**, *13*, 292-295.
26 Bobbink, F. D.; Gruszka, W.; Hulla, M.; Das, S.; Dyson, P. J. *Chem. Commun.* **2016**, *52*, 10787-10790.
27 Reithofer, M. R.; Sum, Y. N.; Zhang, Y. *Green Chem*. **2013**, *15*, 2086-2090.
28 Chen, K.; Shi, G.; Dao, R.; Mei, K.; Zhou, X.; Li, H.; Wang, C. *Chem. Commun*. **2016**, *52*, 7830-7833.
29 Wu, J.; Kozak, J. A.; Simeon, F.; Hatton, T. A.; Jamison, T. F. *Chem. Sci.* **2014**, *5*, 1227-1231.
30 For recent advances made to this area: (a) Shaikh, R. R.; Pornpraprom, S.; D'Elia, V. *ACS Catal*. **2018**, *8*, 419-450. (b) Martín, C.; Fiorani, G.; Kleij, A. W. *ACS Catal*. **2015**, *5*, 1353-1370; (c) Comerford, J. W.; Ingram I. D. V.; North, M.; Wu, X. *Green Chem*. **2015**, *17*, 1966-1987. (d) Büttner, H.; Longwitz, L.; Steinbauer, J.; Eulf, C.; Werner, T. *Top. Curr. Chem*. **2017**, *375*, 50.

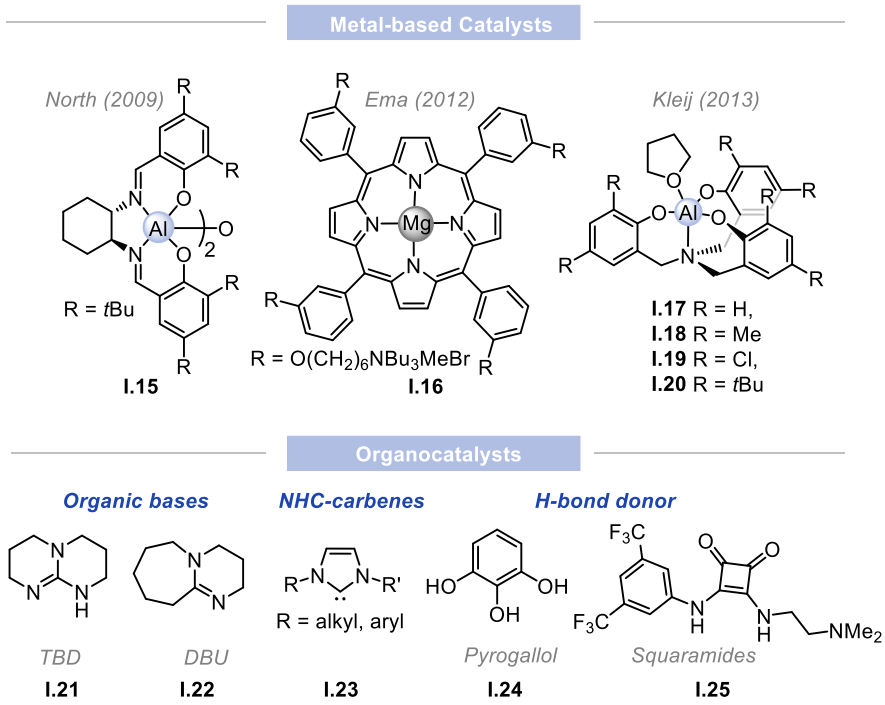


Figure I-3. Representative examples of homogeneous catalysts used for the preparation of COCs.

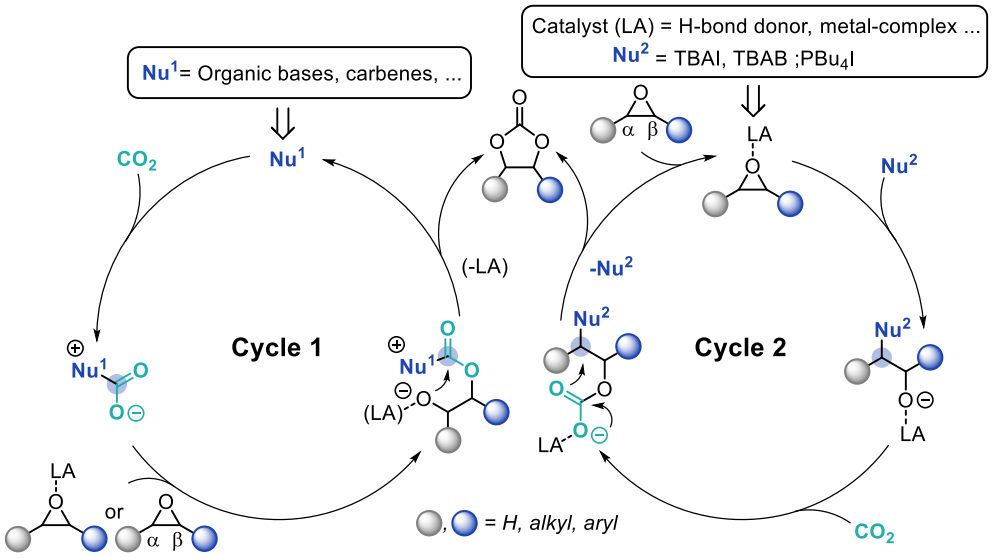
Homogeneous systems have been by far the most widely employed catalysts and within this category, homogeneous metal-based catalysts have proven to be superior to organocatalytic ones. Metal complexes show considerable higher turnover rates and thus can be employed in considerable smaller amounts compared to organocatalysts. Moreover, organocatalysts often show more restricted substrate scopes than the best metal catalysts. Metal-based systems, though, typically require the use of onium salts as nucleophilic co-catalysts, although it is possible to merge both components into bifunctional, single-component catalysts.[31] However, it should be noted that the majority of the studies dedicated to the application of organocatalysts are relatively recent when compared to metal-based systems.[32] Thus, there is still room for further

31 For some examples: (a) North, M.; Villuendas, P.; Young, C. *Tetrahedron Lett*. **2012**, *53*, 2736-2740. (b) Melendez, J.; North, M.; Villuendas, P. *Chem. Commun*. **2009**, 2577-2579.

32 For general reviews, see: (a) Pescarmona, P. P.; Taherimehr, M. *Catal. Sci. Technol*. **2012**, *2*, 2169-2187. (b) Maeda, C.; Miyazaki, Y.; Ema, T. *Catal. Sci. Technol*. **2014**, *4*, 1482-1497. (c) Fiorani, G.; Guo, W; Kleij, A.W. *Green Chem*. **2015**, *17*, 1375-1389. (d) Yu, B.; He, L. N. *ChemSusChem* **2015**, *8*, 52-62. (e) Cokoja, M.; Wilhelm, M. E.; Anthofer, M. H.; Herrmann W. A.; Kühn, F. E. *ChemSusChem* **2015**, *8*, 2436-2454. (f) Song, Q. W.; Zhou, Z. H.; He L. N. *Green Chem*. **2017**, *19*, 3707-3728.

improvement and new conceptual approaches, considering the potential benefits in terms of cost, simplicity and sustainability of organocatalysis.

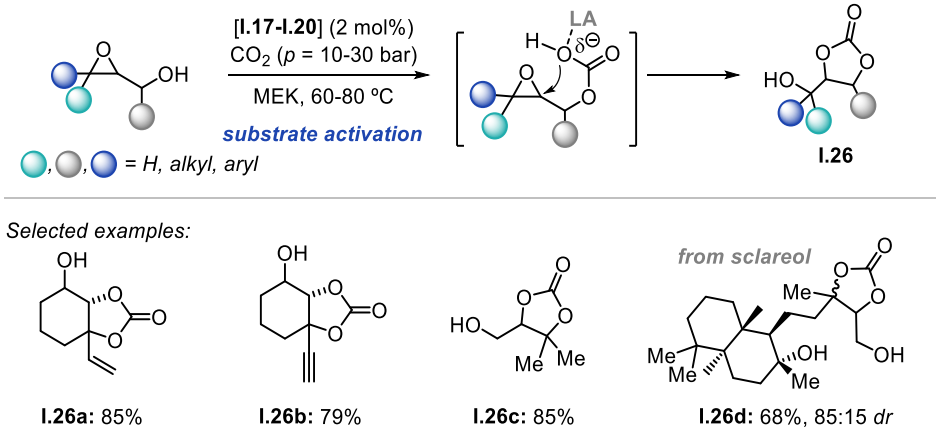
From a mechanistic standpoint, the current methodology for the coupling of CO_2 and epoxides mainly entails two different mechanistic pathways depending on the chosen catalyst (Scheme I-3).[30, 32]



Scheme I-3. Widely accepted catalytic cycles for CO_2 insertion into epoxides. (TBAI stands for tetrabutylammonium iodide; TBAB is the corresponding bromide).

Nucleophilic catalysts (*e.g.*, organic bases and N-heterocyclic carbenes) initially attack the electrophilic carbon atom of carbon dioxide producing a CO_2-adduct. After this, the adduct mediates a ring-opening of the epoxide (or a Lewis-acid (LA) activated epoxide) forming a formal alkoxide species that subsequently cyclizes towards the target carbonate product while releasing Nu^1 and the LA for further catalytic turnover (Scheme I-3, Cycle 1). Conversely, if the catalyst is a hydrogen bond donor (*i.e.* alcohols, polyols or ureas, among others) or a Lewis acidic compound, a different mechanistic route takes place (Scheme I-3, Cycle 2). In this case, the nucleophilic co-catalyst firstly mediates ring-opening of the activated/coordinated epoxide, followed by a nucleophilic attack of the *in situ* formed metal-alkoxide onto CO_2. Finally, a ring-closure step takes place, where the linear metal-carbonate reacts in an S_N2 fashion producing the cyclic carbonate and regenerating the co-catalyst.[30, 32]

Beside these general aforementioned mechanistic scenarios, it is worth noting that changes in the regioselectivity (α- or β-attack, Scheme I-3) of the initial nucleophilic attack may influence the stereochemistry of the final product.[30] Furthermore, alternative mechanistic pathways could be possible in specific cases.[33] For instance, a recent alternative method capitalizes on the use of epoxy alcohols that can participate in the activation of carbon dioxide. These substrates have shown to offer potential to access highly substituted cyclic carbonates (**I.26a-I.26d**) through a substrate-assisted catalytic approach (Scheme I-4).[34] The essence of this approach is the initial activation of CO_2 through the alcohol unit, thus providing an intramolecular nucleophile for epoxy ring opening under either metal[34] or organocatalysis.[35]



Scheme I-4. Concept of substrate-controlled conversion of epoxy alcohols into COCs. (MEK stands for methyl ethyl ketone).

Overall, epoxides have been the primary choice to function as substrates in cycloaddition reactions with CO_2 affording five-membered COCs. Contrary, oxetanes have been much less

33 For representative examples: (a) North, M.; Pasquale, R. *Angew. Chem. Int. Ed*. **2009**, *48*, 2946-2948. (b) Desens, W.; Werner, T. *Adv. Synth. Catal*. **2016**, *358*, 622-630. (c) Chatelet, B.; Joucla, L.; Dutasta, J.-P.; Martinez, A.; Szeto, K. C.; Dufaud, V. *J. Am. Chem. Soc*. **2013**, *135*, 5348-5351. (d) D'Elia, V.; Ghani, A. A.; Monassier, A.; Sofack-Kreutzer, J.; Pelletier, J. D. A.; Drees, M.; Vummaleti, S. V. C.; Poater, A.; Cavallo, L.; Cokoja, M.; Basset, J.-M.; Kühn, F. E. *Chem. Eur. J*. **2014**, *20*, 11870-11882.

34 For recent contributions: (a) Rintjema, J.; Guo, W.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Chem. Eur. J*. **2015**, *21*, 10754-10762. (b) Rintjema, J.; Epping, R.; Fiorani, G.; Martín, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 3972-3976. For mechanistic studies: (c) Huang, R.; Rintjema, J.; González-Fabra, J.; Martín, E.; Escudero-Adán, E. C.; Bo, C.; Urakawa, A.; Kleij, A. W. *Nat. Catal.* **2019**, *2*, 62-70.

35 For an organocatalyzed version: Sopeña, S.; Cozzolino, M.; Maquilón, C.; Escudero-Adán, E. C.; Belmonte, M. M.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2018**, *57*, 11203-11207.

studied in this context. Substituted oxetanes substrates require additional synthetic efforts and, therefore the formation of the resultant six-membered COCs is not as straightforward as compared to their five-membered congeners.[30, 34a, 36] Nonetheless, considering all the advances made in synthetic cyclic carbonate chemistry, a wide library of functionalized cyclic organic carbonates are now synthetically available. Hence, this has spurred renewed interest towards the application of these heterocycles as precursors in synthetic organic chemistry.

In this doctoral thesis, we have taken advantage of functionalized COCs and related heterocyclic substrates prone to participate in transformations promoted by TM-catalysts, to deliver high value added products with exquisite control of chemo-, regio- and stereoselectivity. The following introductory sections will provide the state of the art in the area of catalytic transformations involving COCs.

I.3. Catalytic transformations of functionalized cyclic carbonates

Prior to the implementation of COCs in TM-catalyzed decarboxylative chemistry, the majority of catalytic ring-opening transformations of COCs studied have been mostly CO_2-retentive approaches. These methods were developed with a final focus on the preparation of diols, carbamates or polymers (polyurethanes and polycarbonates).[37, 38, 41, 42]

Early examples of cyclic carbonate conversions include the enantioselective hydrogenation of α-alkylidene carbonates under ruthenium[37] or enzymatic catalysis,[38] followed by hydrolysis of the carbonate unit. These methods provide an alternative route to access chiral diols compared to conventional methods. Furthermore, cyclic organic carbonates can be used as intermediates to steer the stereoselective formation of vicinal *cis*- or *trans*-configured 1,2-diols (Scheme I-5).[39] In these examples, a *cis*-cyclic epoxide is initially transformed into the corresponding *cis*-cyclic organic carbonate intermediate **I.27** with excellent retention of stereochemical information. Treatment of the *cis*-cyclic organic carbonates with sodium hydroxide yields vicinal *cis*-diol

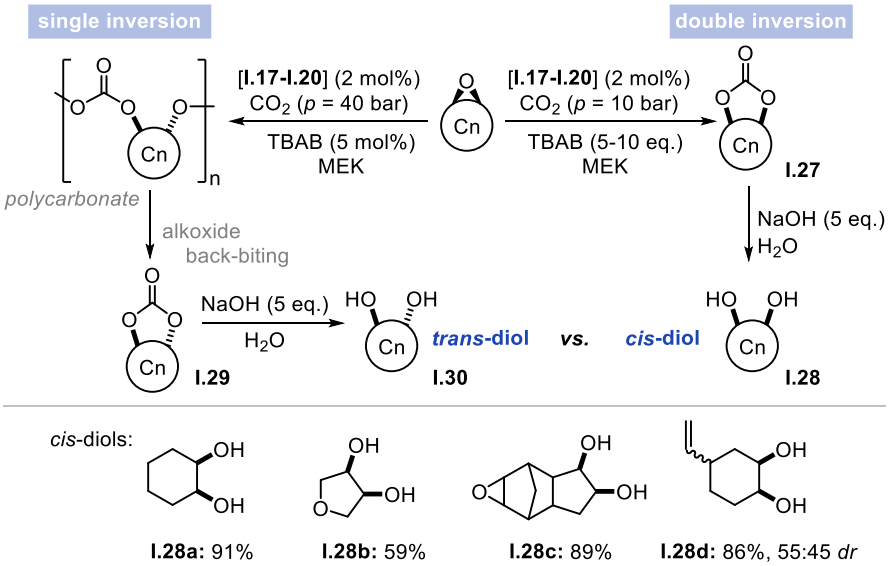
36 Approaches towards 6-membered COCs: (a) Whiteoak, C. W.; Martin, E.; Martínez Belmonte, M.; Benet-Buchholz, J.; Kleij, A. W. *Adv. Synth. Catal*. **2012**, *354*, 469-476. (b) McGuire, T. M.; López-Vidal, E. M.; Gregory, G. L.; Buchard, A. *J. CO_2 Util*. **2018**, *27*, 283-288. (c) Gregory, G. L.; Ulmann, M.; Buchard, A. *RSC Adv*. **2015**, *5*, 39404-39408.

37 Le Gendre, P.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem*. **1996**, *61*, 8453-8455.

38 (a) Matsumoto, K.; Fuwa, S.; Shimojo, M.; Kitajima, H. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 2977-2987. (b) Chang, L.; Ouyang, L. M.; Xu, Y.; Pan, J.; Xu, J. H. *J. Mol. Catal. B.* **2010**, *66*, 95-100.

39 (a) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2014**, *53*, 10416-10419. (b) Beattie, C.; North, M.; Villuendas, P.; Young, C. *J. Org. Chem*. **2013**, *78*, 419-426.

I.28a-I.28d with high stereoselectivity. Reversely, the stereocontrolled formation of *trans*-cyclic carbonates (**I.29**) is possible through depolymerization of a polycarbonate intermediate. As in the previous case, the hydrolysis gives rise to formation of *trans*-diols **I.30**.[40]



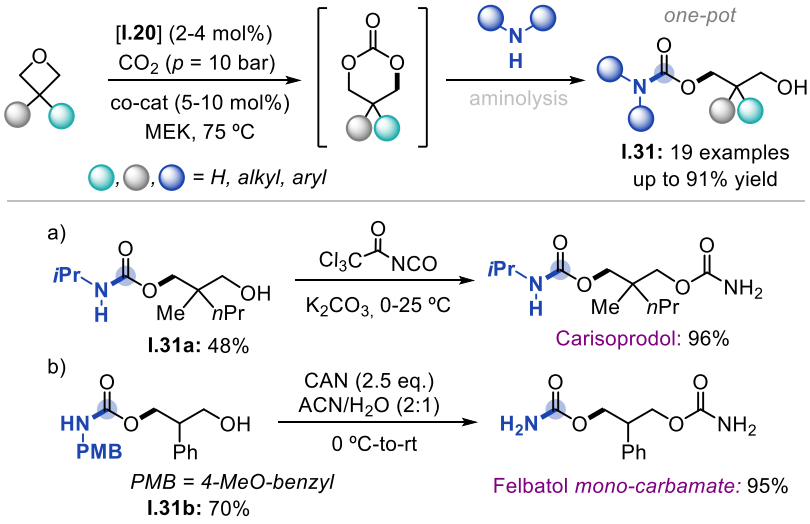
Scheme I-5. Concept of stereoselective conversions of cyclic carbonates into diols.

Another classical CO_2-retentive ring-opening transformation is presented by the aminolysis of cyclic carbonates. This strategy offers a green and straightforward strategy for the preparation of linear carbamates; hence, it has been extensively investigated.[41] Guo *et al.* for example, merged the preparation of six-membered COCs and the *in situ* aminolysis step into a one-pot

40 Darensbourg, D. J. *Chem. Rev*. **2007**, *107*, 2388-2410.

41 For a selection of some examples of the aminolysis of COCs affording carbamate products: (a) Blain, M.; Jean-Gérard, J.; Auvergne, R.; Benazet, D.; Caillol, S.; Andrioletti, B. *Green Chem*. **2014**, *16*, 4286-4291. (b) Blain, M.; Yau, H.; Jean-Gérard, L.; Auvergne, R.; Benazet, D.; Schreiner, P. R.; Caillol, S.; Andrioletti, B. *ChemSusChem* **2016**, *9*, 2269-2272. (c) Iwasaki, T. Kihara, N.; Endo, T. *Bull. Chem. Soc. Jpn*. **2000**, 73, 713-719. (d) Selva, M.; Fabris, M.; Lucchini, V.; Perosa, A.; Noè, M. *Org. Biomol. Chem*. **2010**, *8*, 5187-5198. (e) Guo, W.; González-Fabra, J.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2015**, *54*, 11686-11690. (f) Liu, Y.; Ren, W. M.; He, K. K.; Zhang, W. Z.; Li. W, B.; Wang, M.; Lu, X. B. *J. Org. Chem*. **2016**, *81*, 8959-8966. (g) Guo, W.; Laserna, V.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Chem. Eur. J*. **2016**, *22*, 1722-1727. For some examples of outstanding regiocontrol in the aminolysis of specific COCs: (h) Lombardo, V. M.; Dhulst, E. A.; Leitsch, E. K.; Wilmot, N.; Heath, W. H.; Gies, A. P.; Miller, M. D.; Torkelson, J. M.; Scheidt, K. A. *Eur. J. Org. Chem*. **2015**, 2791-2795. (i) Sopeña, S; Laserna, V.; Guo, W.; Martin, E.; Escudero-Adán, E. C. Kleij, A. W. *Adv. Synth. Catal*. **2016**, *358*, 2172-2178.

process (Scheme I-6). The process is mediated by an aluminium-based catalyst operating under relatively mild conditions, and the developed catalytic methodology can be applied to the formal synthesis of two pharmaceutically relevant carbamates such as *Carisoprodol* (a muscle relaxant) and *Felbatol* (an anticonvulsant).[42]



Scheme I-6. One-pot synthesis of linear carbamates by ring-opening aminolysis of COCs. (CAN stands for cerium ammonium nitrate).

Nevertheless, the value of COCs as synthetic precursors has not been fully exploited. Over the last years, the library of synthetically available functionalized COC synthons has grown exponentially. Therefore, there is an increasing interest in their application as substrates in more complex syntheses. Notably, the emerging field of TM-catalyzed decarboxylative conversion of COCs has been growing substantially and it has demonstrated significant advances allowing for new stereo- and enantioselective C–C and C–heteroatom bond formation reactions.

Of vital importance to the exploration of TM-catalyzed transformations that involve cyclic organic carbonates is the presence of suitable functionalities or activating groups in their structures as pre-requisite to accomplish new reactivity and selectivity. For this reason, vinyl- (**I.32**), alkenyl- (**I.33**), and alkynyl-substituted COCs (**I.34**) have become attractive reaction partners (Figure I-4). The vinyl-substituted cyclic carbonates (VCCs) and alkenyl cyclic

42 Guo, W.; Laserna, V.; Rintjema, J.; Kleij, A. W. *Adv. Synth. Catal*. **2016**, *358*, 1602-1607.

carbonates (ACCs) can be regarded as allylic surrogates upon decarboxylation, and as such provide reactive intermediates for Tsuji–Trost allylic alkylations,[43] whereas the alkyne-substituted cyclic carbonates facilitate an easy entry into propargylic substitution chemistry.[44] Therefore, transition metals such as palladium and copper have led to the major advances in the conversion of such substrates.

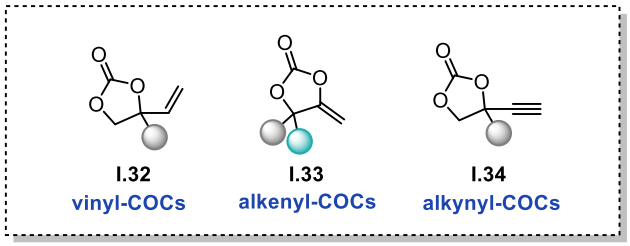


Figure I-4. Vinyl-, alkenyl - and alkynyl-substituted five-membered COCs.

I.3.1 Vinyl cyclic carbonates (VCCs)

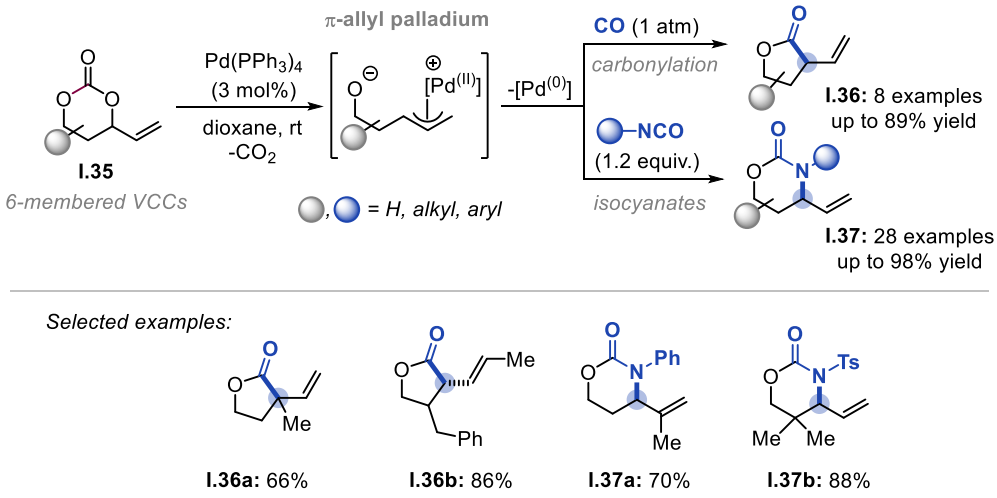
Vinyl cyclic carbonates (VCCs) are by far the most widely investigated substrates in the field of TM-catalyzed conversion of COCs. These reagents can undergo facile decarboxylation in the presence of a palladium(0) catalyst generating highly reactive π-allyl palladium intermediates with a tethered alkoxide group such as presented in Scheme I-7. Hence, the direct trapping of these intermediates have been broadly exploited with both electrophilic and nucleophilic cross-partners.

❑ Reactions of VCCs with electrophiles

The origin of the reaction between VCCs with electrophiles dates back to the seminal work of Tamaru and co-workers reported in 1987. The authors demonstrated the [4+1] decarboxylative carbonylation of 6-membered VCCs (**I.35**) under Pd catalysis (Scheme I-7).[45] Notably, this approach makes use of the nucleophilic character of the pending alkoxide group to activate CO and enables the construction of 5-membered lactones (**I.36**). This original report was followed

43 Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci*. **2010**, *1*, 427-440.
44 Reviews: (a) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. **2009**, 6263-6276. (b) Nishibayashi, Y. *Synthesis* **2012**, *44*, 489-503. (c) Zhang, D.-Y.; Hu, X.-P. *Tetrahedron Lett.* **2015**, *56*, 283-295. (d) Ding, C.-H.; Hou, X.-L. *Chem. Rev*. **2011**, *111*, 1914-1937. (e) Roya, R.; Saha, S. *RSC Adv*. **2018**, *8*, 31129-31193.
45 Tamaru, Y.; Bando, T.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett*. **1987**, *28*, 3497-3500.

by a further example in 1994 that expanded the scope of this remarkable Pd-catalyzed transformation to the synthesis of cyclic carbamates (**I.37**) (Scheme I-7).[46]



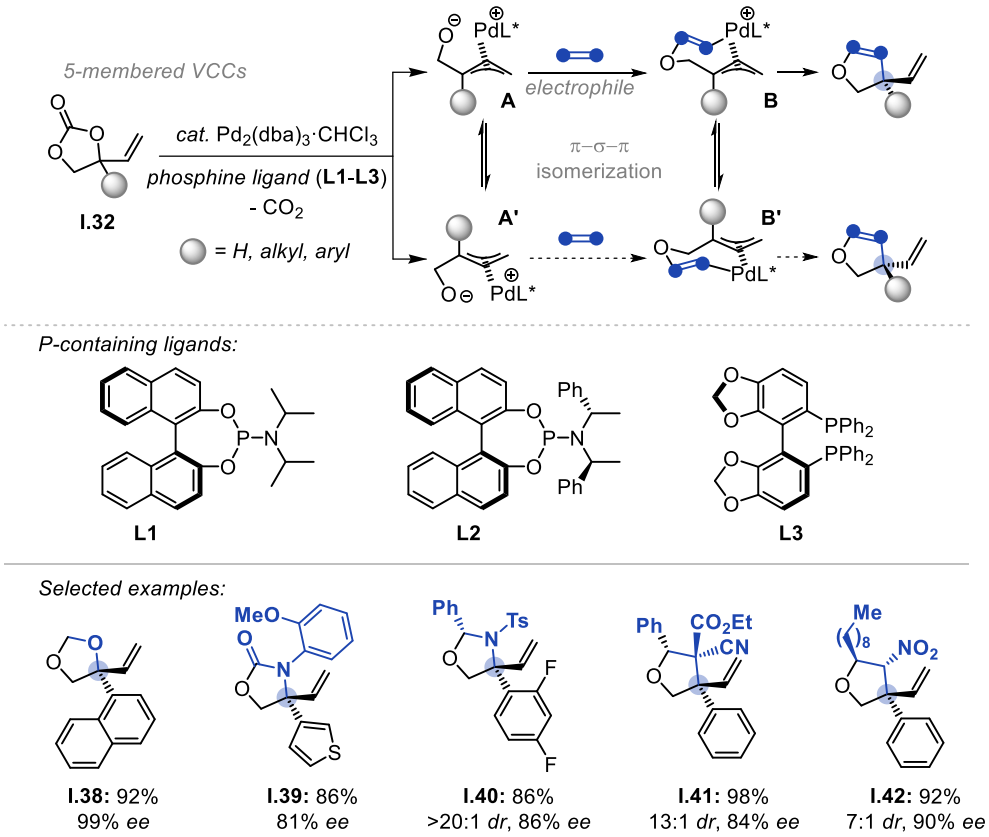
Scheme I-7. Initial reports on the Pd-catalyzed decarboxylative conversion of 6-membered VCCs.

Outstandingly, an important progress in the field was achieved in 2014, when five-membered VCCs **I.32**, and their asymmetric [3+2] decarboxylative cycloadditions in the presence of unsaturated electrophiles were thoroughly investigated by Zhang *et al*. to afford five-membered heterocycles featuring quaternary stereocenters.[47]

The general reaction mechanism of these decarboxylative cycloadditions of VCCs is illustrated in Scheme I-8. Using catalytic amounts of a chiral palladium catalyst, racemic VCCs **I.32** undergo decarboxylation affording an analogous π-allyl palladium intermediate (**A** and/or **A′**), as the previous one proposed by Tamaru (Scheme I-7). Consecutively, the intermediate could be trapped by unsaturated electrophiles to form intermediates **B** and/or **B′**, which undergo reductive elimination to yield oxygen-containing heterocycles. Generally, the products were prepared in the presence of a chiral phosphoramidite-type ligand that helps to control both the overall reactivity and enantioselectivity of the process.

46 Bando, T.; Harayama, H.; Fukazawa, Y.; Shiro, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem*. **1994**, *59*, 1465-1474.

47 For a recent review: Khan, A.; Zhang, Y. J. *Synlett*. **2015**, *26*, 853-860.



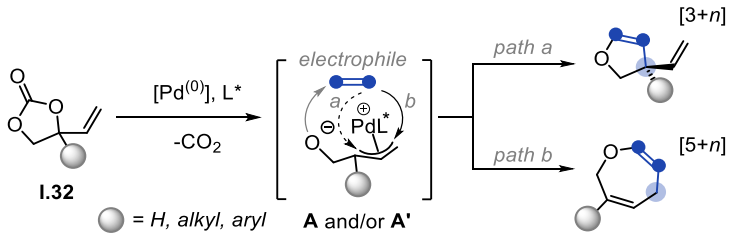
Scheme I-8. Pd-catalyzed asymmetric [3+2] decarboxylative cycloaddition of VCCs with unsaturated electrophiles.

Initial studies focused on the palladium-catalyzed decarboxylative cycloaddition of VCCs **I.32** with formaldehyde representing one of the most simplest and abundant electrophiles.[48] This transformation allowed to convert VCCs **I.32** into the corresponding 1,3-dioxolanes, which from a synthetic viewpoint can be seen as methylene acetal-protected tertiary vinyl glycols (**I.38**). It is worth mentioning that various functionalities can be introduced in the VCC substrate, allowing the synthesis of highly functionalized products. In addition, an important feature of Zhang's work is the possible application of this methodology to several unsaturated electrophiles prone to participate in formal [3+2] cycloadditions including aldehydes,[48] isocyanates,[49] imines,[50] and

48 Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6439-6442.
49 Khan, A.; Xing, J.; Zhao, J.; Kan, Y.; Zhang, W.; Zhang, Y. J. *Chem. Eur. J.* **2015**, *21*, 120-124.
50 Yang, L.; Khan, A.; Zheng, R.; Jin, L. Y.; Zhang, Y. J. *Org. Lett.* **2015**, *17*, 6230-6233.

different classes of Michael acceptors.[51] Therefore, it showcases the prospective impact of VCCs **I.32** to enable rapid access to 5-membered multi-functionalized oxazolidinones (**I.39**), oxazolidines (**I.40**) and furans (*i.e.* **I.41**-**I.42**), respectively. All products feature difficult to access tertiary or quaternary carbon stereocenters in high yields and selectivities (Scheme I-8).

On the other hand, efficient access to medium-sized rings such as 7-, 8- and 9-membered ones, remains a challenging goal in synthetic organic chemistry.[52] As a direct strategy for the formation of medium-sized rings from readily available building blocks, cycloaddition reactions have attracted much attention in recent years.[53] Aside from the use of VCCs as a π-allyl precursor for [3+2] cycloaddition (Scheme I-9, path a), Zhao and co-workers recently demonstrated that VCCs **I.32** can be employed to produce larger ring size products in an efficient and stereoselective way (Scheme I-9, path b).[54]



Scheme I-9. Decarboxylated VCCs used as 1,3-dipole or 1,5-dipole reagents.

The authors found that under palladium catalysis, the reaction of *N*-tosyl azadienes **I.43** and substituted VCCs **I.32** proceeds through intermediate **A** and/or **A′**, in which the sulfonamide attacks the Pd-π-allyl moiety to deliver the cycloaddition product. While internal attack on the π-allyl could result in a [4+3] cycloaddition to give a seven-membered heterocycle, steric

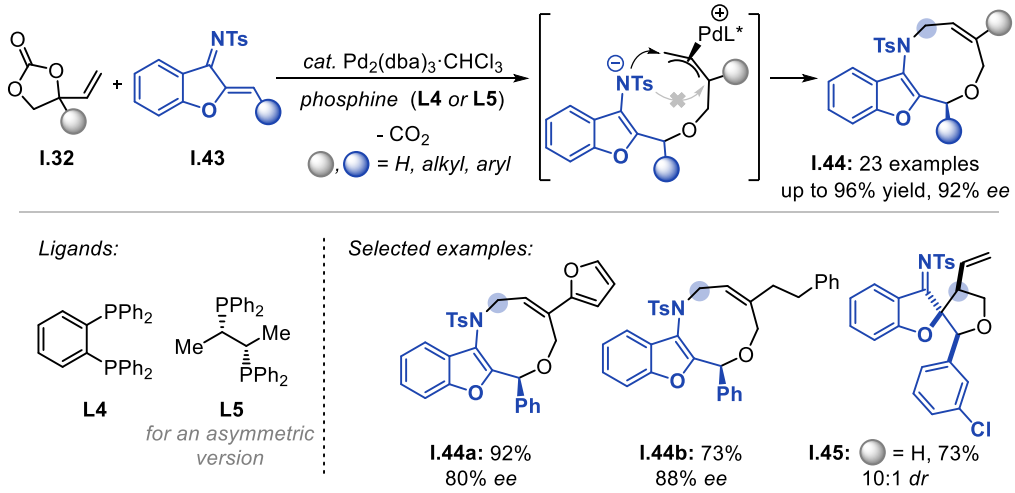
51 (a) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 11257-11260. (b) Khan, I.; Zhao, C.; Zhang, Y. J. *Chem. Commun.* **2018**, *54*, 4708-4711. (c) Liu, K.; Khan, I.; Cheng, J.; Hsueh, Y. J.; Zhang, Y. J. *ACS Catal*. **2018**, *8*, 11600-11604.

52 Selected reviews: (a) Molander, G. A. *Acc. Chem. Res*. **1998**, *31*, 603-609. (b) Yet, L. *Tetrahedron* **1999**, *55*, 9349-9403. (c) Yet, L. *Chem. Rev*. **2000**, *100*, 2963-3007. (d) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199-2238. (e) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243-251.

53 Selected recent examples: (a) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc*. **2002**, *124*, 8784-8785. (b) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc*. **2007**, *129*, 12356-12357. (c) He, H.; Liu, W.-B.; Dai, L.-X.; You, S.-L. *Angew. Chem. Int. Ed*. **2010**, *49*, 1496- 1499. (d) Lv, H.; Jia, W.- Q.; Sun, L.-H.; Ye, S. *Angew. Chem. Int. Ed*. **2013**, *52*, 8607-8610.

54 (a) Yang, L.C.; Rong, Z. Q.; Wang, Y. N.; Tan, Z. Y.; Wang, M.; Zhao, Y. *Angew. Chem. Int. Ed*. **2017**, *56*, 2927-2931. (b) Rong, Z. Q.; Yang, L. C.; Liu, S.; Yu, Z.; Wang, Y. N.; Tan, Z. Y.; Huang, R. Z.; Lan, Y.; Zhao, Y. *J. Am. Chem. Soc*. **2017**, *139*, 15304-15307.

hindrance within the substrate (*i.e.*, the NTs group as well as the quaternary center in **I.32**) play a significant role in switching the regioselectivity of this process. A terminal attack on the π-allyl intermediate instead resulted, at that point in time, in an unprecedented [5+4] cycloaddition forming exclusively challenging nine-membered macrocyclic products **I.44** (Scheme I-10).[54a] Importantly, the asymmetric variant of this reaction was also successfully achieved by employing a chiral bisphosphine-ligand backbone.[54b] On the other hand, the use of non-substituted, sterically unhindered VCCs (R = H) favor a diasteroselective [3+2] cycloaddition reaction giving rise to formation of five-membered spiro-heterocycles **I.45** (Scheme I-10).



Scheme I-10. Pd-catalyzed asymmetric decarboxylative cycloaddition of VCCs to azadienes.

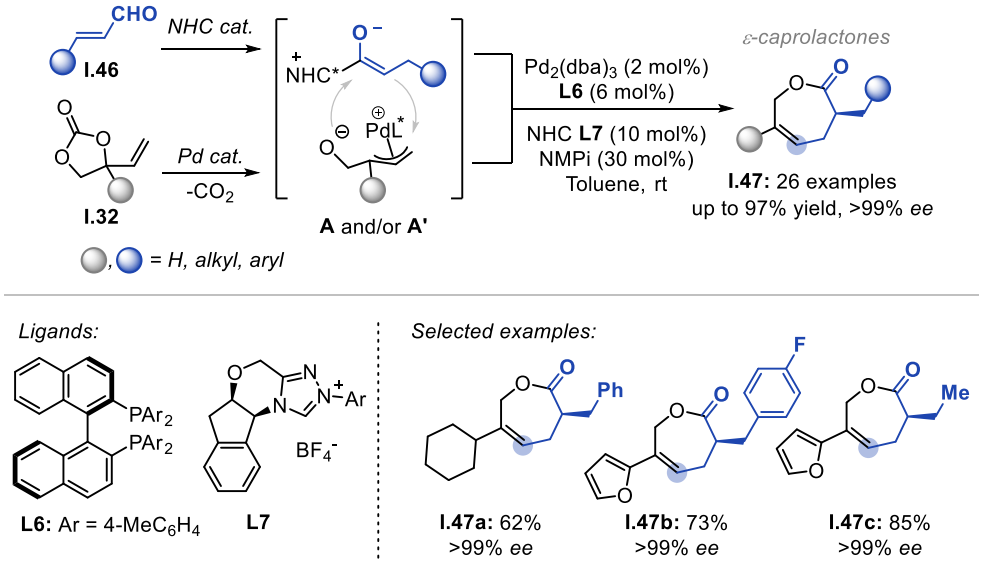
Following these reports, novel decarboxylative cycloaddition concepts have recently emerged. As a result, analogous VCC-involved [5+*n*] cycloadditions (with *n* being 2, 3 or 4) were developed for the efficient synthesis of oxygen-containing seven-,[55] eight-[56] and nine-membered heterocycles.[57] For example, the Glorius group developed in 2018 a cooperative

55 [5+2] cycloadditions: (a) Singha, S.; Patra, T.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc*. **2018**, *140*, 3551-3554. (b) Wei, Y.; Liu, S.; Li, M. M.; Li, Y.; Lan, Y.; Lu, L. Q.; Xiao, W. J. *J. Am. Chem. Soc*. **2019**, *141*, 133-137. (c) Zhao, H. W.; Du, J.; Guo, J. M.; Feng, N. N.; Wang, L. R.; Ding, W. Q.; Song, X. Q. *Chem. Commun*. **2018**, *54*, 9178-9181. (d) Yanga, Y.; Yang, W. *Chem. Commun*. **2018**, *54*, 12182-12185.

56 [5+3] cycloadditions: (a) Yuan, C.; Wu, Y.; Wang, D.; Zhang, Z.; Wang, C.; Zhou, L.; Zhang, C.; Song, B.; Guo, H. *Adv. Synth. Catal*. **2018**, *360*, 652-658.

57 [5+4] cycloadditions: (a) Das, P.; Gondo, S.; Nagender, P.; Uno, H.; Tokunaga, E.; Shibata, N. *Chem. Sci*. **2018**, *9*, 3276-3281. (b) Gao, X.; Xia, M.; Yuan, C.; Zhou, L.; Sun, W.; Li, C.; Wu, B.; Zhu, D.; Zhang, C.; Zheng, B.; Wang, D.; Guo, H. *ACS Catal*. **2019**, *9*, 1645-1654.

N-heterocyclic carbene (NHC)/palladium-catalyzed [5+2] cycloaddition of vinyl cyclic carbonates **I.32** and α,β-unsaturated aldehydes **I.46** (Scheme I-11).[55a] Considering the tremendous potential that *N*-heterocyclic carbenes (NHCs) have demonstrated in umpolung strategies, the authors proposed the *in situ* formation of a nucleophilic enolate in the presence of the NHC catalyst, and subsequent addition to provide access to enantioenriched ε-caprolactones **I.47**. A comprehensive investigation of the mechanism supported the postulated dual catalytic process, were the NHC catalyst is operating independently and does not bind to the TM-catalyst.

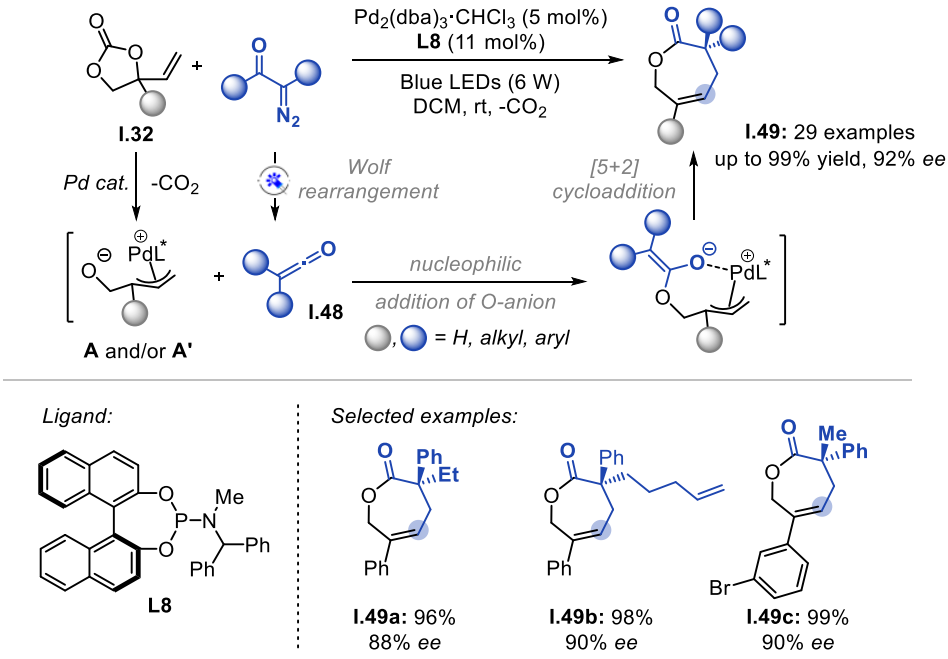


Scheme I-11. A cooperative NHC/Pd catalyzed enantioselective annulation strategy of VCCs. (NMPi stands for N-Methylpiperidine).

In the beginning of 2019, Xiao and co-workers achieved another important milestone in the field. They merged for the first time visible-light photoactivation and palladium catalysis to perform a [5+2] cycloaddition of VCCs **I.32** with photogenerated reactive ketene intermediates **I.48** that allowed the synthesis of ε-caprolactones bearing a chiral quaternary stereocenter (Scheme I-12).[55b] The trapping of the Pd-allyl intermediates **A** and/or **A′** with highly reactive and unstable coupling partners such as ketenes represented a hitherto underexplored and challenging goal in this chemistry. The traditional generation of ketenes is generally performed from the corresponding acyl chlorides and amines via thermally controlled reactions, a strategy that is incompatible with TM-catalysis. Moreover, these highly electron-deficient species are

prone to decomposition in the presence of palladium species.[58] However, they found that the sequential visible light-induced Wolff rearrangement and Pd-catalyzed asymmetric [5+2] cycloaddition of generated ketene species with VCCs could be efficiently carried out under mild conditions.

The initial reaction between VCCs **I.32** and a Pd(0) catalyst generates a Pd-containing π-allyl dipolar intermediate **A** and/or **A'**, and irradiation of α-diazoketones with visible light produces the requisite ketene species **I.48** via a Wolff rearrangement. Then, the nucleophilic addition of the oxoanion of intermediate **A** and/or **A'** to the ketene followed by intramolecular asymmetric allylic alkylation of the intermediate enolate species furnishes the desired ε-caprolactones. Regarding the regioselectivity in the ring-closing step, in which the terminal attack leads to the desired 7-membered ring and the inner attack produces the undesired 5-membered ring product, as demonstrated in Zhao work,[54] the use of VCCs as 1,5-dipolar synthons is feasible by choosing appropriate palladium catalytic system.

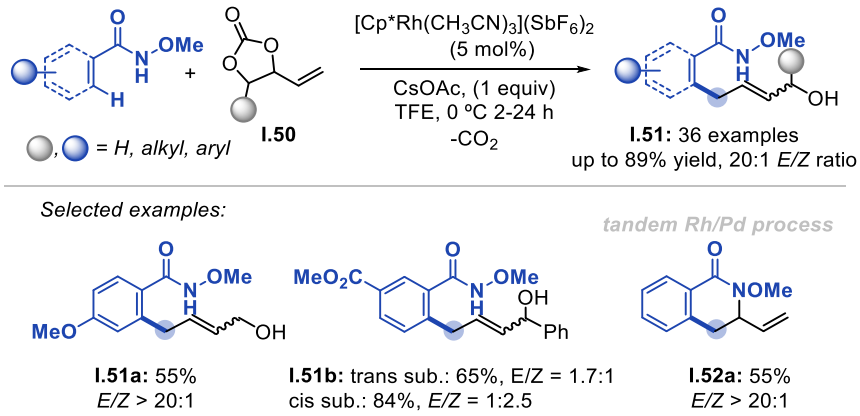


Scheme I-12. Sequential visible-light photoactivation/Pd-catalyzed [5+2] cycloaddition of VCCs.

58 (a) Kumar, P.; Troast, D. M.; Cella, R.; Louie, J. *J. Am. Chem. Soc*. **2011**, *133*, 7719-7721. (b) Wack, H.; Drury, W. J., Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett*. **1999**, *1*, 1985-1988.

Functionalized cyclic carbonates, such as VCCs, have been also applied as electrophilic reagents in decarboxylative C–H functionalization reactions over the last years. The direct functionalization of inert C–H bonds has been recognized as a successful approach to streamline the synthesis of pharmaceuticals and natural products.[59] As this chemistry is remotely relevant to the scope of this thesis, only some notorious cases will be mentioned here.

The use of VCCs as allylation reagents was first introduced in the Rh(III)-catalyzed C–H functionalization of different aromatic compounds bearing miscellaneous directing groups (DGs).[60] In these cases, VCCs **I.50** can be considered as synthetic equivalents of allylic alcohols. Notably, the resulted allylated arenes **I.51** are valuable synthons that can undergo cyclization under palladium catalysis and afford as such vinyl-substituted heterocycles as depicted for **I.52a** (Scheme I.13).[61]



Scheme I-13. Rh(III)-catalyzed C–H allylation using VCCs.

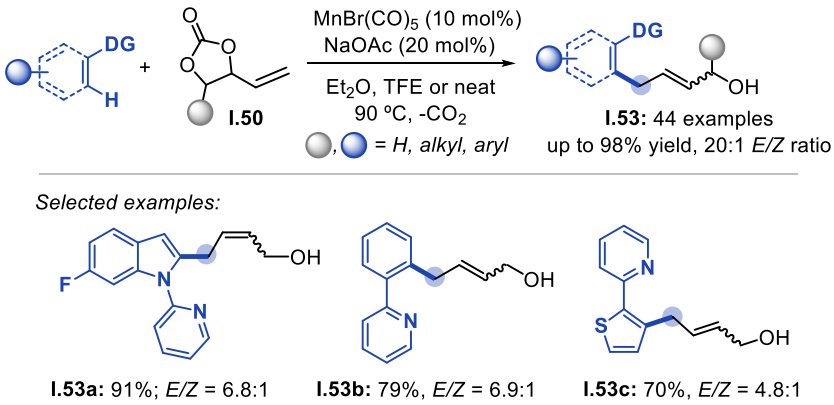
In recent years, however, C–H activation chemistry using non-precious metals (*i.e.* Mn and Co) has conquered a more prominent position in this area. For example, seminal contributions from Ackermann and Glorius report the use of Mn(I) and Co(III) catalysts for the

59 (a) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal*. **2016**, *6*, 498-525. (b) Gao, K.; Yoshikai, N. *Acc. Chem. Res*. **2014**, *47*, 1208-1219.

60 (a) Zhang, S. S.; Wu, J. Q.; Lao, Y. X.; Liu, X. G.; Liu, Y.; Lv, W. X.; Tan, D. H.; Zeng, Y. F.; Wang, H. *Org. Lett*. **2014**, *16*, 6412-6415. (b) Zhang, S. S.; Wu, J. Q.; Liu, X.; Wang, H. *ACS Catal*. **2015**, *5*, 210-214.

61 (a) Sharma, S.; Han, S. H.; Oh, Y.; Mishra, N. K.; Han, S.; Kwak, J. H.; Lee, S. Y.; Jung, Y. H.; Kim, I. S. *J. Org. Chem*. **2016**, *81*, 2243-2251. (b) Sharma, S.; Shin, Y.; Mishra, N. K.; Park, J.; Han, S.; Jeong, T.; Oh, Y.; Lee, Y.; Choi, M.; Kim, I. S. *Tetrahedron* **2015**, *71*, 2435-2441.

functionalization of C(sp^2)-H bonds in several types of arenes (**I.53**, Scheme I-14) and are representative examples where VCCs (**I.50)** are employed as formal allylation reagents.[62, 63, 64]



Scheme I-14. Mn(I)-catalyzed C–H allylation using VCCs.

❑ Reactions of VCCs with nucleophiles

Complementary to the utility of VCCs for the synthesis of chiral heterocycles via coupling with electrophiles, the reactivity of VCCs in the presence of nucleophiles has allowed to design attractive methods for the stereoselective and enantioselective preparation of stereodefined acyclic allylic scaffolds.[21] The TM-catalyzed conversions of VCCs in the presence of nucleophiles were firstly introduced in the early 1990s, when VCCs arose as synthetic equivalents of vinyl epoxides as the reactivity of both allylic surrogates proved to be quite different since the choice of the leaving group has a dramatic impact in the resultant olefin geometry of the final product.[65] Nevertheless, since these initial works the reaction of VCCs with various nucleophiles via π-allyl palladium complexes has remained dormant until recently.

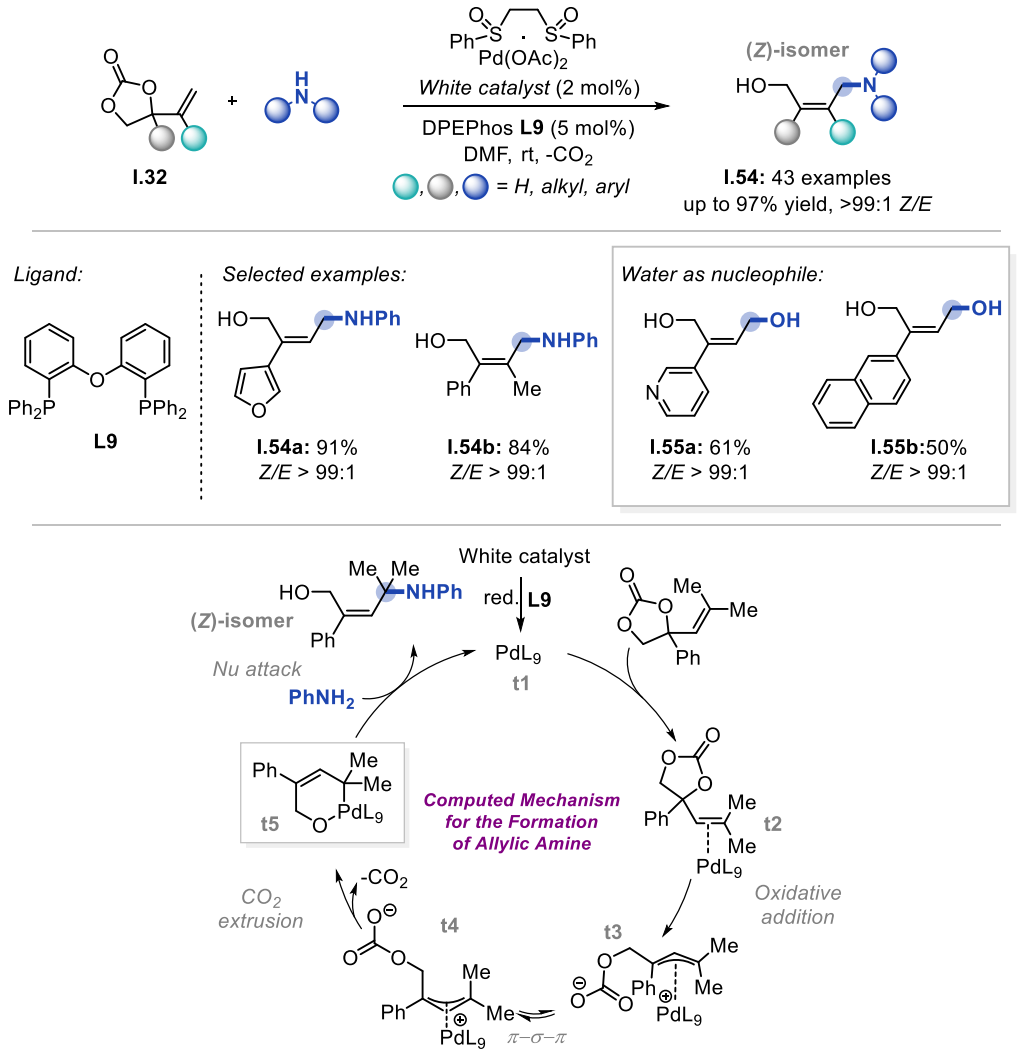
62 (a) Wang, H.; Lorion, M. M.; Ackermann, L. *Angew. Chem. Int. Ed*. **2017**, *56*, 6339-6342. (b) Lu, Q.; Klauck, F. J. R.; Glorius, F. *Chem. Sci*. **2017**, *8*, 3379-3383.

63 Jiang, X.; Chen, J.; Zhu, W.; Cheng, K.; Liu, Y.; Su, W. K.; Yu, C. *J. Org. Chem*. **2017**, *82*, 10665-10672.

64 Wang, H.; Lorion, M. M.; Ackermann, L. *ACS Catal*. **2017**, *7*, 3430-3433.

65 (a) Trost, B. M.; Granja, J. R. *Tetrahedron Lett*. **1991**, *32*, 2193-2196. (b) Mizojiri, R.; Kobayashi, Y. *J. Chem. Soc. Perkin Trans. 1*. **1995**, 2073-2075. (c) Rang, S. K.; Kim, S. G.; Lee, J. S. *Tetrahedron Asymmetr*. **1992**, *3*, 1139-1140.

In 2016, our group reported a Pd-catalyzed regio- and stereoselective functionalization of VCCs with amines and other weak nucleophiles such as water towards the synthesis of tri- and tetra-substituted (*Z*)-configured linear allylic amines (**I.54**)[66] and (*Z*)-1,4-but-2-ene diols (**I.55**)[67] in high yields and with excellent levels of stereoselectivity, respectively (Scheme I-15).



Scheme I-15. Pd-catalyzed decarboxylative amination/hydration of VCCs affording (*Z*)-allylic scaffolds.

66 Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc.* **2016**, *138*, 11970-11978.

67 Guo, W.; Martínez-Rodríguez, L.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 11037-11040.

The origin of the stereocontrol in the Pd-catalyzed synthesis of (*Z*)-configured allylic amines **I.54** was investigated by computational methods and the main features of the computed mechanism for the formation of (*Z*)-configured allylic amines are shown in the simplified Scheme I-15. We recognized that the alkoxide group of the decarboxylated VCCs play a role in both the stereoselective outcome and the site-selective nucleophilic attack on the π-allyl-Pd component, acting as a base towards the activation of pro-nucleophiles without the need for further additives.[59]

The initial steps of the reaction are those expected, *i.e.*, the reduced form of the White catalyst **t1** coordinates the vinyl double bond to yield intermediate **t2**. Then an oxidative cleavage of the cyclic carbonate takes place. There is a formal transfer of two electrons from the Pd center to the organic substrate, and the resulting intermediate **t3** contains an η^3-allylic group attached to an open carbonate. Isomerization of **t3** through a π-σ-π interconversion process leads to intermediate **t4**. It is worth noting that at this stage it is far from obvious how stereoselectivity can be achieved from this open chain species. Intermediate **t4** contains an allylic group arranged in a way leading to the (*Z*)-configuration in the final product. However, the key to the stereoselectivity is in the continuation of the process: Computational analysis afforded that the extrusion of a CO_2 molecule results in the formation of intermediate **t5** containing a six-membered palladacyclic ring. The arrangement of the substituents in intermediate **t5** is such that subsequent nucleophilic attack by the aniline results in release of a stereodefined product molecule and recovery of the catalyst **t1**. The formation of intermediate **t5** thus results key to the overall selectivity of the process, where the employment of a bisphosphine ligand (DPEPhos **L9**), is crucial towards the selective formation of such intermediate.

Therefore, DFT calculations revealed the rationale of the excellent stereocontrol (*Z*/*E* > 99:1) in these transformations and the transition state **t(4-5)‡**, with a lower barrier, leading to a (*Z*)-configured six-membered palladacycle **t5** was computed as a crucial intermediate toward a kinetic differentiation between the pathways leading to either the (*E*)- or (*Z*)-product, with Pd−O chelation as a stabilizing structural feature. This can be further rationalized when comparing with the pathway leading to (*E*)-product that proceeds through an epoxide intermediate (**t9**), and requiring significantly higher energy for the CO_2 release step (Figure I-5).[66,]

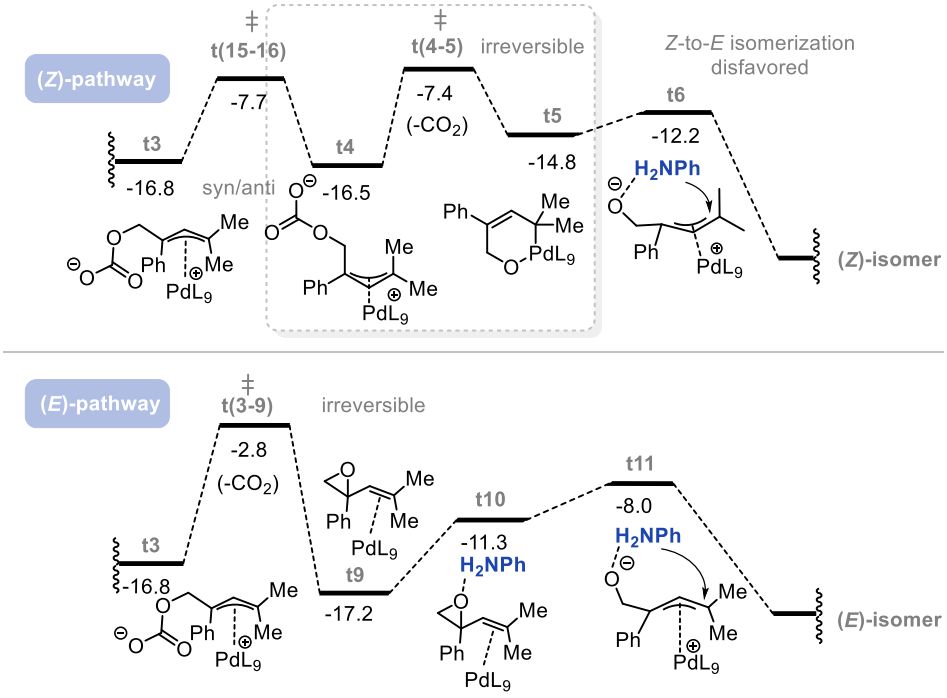


Figure I-5. Simplified computed pathways towards the (*Z*)- and (*E*)-products.

This new mode of stereocontrol provides further synthetic potential for the functionalization of allylic surrogates, giving prospectively access to various types of stereopure and functionalized olefin building blocks being of general synthetic interest.[68, 69]

One of the major challenges in palladium-catalyzed allylic substitution chemistry is the control over the regioselectivity in the alkylation step.[70] Concerning the Pd-catalyzed nucleophilic substitution of VCCs, the allyl-Pd complex formed *in situ* can be attacked by

68 In addition to the investigations disclosed herein, our group contributed to the expansion of this concept by using other pro-nucleophiles such as phenols, nitroalkanes and N-sulfonylhydrazones, see: (a) Xie, J.; Guo, W.; Cai, A.; Escudero-Adán, E. C.; Kleij, A. W. *Org. Lett.* **2017**, *19*, 6388-6391. (b) Cristòfol, À.; Escudero-Adán, E. C.; Kleij, A. W. *J. Org. Chem.* **2018**, *83*, 9978-9990. (c) Deng, L.; Kleij, A. W.; Yang, W. *Chem. Eur. J.* **2018**, *24*, 19156-19161.

69 Using a cyclic carbonate with a terminal substituted vinyl group, it is possible to achieve asymmetric decarboxylative alkylation of VCCs at the terminal site of the Pd-allyl intermediate: Wei, X.; Liu, D.; An, Q.; Zhang, W. *Org. Lett.* **2015**, *17*, 5768-5771.

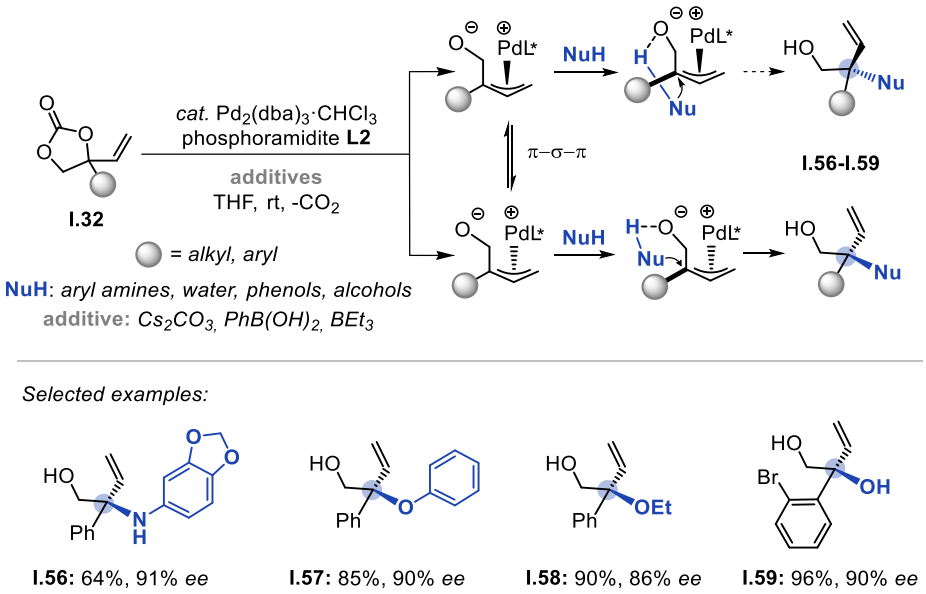
70 (a) Trost. B. M.; Lee, C. *Asymmetric Allylic Alkylation Reactions.* Wiley-VCH, New York, **2000**. (b) Kazmaier, U.; Alexakis, A. *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*. Springer-Verlag Berlin, Heidelberg, **2012**. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395-422; (d) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921-2943. (e) Lu Z.; Ma, S. *Angew. Chem. Int. Ed*. **2008**, 47, 258-297.

nucleophiles at both termini of the allylic system posing thus a regioselectivity issue. Control over the regioselectivity is influenced by several factors. In general, the nucleophilic attack on the sterically more crowded internal carbon center (branched isomer) of the Pd-allyl species is disfavored. The terminal position (giving rise to the linear isomeric product) is sterically less hindered, and thus the regioselectivity is typically biased by steric factors imposed by the ligand, substrate and nucleophile resulting preferably in linear rather than branched allylic products. Reversing this preferred selectivity thus needs to be accomplished with the engineering of alternative synthetic strategies and/or ligands.

In this sense, we recently demonstrated that conducting the abovementioned Pd-catalyzed allylic amination of VCCs in the presence of a chiral, bulky phosphoramidite ligand (**L2**) it is possible to reverse the regioselectivity towards the branched product (**I.56**-**I.59**). As such, our group reported the first general regio- and enantioselective synthesis of α,α-disubstituted allylic *N*-aryl amines **I.56** (Scheme I-16).[71] This catalytic process features ample scope in aryl amines with products typically obtained in high yields and with high enantioselectivities. Mechanistic studies to uncover the origin of both regio- and enantioselectivity are currently being performed in our group.

The synthetic importance of controlling the regio- and enantioselectivity towards chiral branched allylic compounds using a Pd catalyst could be further extended to the use of oxygen-based nucleophiles such as phenols (**I.57**),[68a] alcohols (**I.58**) and water (**I.59**).[72] In the case of phenolic nucleophiles, the addition of cesium carbonate (Cs_2CO_3) proved to be necessary in order to increase the yields of the corresponding aryl ethers. In the case of water and alcohol-based nucleophiles, Zhang and co-workers showed that the attack on the more crowded internal carbon required the presence of a catalytic amount of a boron compound. In this latter case, the formation of a boronate intermediate helps to stir the formation of a branched-alcohol or ether product (Scheme I-16).

71 Cai, A.; Guo, W.; Martínez-Rodríguez, L.; Kleij, A. W. *J. Am. Chem. Soc*. **2016**, *138*, 14194-14197.
72 Khan, A.; Khan, S.; Khan, I.; Zhao, C.; Mao, Y.; Chen, Y.; Zhang, Y. J. *J. Am. Chem. Soc*. **2017**, *139*, 10733-10741.



Scheme I-16. Pd-catalyzed decarboxylation of VCCs affording enantioenriched branched allylic products.

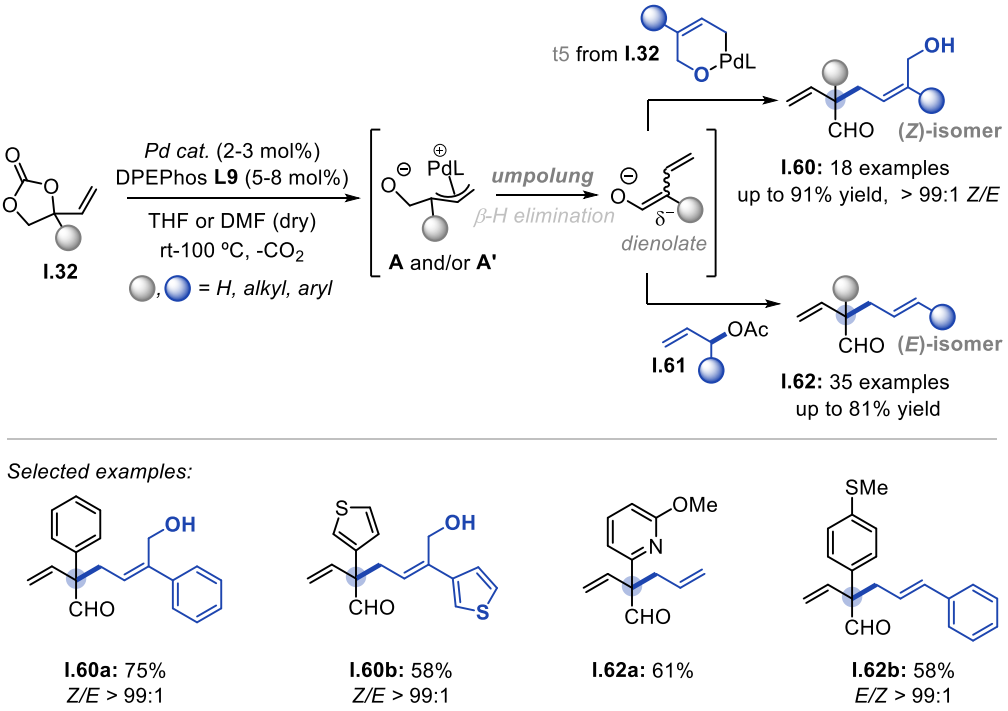
❑ Umpolung reactivity of VCCs

While most reports are based on the use of VCCs as electrophiles, umpolung reactivity based on VCCs producing *in situ* nucleophiles is rare. Recently, our group developed a unique umpolung-based palladium-catalyzed decarboxylation reaction that converts readily available VCCs to scaffolds containing a synthetically challenging, but moreover highly functional quaternary carbon center (**I.60**) (Scheme I-17).[73] These compounds also feature an aldehyde functionality and a stereodefined (*Z*)-allylic alcohol; fragments tan can be selectively post-modified to access other functionalized compounds.

Mechanistic investigations including control experiments and DFT calculations offered a detailed rationale and rather complex pathway for these transformations. Micro-kinetic modeling results show that the pathway towards the main product depends on subtle electronic effects in the VCC substrate. First, one equivalent of VCC forms a β-unsaturated aldehyde through β-H elimination in the π-allyl palladium intermediate, while a second VCC is converted into a six-membered palladacycle (see **t5**) after decarboxylation. Then, the palladacycle activates the *in*

73 Guo, W.; Kuniyil, R.; Gómez, J. E.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc.* **2018**, *140*, 3981-3987. A brief description of this project can be also found in the annex of this thesis.

situ formed β-unsaturated aldehyde allowing for nucleophilic attack by a dienolate species after proton transfer to the palladacycle (not shown), yielding the final product **I.60**. Later on, this umpolung strategy was further extended by the Zhai group using allylic acetates **I.61** as the electrophilic partners thus producing similar cross-coupling products **I.62** (Scheme I-17).[74]

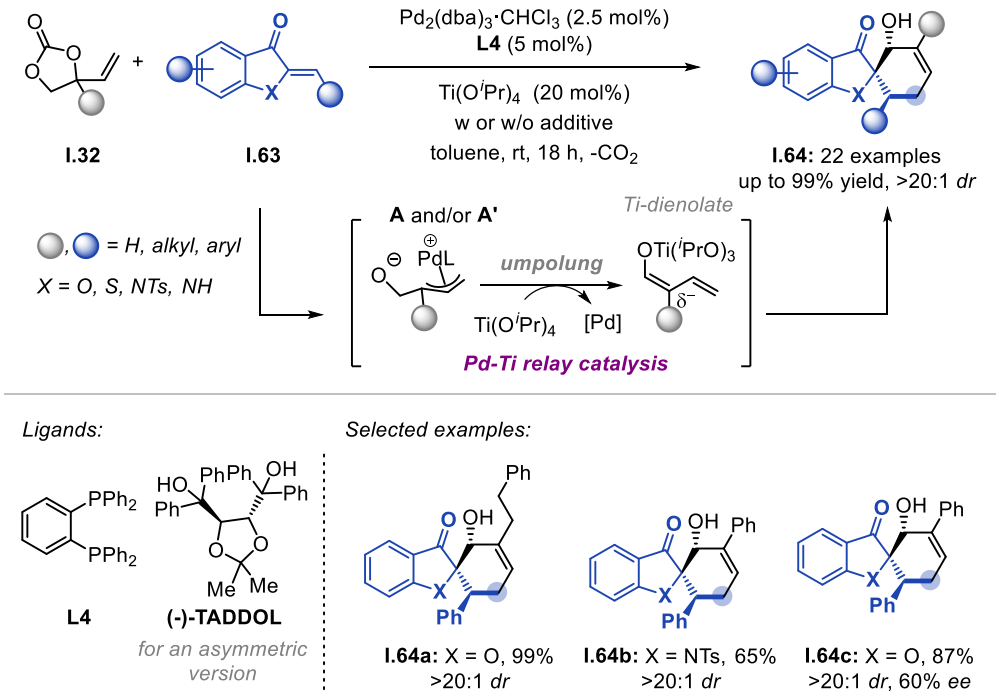


Scheme I-17. Pd-catalyzed decarboxylative umpolung reactivity of VCCs.

Shortly after the conclusion of our study, the Zhao group reported another sophisticated umpolung reactivity of VCCs through Lewis acid-assisted palladium catalysis.[75] In this case, the initially formed π-allyl palladium intermediate was transformed into a dienolate species by reacting with $Ti(O^iPr)_4$. Subsequently, the Ti-bound dienolate was trapped with enone electrophiles **I.63** undergoing highly diasteroselective [4+2] cycloadditions towards the formation of the [6,5] spirocycles **I.64** with a wide range of different functionalities in high yields and excellent diastereoselectivities (Scheme I-18). Remarkably, the authors managed to develop the reaction in an enantioselective fashion. Nonetheless, enantioselectivity is only observed

74 Wang, H.; Qiu, S.; Wang, S.; Zhai, H. *ACS Catal*. **2018**, *8*, 11960-11965.
75 Yang, L. C.; Tan, Z. Y.; Rong, Z. Q.; Liu, R.; Wang, Y. N.; Zhao, Y. *Angew. Chem. Int. Ed*. **2018**, *57*, 7860-7864.

when a chiral co-catalyst such as Ti[(-)-TADDOL] is employed, which provides additional support for the presence of a Ti-bound dienolate species in the stereodetermining cycloaddition step.

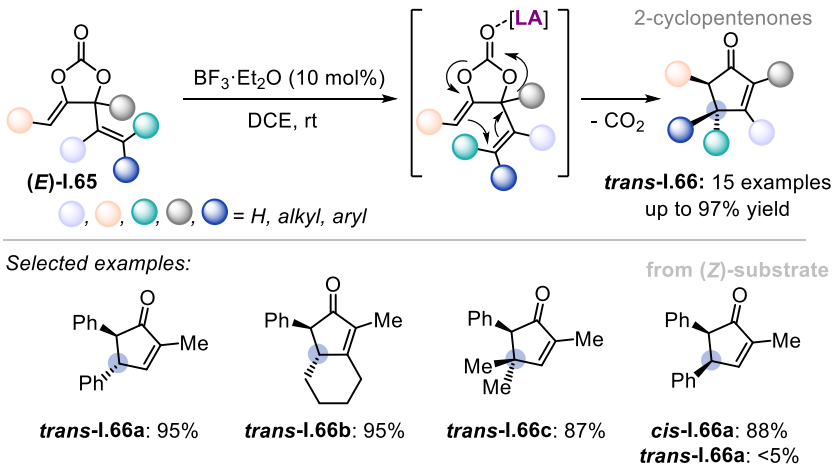


Scheme I-18. Pd-catalyzed Lewis-acid assisted decarboxylative umpolung reactivity of VCCs.

❑ Rearrangements using VCCs

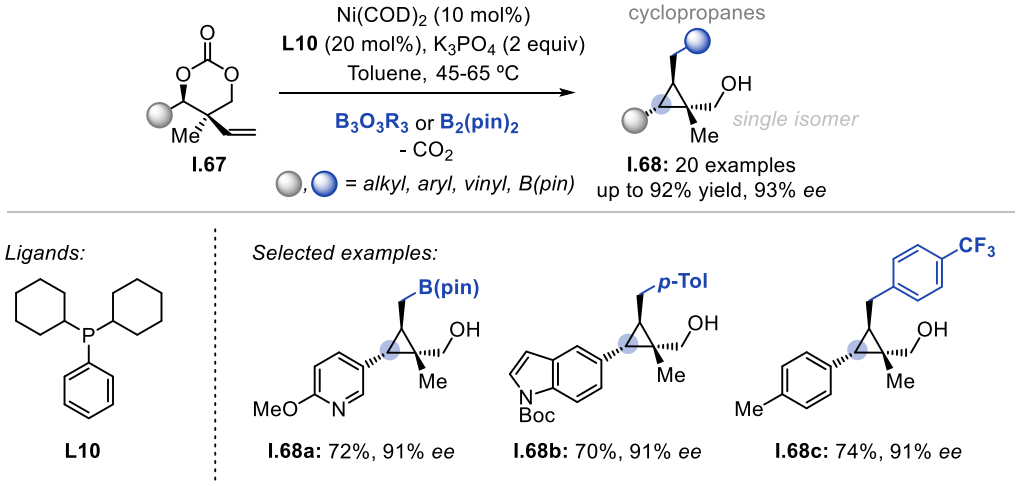
Apart from transition-metal-based catalysis using cyclic organic carbonates as electrophiles or nucleophiles, other methods such as rearrangement approaches are attractive to give value-added products and have been scrutinized in parallel. In 2017, Yamada and co-workers employed a simple Lewis acid ($BF_3{\cdot}Et_2O$) to develop a decarboxylative Nazarov-type cyclization of stereodefined *E*- or *Z*-configured VCCs such as **(*E*)-I.65**.[76] Noteworthy, these stereospecific and regioselective rearrangements lead to multifunctionalized *trans*-2-cyclopentenone motifs ***trans*-I.66** and/or ***cis*-I.66**, where the relative configuration of the product is attributed to the geometry of the substituted allyl group in the initial cyclic carbonate derivative (Scheme I-19).

76 Komatsuki, K.; Sadamitsu, Y.; Sekine, K.; Saito, K.; Yamada, T. *Angew. Chem. Int. Ed*. **2017**, *56*, 11594-11598.



Scheme I-19. Lewis acid catalyzed decarboxylative Nazarov cyclization using VCCs. (LA =Lewis acid).

Earth-abundant transition metals, such as nickel, have also been introduced to perform rearrangements of VCC substrates. The Krische group described a set of conditions that promote the stereospecific synthesis of cyclopropanes (**I.68**) starting from enantioenriched 6-membered VCCs (**I.67**) and boroxines or B_2pin_2 (Scheme I-20).[77] Although, a detailed and clear understanding of the origin of the stereospecificity in this reaction is unfortunately still lacking.



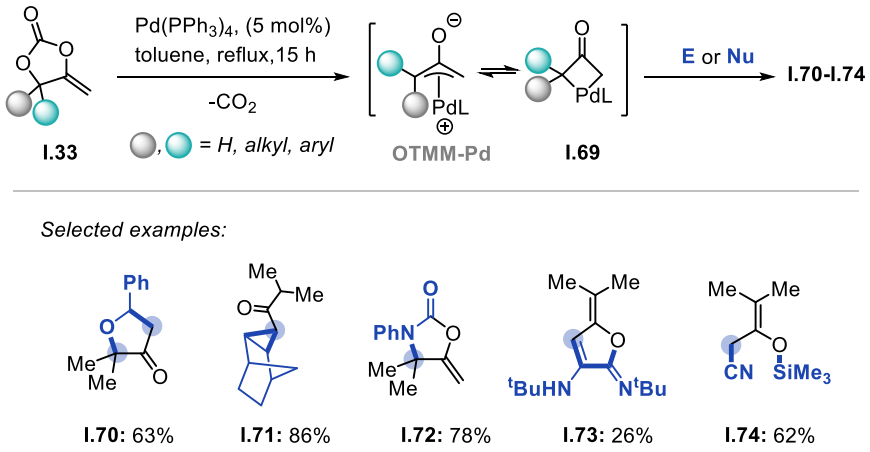
Scheme I-20. Ni-catalyzed stereospecific decarboxylative conversion of VCCs into cyclopropanes.

77 Guo, Y. A.; Liang, T.; Kim, S. W.; Xiao, H.; Krische, M. J. *J. Am. Chem. Soc.* **2017**, 139, 6847-6850.

I.3.2 Alkenyl cyclic carbonates (ACCs)

In addition to VCCs, alkenyl cyclic carbonates (ACCs) have also employed as allylic surrogates. Trost and co-workers pioneered the use of ACCs **I.33** and anticipated their utility for the Pd-catalyzed generation of oxatrimethylenemethane-palladium (OTMM-Pd) intermediates.[78] It was proposed that these zwitterionic intermediates are in dynamic equilibrium with a η^2-palladacyclobutanone intermediate such as **I.69**, and possess both nucleophilic and electrophilic character. Consequently, a variety of electrophiles and nucleophiles may trap these reactive intermediates.

For instance, in 1991 the Inoue group showed that heating a mixture of ACCs **I.33** and aromatic aldehydes in the presence of catalytic amounts of a Pd(II) complex give rise to dihydrofuranone derivatives **I.70** (Scheme I-21).[79] Building on these initial findings, the Murai group extended the reaction scope to related cycloadditions. The *in situ* trapping of the OTMM-Pd intermediate with both electrophiles and nucleophiles produced functionalized norbornenes (**I.71**), oxazolidinones (**I.72**), 2,5-dihydrofurans (**I.73**) and silyl enol ethers (**I.74**) (Scheme I-21).[80]



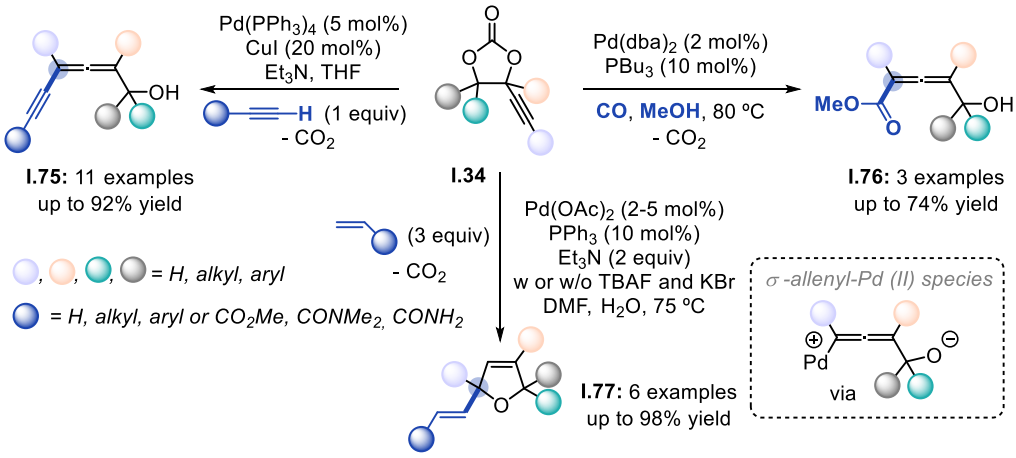
Scheme I-21. Pd-catalyzed generation of OTMM-Pd species from ACCs and their conversion into various products.

78 Trost, B. M.; Chan, D. T. *J. Org. Chem*. **1983**, *48*, 3346-3347.
79 Inoue, Y.; Matsushita, K.; Yen, I. F.; Imaizumi, S. *Chem. Lett*. **1991**, *20*, 1377-1378.
80 Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem*. **1993**, *58*, 1173-1177.

Remarkably, application of 6-membered alkenyl cyclic carbonates as substrates is also feasible under Pd-catalyzed decarboxylative conditions as demonstrated by the Hayashi group.[81] Last but not least, similar to VCCs, ACCs have also been employed as synthetic pro-electrophiles in the rhodium-catalyzed C–H bond functionalization of aryl pyridines and aryl amides.[82]

I.3.3 Alkyne-substituted cyclic carbonates

In contrast to VCCs and ACCs, the literature on metal catalyzed methods that use alkynyl-substituted cyclic carbonates is much more limited. Seminal studies performed in 1994 by Bruneau, Dixneuf and co-workers paved the way for the development of recent methodologies using alkyne-substituted cyclic carbonates such as **I.34**. Specifically, these studies showed that Pd-catalyzed coupling of **I.34** with multiple reaction partners occurs via a common σ-allenyl-Pd(II) species. These intermediates can undergo insertion of different electrophiles into the C–Pd bond and selectively afford both acyclic and cyclic products. They investigated the synthesis of α-hydroxyallenes **I.75** by cross-coupling with alkynes,[83] the synthesis of allenic carboxylic esters **I.76** by trapping of carbon monoxide[84] and the cyclization of electron-deficient alkenes to obtain dihydrofurans **I.77** (Scheme I-22).[85]



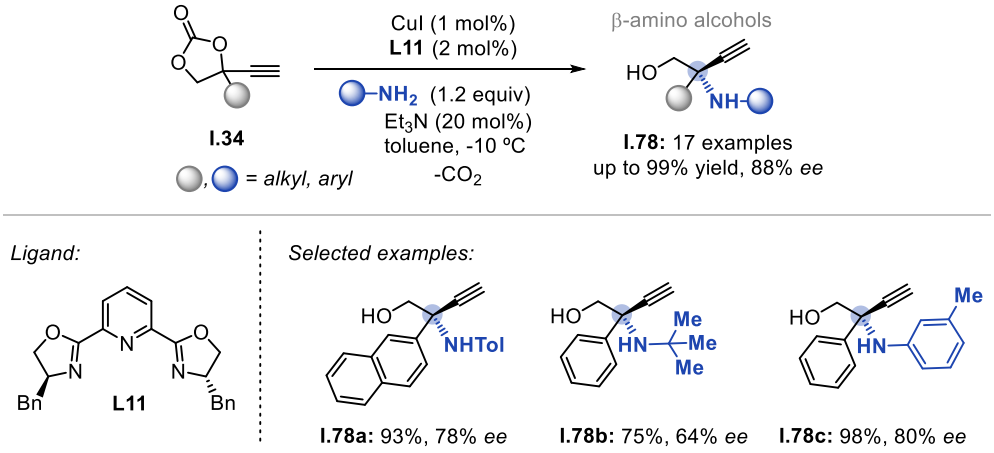
Scheme I-22. Pd-catalyzed decarboxylative coupling of alkyne-substituted cyclic carbonates.

81 Shintani, R.; Moriya, K.; Hayashi, T. *Chem. Commun*. **2011**, *47*, 3057-3059.
82 Hara, Y.; Onodera, S.; Kochi, T.; Kakiuchi, F. *Org. Lett*. **2015**, *17*, 4850-4853.
83 Darcel, C.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Chem. Commun*. **1994**, 1845-1846.
84 Darcel, C.; Bruneau, C.; Dixneuf, P. H. *Synlett*. **1996**, 218-220.
85 Darcel, C.; Bruneau, C.; Albert, M.; Dixneuf, P. H. *Chem. Commun*. **1996**, 919-920.

Furthermore, the same researchers also reported the direct hydrogenolysis of alkyne-substituted cyclic carbonates with triethyl ammonium formate, in the presence of a Pd(0) catalyst.[86] Depending on the phosphine ligand employed, α-hydroxyallenes or homopropargylic alcohols were selectively obtained.

On the other hand, complementary to vinyl cyclic carbonates that have been applied successfully as allylic surrogates in palladium-catalyzed decarboxylative reactions (section I.3.1), alkyne-substituted cyclic carbonates have emerged as versatile propargylic electrophiles for related copper-catalyzed decarboxylative propargylic substitution chemistry. Over the past decades, copper-catalyzed propargylic substitution and cycloaddition reactions via copper-allenylidene complexes have emerged as a strategy for the construction of complex molecules.[87] However, the role of these functionalized carbonates serving as synthons in this chemistry has never been investigated until most recently.

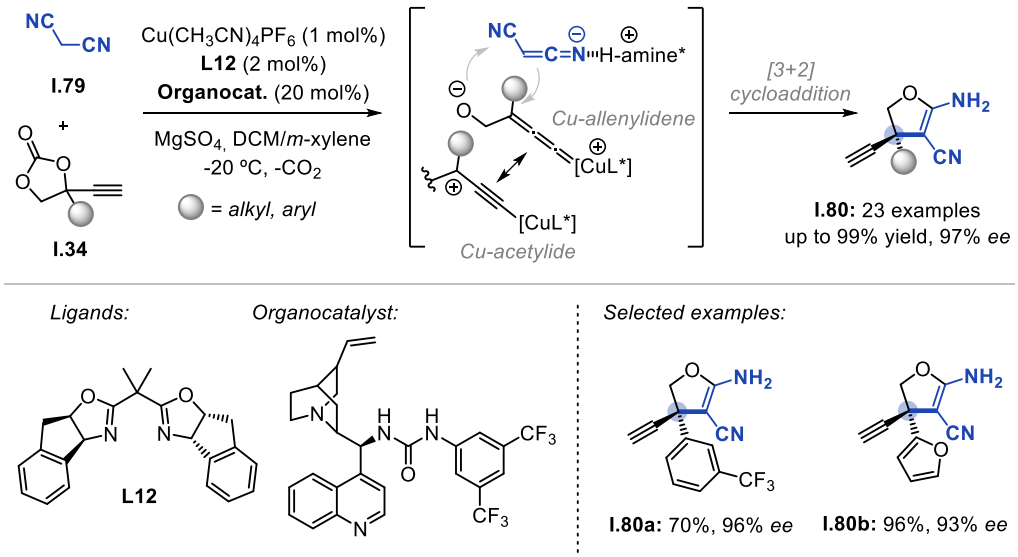
In this context, Zhang and co-workers reported the first copper-catalyzed asymmetric decarboxylative propargylic substitution reaction based on alkyne-substituted cyclic carbonates for the enantioselective construction of β-amino alcohols **I.78**.[88] Interestingly, this strategy allowed to convey a complementary protocol for the synthesis of β-amino alcohols to the one based on palladium-catalyzed allylic amination (Scheme I-23 vs Scheme I-16).



Scheme I-23. Cu-catalyzed decarboxylative propargylic amination of alkyne-substituted cyclic carbonates.

86 Darcel, C.; Bartsch, S.; Bruneau, C.; Dixneuf, P. H. Synlett. **1994**, 457-458.
87 For a general overview: Zhang D.-Y.; Hu, X.-P. *Tetrahedron Lett*. **2015**, *56*, 283-295.
88 Tian, L.; Gong, L.; Zhang, X. *Adv. Synth. Catal*. **2018**, *360*, 2055-2059.

Latter, the Song group also achieved the first applications of alkyne-substituted cyclic carbonates as dipole precursors in copper-catalyzed asymmetric cycloaddition reactions (Scheme I-24). The authors reported an asymmetric [3+2] cycloaddition reaction of alkyne-substituted cyclic carbonates **I.34** with malononitrile (**I.79**). Malononitrile was chosen as suitable reaction partner due to its high reactivity as a dipolar compound in the presence of amine catalysts such as urea-cinchona alkaloids. While the copper complex mediates the decarboxylation of the carbonate precursor to *in situ* form a copper-allenylidene species, a nucleophilic intermediate from malononitrile is generated in the presence of the chiral organocatalyst. This amine/copper mediated cooperative reaction provided a new asymmetric strategy to access highly substituted dihydrofurans (**I.80**) with an all carbon quaternary stereocenter bearing synthetically versatile terminal alkyne and cyano groups (Scheme I-24).[89]



Scheme I-24. Cu-catalyzed asymmetric [3+2] cycloaddition of alkyne-substituted cyclic carbonates.

These contributions represent rare though highly valuable examples describing the use of alkyne-substituted cyclic carbonates. Thus, it can be expected that alkyne-substituted cyclic carbonates provide meaningful platform molecules for related Cu-catalyzed decarboxylative transformations. The project described in Chapter III of this doctoral thesis indeed was developed in parallel to the aforementioned contributions, as it also employs alkyne-substituted cyclic carbonates as reactive electrophiles in Cu-catalyzed propargylic substitution chemistry.

89 Zhang, Y. C.; Zhang, B. W.; Geng, R. L.; Song, J. *Org. Lett.* **2018**, *20*, 7907-7911.

I.4. Thesis aims

Organic cyclic carbonates, particularly functionalized carbonates (vinyl-, alkenyl and alkynyl-substituted COCs), have been witnessed in recent years as privileged motifs enabling facile access to structurally diverse and complex building blocks. One of the main advantages of these heterocyclic scaffolds is their ease of synthesis and their modular character making them ideally precursors for synthetic applications within organometallic catalysis.

Considering their potential, the general objective of this Doctoral Thesis was the development of new catalytic processes using functionalized COCs and other structurally related heterocycles (*e.g.*, minimally strained lactones), aimed to furnish previously inaccessible stereodefined and enantioenriched building blocks that have value in both academic and industrial settings. In these studies, TM-catalysis will offer a rich alternative platform to develop uncovered ring-opening and decarboxylative manifolds with specific impact in the prominent areas of allylic and propargylic substitution reactions. In particular, we established the following main objectives for each chapter:

In **Chapter II** we aimed to harness the ability of vinyl cyclic carbonates to behave as allylic surrogates in the presence of a palladium catalyst, to overcome the challenging stereoselective synthesis of highly functionalized (*Z*)-configured allylic thioethers and sulfones.

On the other hand, **Chapter III** was aimed to provide the first general asymmetric synthesis of tertiary propargylic sulfones, by means of a copper catalysis, using modular alkynyl-substituted cyclic carbonates as propargylic surrogates.

Lastly, in line with the previous project the goal of **Chapter IV** was the development of a general and practical copper-catalyzed asymmetric ring-opening route to enable the stereoselective assembly of previously inaccessible γ,γ-disubstituted γ-amino acids, and provide applications; using in this case structurally related alkyne-substituted lactones as precursors.

Following these general guidelines, each chapter of this thesis manuscript contains a more detailed description of its objectives.

Chapter II

Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones

The results described in this chapter have been published in:

Gómez, J. E.; Guo, W.; Kleij, A. W. *Org. Lett*. **2016**, *18*, 6042-6045

UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE SYNTHESIS OF SULFONES AND AMINO ACIDS FROM FUNCTIONALIZED HETEROCYCLES
José Enrique Gómez Pulido

II.1. Introduction

II.1.1 Organosulfur compounds

Thioethers[1] and sulfones[2] are ubiquitously distributed sulfur-containing compounds with important intermediary functions in general organic synthesis. Moreover, these classes of derivatives often show biological activities, and represent important building blocks in pharmaceutical industry. Approximately 20% of all Food and Drug Administration (FDA) approved drugs are organosulfur compounds (Figure II-1).[3]

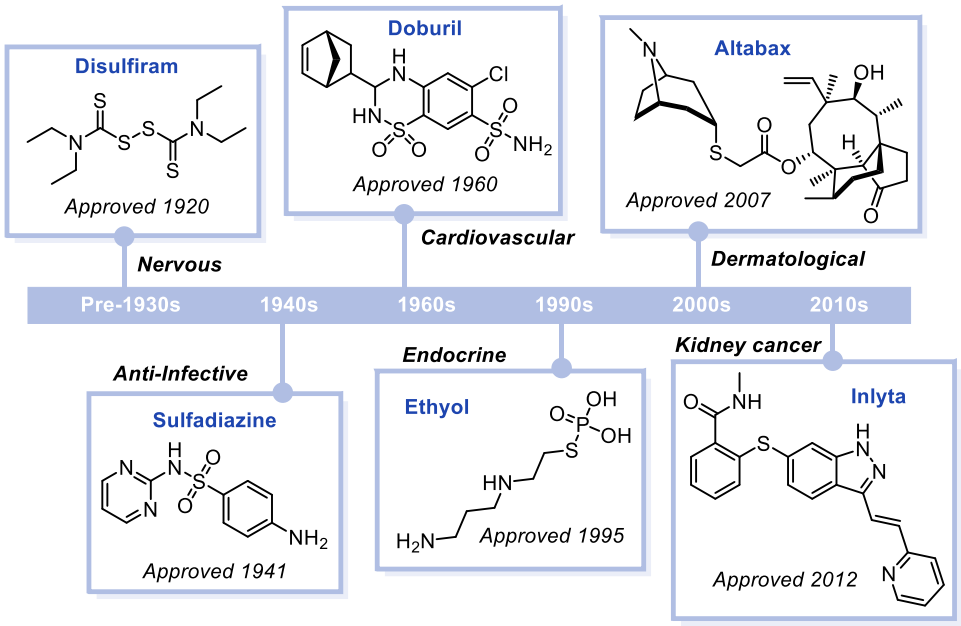


Figure II-1. Representative sulfur-containing pharmaceuticals introduced over the past century.

1 For general reviews, see: (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133-5209. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832-2842. (c) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216. (d) Scott, K. A.; Njardarson, J. T. *Top. Curr. Chem.* **2018**, *376*, 5.

2 For reviews, see: (a) Szilágyi, Á.; Fenyvesi, F.; Majercsik, O.; Pelyvás, I. S.; Bácskay, I.; Fehér, P.; Váradi, J.; Vecsernyés, M.; Herczegh, P. *J. Med. Chem.* **2006**, *49*, 5626-5630. (b) Simpkins, N. S. *Sulfones in Organic Synthesis.* Pergamon, Oxford, **1993**. (c) Toru, T.; Bolm, C. *Organosulfur Chemistry in Asymmetric Synthesis.* Wiley-VCH, Weinheim, **2008**. (d) Vogel, P.; Turks, M.; Bouchez, L.; Markovic, D.; Varela-Álvarez, A.; Sordo, J. Á. *Acc. Chem. Res.* **2007**, *40*, 931-942. (e) Trivedi, S.; Patidar, P. C.; Chaurasiya, P. K. *Pharma Chem.* **2010**, *2*, 369-377. (f) Yamada, M.; Ichikawa, T.; Ii, M.; Itoh, K.; Tamura, N.; Kitazaki, T. *Bioorg. Med. Chem.* **2008**, *16*, 3941-3958.

3 McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348-1349.

II.1.2 Allylic thioethers and sulfones

As a subclass of organosulfur compounds, both allylic thioethers and allylic sulfones have found important applications as reaction intermediates in a number of carbon-carbon bond-forming reactions.[4] Additionally, certain allylic thioethers and sulfones based on natural products and analogs have a wide range of properties[5] such as anticancer activity,[6] antibacterial behavior,[7] representing TSH receptor antagonists[8] and functioning as herbicides (Figure II-2).[9] Because of their significance, synthetic chemists continuously strive to develop versatile catalytic methods to access highly substituted allylic thioethers and sulfones.[10, 11] In this sense, thiols and oxidized derivatives have been widely utilized as nucleophiles in combination with late transition metals to afford organosulfur compounds. For decades, this has been troublesome owing to the strong coordination properties of sulfur, which is well-known to deactivate/poison late transition metal

4 (a) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc*. **2008**, *130*, 9642-9643. (b) Liu, T.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett*. **2009**, *11*, 4576-4579. (c) Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N. *Angew. Chem. Int. Ed*. **2004**, *43*, 3467-3470. (d) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem. Int. Ed*. **2001**, *40*, 1128-1130.

5 (a) Sumiyoshi, H.; Wargovich, M. *J. Cancer Res*. **1990**, *50*, 5084-5087. (b) Arora, A.; Siddiqui, I. A.; Shukla, Y. *Mol. Cancer Ther*. **2004**, *3*, 1459-1466. (c) Arunkumar, A.; Vijayababu, M. R.; Venkataraman, P.; Senthilkumar, K.; Arunakaran, *J. Biol. Pharm. Bull*. **2006**, *29*, 375-379. (d) Bernström, K.; Hammarström, S. *Biochem. Biophys. Res. Commun*. **1982**, *109*, 800-804. (e) Nakamura, H.; Wu, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y.; Higashijima, T; Miyazawa, T. *Tetrahedron Lett*. **1983**, *24*, 4105-4108. (f) Taori, K.; Paul, V. J.; Luesch, H. *J. Am. Chem. Soc.* **2008**, *130*, 1806-1807.

6 Neamati, N.; Kabalka, G. W.; Venkataiah, B.; Dayam, R. *W.O. Patent* 081966, **2007**.

7 Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem*. **2005**, *48*, 499-506.

8 Gershengorn, M. C.; Neumann, S.; Thomas, C. J.; Jaeschke, H.; Moore, S.; Krause, G.; Raaka, B.; Paschke, R.; Kleinau, G. *U.S. Patent* 203716, **2009**.

9 Muehlebach, M.; Lutz, W.; Wenger, J.; Finney, J.; Mathews, C. J.; Fawke, D. *W.O. Patent* 110308, **2008**.

10 For reviews on C−S bond formation, see: (a) Kondo, T.; Mitsudo, T.-A. *Chem. Rev*. **2000**, *100*, 3205-3220. (b) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem*. **2008**, *80*, 993-1003. (c) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev*. **2014**, *114*, 8807-8864. (d) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev*. **2015**, *44*, 291-314. (e) Yu, J.-S.; Huang, H.-M.; Ding, P.-G.; Hu, X.-S.; Zhou, F.; Zhou, J. *ACS Catal*. **2016**, *6*, 5319-5344. (f) Qian, Z.; Jiang, X. *Org. Biomol. Chem*. **2017**, *15*, 1942-1946. For a review on enzymatic C−S bond formation, see: (g) Dunbar, K. L.; Scharf, D. H.; Litomska, A.; Hertweck, C. *Chem. Rev*. **2017**, *117*, 5521-5577.

11 (a) Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc*. **1999**, *121*, 8657-8658. (b) Herkert, L.; Green, S. L. J.; Barker, G.; Johnson, D. G.; Young, P. C.; Macgregor, S. A.; Lee, A.-L. *Chem. Eur. J*. **2014**, *20*, 11540-11548. (c) Roggen, M.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 8652-8655. (d) Tanaka, S.; Pradhan, P. K.; Maegawa, Y.; Kitamura, M. *Chem. Commun*. **2010**, *46*, 3996-3998. (e) Gao, N.; Zheng, S.; Yang, W.; Zhao, X. *Org. Lett*. **2011**, *13*, 1514-1516. (f) Sun, J.; Fu, G. C. *J. Am. Chem. Soc*. **2010**, *132*, 4568-4569.

catalysts.[12] Yet, these issues have been partially overcome with recent progress in organometallic chemistry and nowadays many effective procedures are available for the synthesis of allylic thioethers and sulfones.[10, 11]

Effective routes for the preparation of these motifs include conventional allylic substitution,[13] hydrothiolation of allenes,[14] dienes[15] or alkynes[16] and more recently developed C–H bond functionalization protocols.[17] Apart from these catalytic methodologies, stoichiometric approaches have also been established as effective in this context.[18] Despite the notable progress in this area, there is a lack of efficient and mild catalytic procedures focusing on the stereoselective construction of multi-functionalized tri- and tetra-substituted allylic thioethers and derivatives thereof.

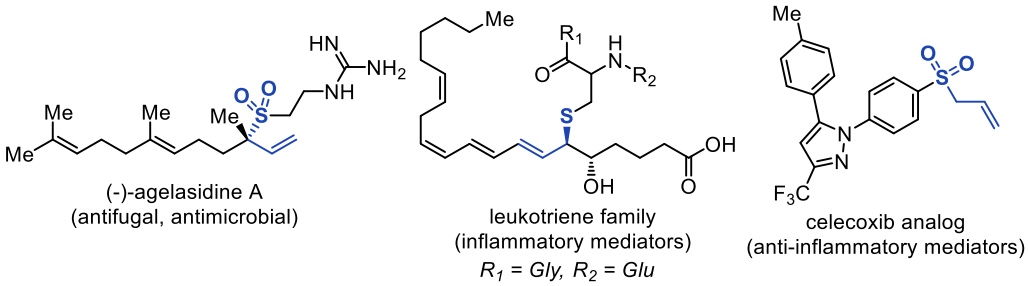


Figure II-2. Natural products and analogs containing allylic thioether and similar fragments.

Generally, the stereocontrolled introduction of various, different substituents in an olefin unit represents a huge challenge in synthetic chemistry.[19] Moreover, it is important to point out

12 Hegedus, L.; McCabe, R. W. *Catalyst Poisoning*. Marcel Dekker, New York, **1984**.

13 For some examples, see: (a) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc*. **1995**, *117*, 9662-9670. (b) Wu, X.-S.; Chen, Y.; Li, M.-B.; Zhou, M.-G.; Tian, S. K. *J. Am. Chem. Soc*. **2012**, *134*, 14694-14697. (c) Jegelka, M.; Plietker, B. *Org. Lett*. **2009**, *11*, 3462-3465.

14 For relevant examples, see: (a) Pritzius, A. B.; Breit, B. *Angew. Chem. Int. Ed*. **2015**, *54*, 3121-3125. For related hydrothiocarbonylation reactions, see: (b) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem*. **1998**, *63*, 2609-2612. (c) Xiao, W.-J.; Alper, H. *J. Org. Chem*. **1999**, *64*, 9646-9652.

15 (a) Yang, X.-H.; Davison, R. T.; Dong, V. M. *J. Am. Chem. Soc*. **2018**, *140*, 10443-10446. (b) Yang, X. -H.; Davison, R. T.; Nie, S.-Z.; Cruz, F. A.; McGinnis, T. M.; Dong, V. M. *J. Am. Chem. Soc*. **2019**, *141*, 3006-3013.

16 For selected examples, see: (a) Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc*. **2014**, *136*, 16124-16127. (b) Cao, C.; Fraser, L. R.; Love. *J. Am. Chem. Soc*. **2005**, *127*, 17614-17615. (c) Nurhanna, R. S.; Ying, J. Y.; Zhang, Y. *Org. Lett*. **2012**, *14*, 1780-1783. (d) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem*. **2005**, *70*, 6468-6473.

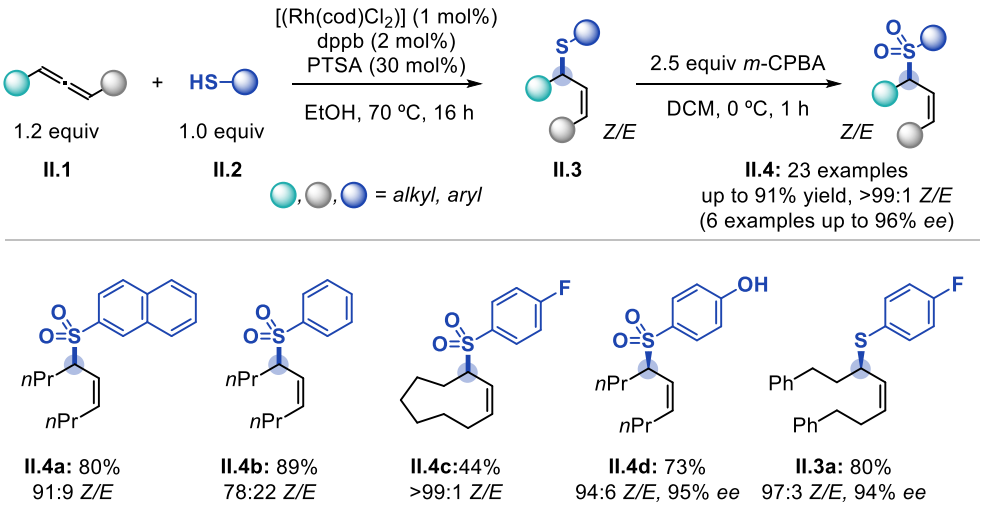
17 Rao, W.-H.; Zhan, B.-B.; Chen, K.; Ling, P.-X.; Zhang, Z.-Z.; Shi, B.-F. *Org. Lett*. **2015**, *17*, 3552-3555.

18 (a) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem. Int. Ed*. **2009**, *48*, 172-174. (b) Chu, X.-Q.; Meng, H.; Xu, X.-P.; Ji, S.-J. *Chem. Eur. J*. **2015**, *21*, 11359-11368.

19 Flynn, A. B.; Ogilvie, W. W. *Chem. Rev*. **2007**, *107*, 4698-4745.

that methods for highly selective access to (*Z*)-alkenes are less developed than those for the corresponding (*E*)-isomers. One major reason is the thermodynamic control that favors the typically lower-in-energy (*E*)-alkenes.[20] Therefore, the development of a mild and operationally simple catalytic protocol allowing for the stereoselective synthesis of (*Z*)-multisubstituted allylic thioethers and sulfones remains underdeveloped and an inspiring goal.[21]

As far as we know, at the time this project was started, the only catalytic example of (*Z*)-selective allylic thioether and sulfone synthesis had been reported by Breit *et al.* in 2015.[22] This methodology is based on a rhodium-catalyzed hydrothiolation of 1,3-disubstituted allenes (**II.1**), and subsequent oxidation towards the corresponding allylic sulfones (**II.4**, Scheme II-1).



Scheme II-1. Rh-catalyzed (*Z*)-selective (asymmetric) hydrothiolation of allenes.

Using the bidentate 1,4-bis(diphenylphophino)butane (dppb) ligand, the authors were able to generate the corresponding allylic products in good to high *Z*/*E*-selectivities. Moreover, the protocol tolerated both aromatic and aliphatic thiols as reaction partners (**II.2**), and a variety of either symmetrical or unsymmetrical 1,3-disubstituted allenes (**II.1**). The observed stereocontrol likely depends on steric factors exerted by the employed pro-nucleophiles, as evidenced by the high (*Z*)-selectivity noted when using bulky naphthalene-2-thiol compared to the parent

20 Siau, W.-Y.; Zhang, Y.; Zhao, Y. *Top. Curr. Chem.* **2012**, *327*, 33-58.
21 Only a few non-catalytic methods are known but with limited product diversity: (a) Das, B.; Chowdhury, N.; Damodar, K.; Banerjee, J. *Chem. Pharm. Bull.* **2007**, *55*, 1274-1276. (b) Karnakar, K.; Ramesh, K.; Murthy, S. N.; Nageswar, Y. V. D. *Helv. Chim. Acta.* **2013**, *96*, 2276-2281. (c) Liu, Y.; Xu, X.; Zheng, H.; Xu, Z.; Zhang, Y. *Synlett.* **2006**, 571-574.
22 Pritzius, A. B.; Breit, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 15818-15822.

thiophenol. Notably, starting from racemic internal allenes, the authors demonstrated the feasibility towards a dynamic kinetic resolution (DKR) by applying a Rh(I)/(*S*,*S*)-Me-DuPhos catalytic system.

Although Breit's work presented a breakthrough in the catalytic, stereocontrolled preparation of (*Z*)-configured allylic thioethers (**II.3**) and sulfones (**II.4**), this synthetic approach requires the use of expensive rhodium catalysts, acid additives (PTSA) and importantly, it is limited in substitution diversity around the allylic double bond. Hence, these features adversely affect its practical application. With this in mind, the pursuit of complementary and more general strategies able to generate multi-functionalized allylic thioethers and sulfones in a regio- and stereoselective fashion remains a highly desirable, though elusive target.

II.1.3 Aim of the project

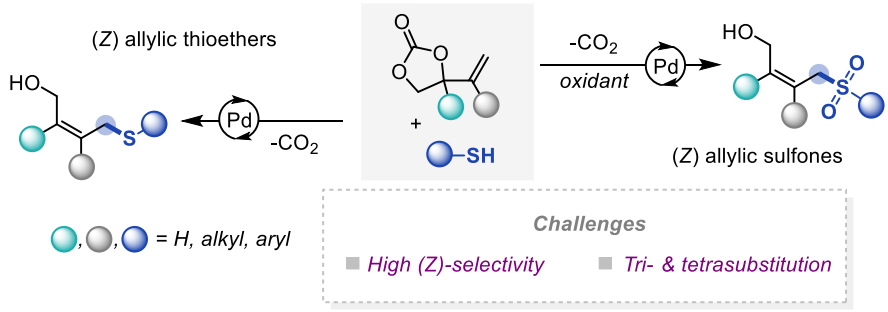
As introduced in Chapter I, our group recently described a Pd-catalyzed regio- and stereoselective strategy for the decarboxylative functionalization of vinyl cyclic carbonates (VCCs) with different pro-nucleophiles (*i.e*., amines and water). In this respect, by judiciously tuning the nature of the ligands, the metal precursor and the reaction conditions, we developed the first general methodologies toward either multi-substituted (*Z*)-configured linear allylic amines[23] and 1,4-but-2-ene diols. Key to the high (*Z*) selectivity found in these transformations is the *in situ* formation of a six-membered palladacyclic complex as supported by DFT calculations (see Chapter I, Scheme I-15).[24]

Taking into account the aforementioned limited knowledge in the area of stereocontrolled preparation of highly substituted (*Z*)-configured allylic thioethers and sulfones, we were curious to see whether we could transfer our initial conditions to the use of more challenging thiol pro-nucleophiles. Though stereoselective allylic amination and hydration of VCCs have been demonstrated, thiols are more nucleophilic and acidic than amines, thus providing distinct challenges and opportunities. As such, in this chapter we aim to develop *a general and practical route for the preparation of highly functionalized (Z)-configured allylic thioethers and (upon oxidation) the corresponding (Z)-configured sulfones.* We envisaged that, under suitable reaction conditions, the reaction of modular VCCs and thiol nucleophiles would give access to (*Z*)-allylic

23 Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc*. **2016**, *138*, 11970-11978.

24 Guo, W.; Martínez-Rodríguez, L.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2016**, *55*, 11037-11040.

thioethers through nucleophilic attack onto the *in situ* formed palladacyclic intermediate (Scheme II-2).



Scheme II-2. Outline towards Pd-catalyzed stereoselective synthesis of (*Z*)-allylic thioethers and sulfones.

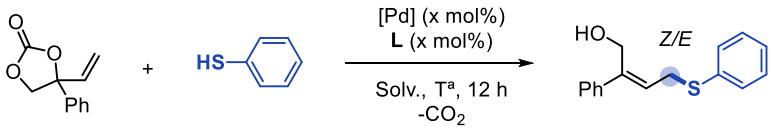
II.2. Results and discussion

II.2.1 Screening Studies

At the outset of this study, the reaction between vinyl cyclic carbonate **II.5a** and thiophenol **II.6a** was selected as a benchmark reaction to evaluate suitable reaction conditions for the synthesis of (*Z*)-configured allylic thioether **II.7a** (Table II-1). The choice of this model system was based on previous studies carried out in our group on the stereocontrolled allylic amination of vinyl cyclic carbonates.[23, 24] With this initial system, considerable screening of reaction conditions, including parameters such as the palladium source, type of ligand, solvent and temperature was performed.

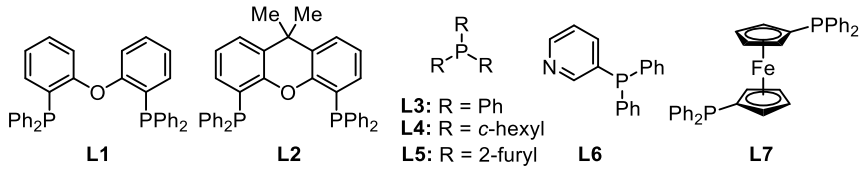
Inspired by previous success,[23, 24] we firstly evaluated the combination of the White catalyst precursor ($Pd(OAc)_2$ ligated by a bis-sulfoxide; 2 mol%) and bidentate phosphine ligand DPEPhos (**L1**, 5 mol%) at room temperature. Unfortunately, no reaction was observed even when conducting the reaction in different solvents such as DMF, THF, MeOH and ACN or using simple $Pd(OAc)_2$ as metal precursor (Table II-1, entries 1-6). However, to our delight after switching to $Pd_2(dba)_3{\cdot}CHCl_3$ in ACN an encouraging 16% yield of allylic thioether (*Z*)-**II.7a** (*Z*/*E* = 70:30) was noted (Table II-1, entry 7). By using $Pd(dba)_2$ a similar yield though enhanced stereoselectivity was achieved (Table II-1, entry 8; *Z*/*E* = 86:14).

Table II-1. Optimization of the reaction conditions towards allylic thioether (*Z*)-**II.7a**. [a]



II.5a **II.6a** **II.7a**

Entry	[Pd] precursor	L	Solvent	T [ºC]	Yield [%][b]	*Z*/*E*[c]
1	White catalyst	**L1**	none	rt	0	-
2	White catalyst	**L1**	DMF	rt	0	-
3	White catalyst	**L1**	THF	rt	0	-
4	White catalyst	**L1**	MeOH	rt	0	-
5	White catalyst	**L1**	ACN	rt	0	-
6	$Pd(OAc)_2$	**L1**	ACN	rt	0	-
7	$Pd_2(dba)_3{\cdot}CHCl_3$	**L1**	ACN	rt	16	70:30
8	$Pd(dba)_2$	**L1**	ACN	rt	16	86:14
9	$Pd(dba)_2$	**L1**	ACN	50	77	91:9
10	$Pd(dba)_2$	**L1**	ACN	70	84	92:8
11[d]	**$Pd(dba)_2$**	**L1**	**ACN**	**70**	**91**	**94:6**
12	$Pd(dba)_2$	**L2**	ACN	70	83	94:6
13	$Pd(dba)_2$	**L3**	ACN	70	0	-
14	$Pd(dba)_2$	**L4**	ACN	70	0	-
15	$Pd(dba)_2$	**L5**	ACN	70	0	-
16	$Pd(dba)_2$	**L6**	ACN	70	0	-
17	$Pd(dba)_2$	**L7**	ACN	70	0	-
18[e]	$Pd(dba)_2$	**L1**	ACN	70	73	90:10
19[f]	$Pd(dba)_2$	**L1**	ACN	70	92	91:9
20	-	-	ACN	70	0	-
21	$Pd(dba)_2$	-	ACN	70	0	-



[*a*] Reaction conditions unless otherwise stated: carbonate **II.5a** (0.20 mmol), **II.6a** (1.5 equiv), solvent (0.20 mL), palladium precursor (2 mol%), **L** (5 mol%), open to air, 12 h. [*b*] NMR yield using toluene as an internal standard. [*c*] Based on ^{1}H NMR integration. [*d*] $Pd(dba)_2$ = 3 mol%. [*e*] $Pd(dba)_2$ = 3 mol%, **II.6a** (1.2 equiv). [*f*] $Pd(dba)_2$ = 3 mol %, **II.6a** (0.20 mmol) and carbonate **II.5a** (0.22 mmol).

In order to advance the efficiency of the protocol, different temperatures were screened (Table II-1, entries 9 and 10), and at 70 ºC an appreciable yield (84%) and high selectivity (*Z/E* = 92:8) for **II.7a** was obtained. After increasing the palladium loading to 3 mol%, the protocol was further optimized producing (*Z*)-**II.7a** in 91% yield and in high selectivity (*Z/E* = 94:6; Table II-1, entry 11).

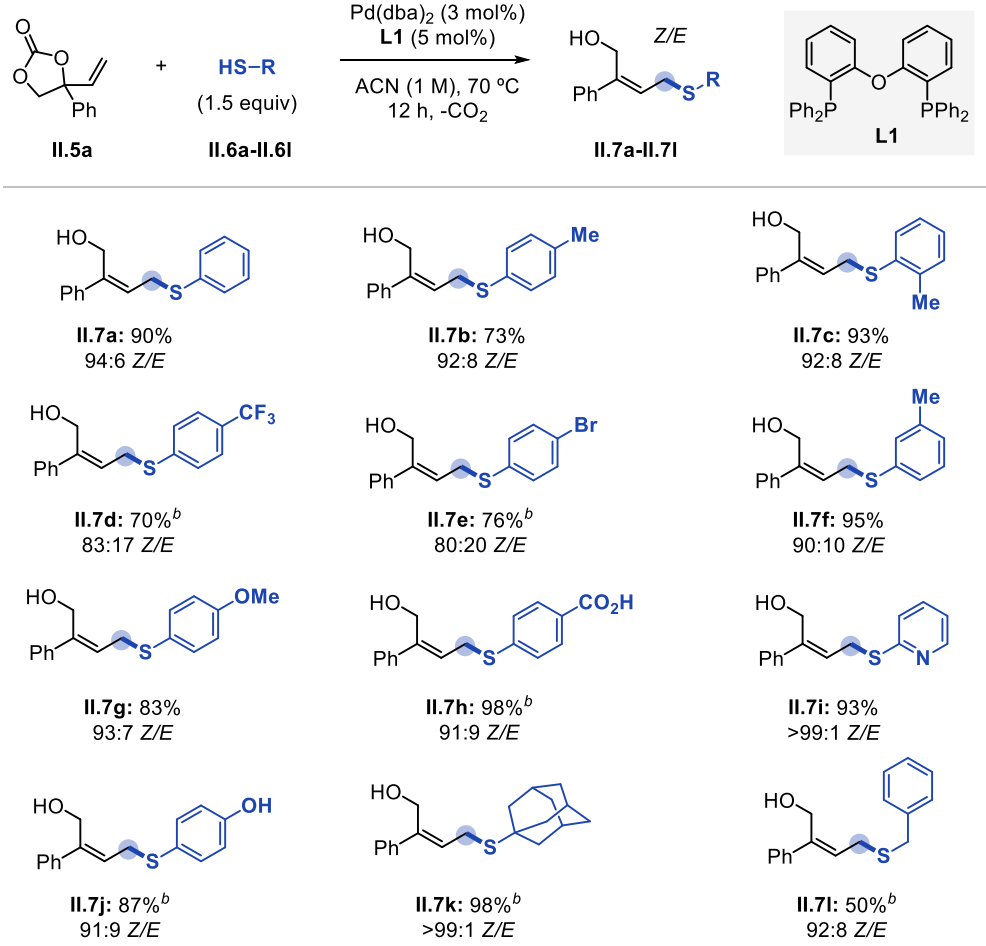
At this point, other bidentate and monodentate phosphine ligands **L2**-**L7** combined with $Pd(dba)_2$ were also tested in the formation of (*Z*)-**II.7a**, but these catalytic systems proved to be less productive. The use of structural related bidentate Xantphos ligand **L2** also showed to be effective although diminished yield of desired product was obtained (Table II-1, entry 12), whereas the use of monodentate phosphine ligands **L3**-**L6** and ferrocenyl biphosphine **L7** did not result in any observable formation of the desired product (*Z*)-**II.7a** (Table II-1, entries 13-17). These combined data point at a crucial role of the ligand structure in the present protocol. Any efforts to lower the amount of thiophenol resulted in a decrease of the yield of (*Z*)-**II.7a** (1.2 equiv, Table II.1, entry 18). The use of a slight excess of carbonate gave fairly similar results (Table II-1, entry 19; 92% yield, *Z/E* = 91:9) to those obtained under the optimized conditions reported in entry 11.

Finally, some blank experiments were performed to corroborate that both the Pd precursor and supporting ligand are necessary as in their absence no thioether product was formed (entries 20 and 21). Thus, the best conditions toward the formation of allylic thioether (*Z*)-**II.7a** were the use of $Pd(dba)_2$ (3 mol%) and **L1** (5 mol%) in ACN at 70 °C (Table II-1, entry 11). It is worth noting that in these screening reactions we were unable to detect any formation of the branched allylic thioether product. In addition, no basic additive[25] or special precautions were required, making the procedure thus attractive from a practical point of view.

25 Addition of base may lead to competitive 1,2-diol or carbamate formation: (a) Guo, W.; González-Fabra, J.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2015**, *54*, 11686-11690. (b) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2014**, *53*, 10416-10419.

II.2.2 Product scope of (*Z*)-allylic thioethers

Having optimized the reaction conditions, the scope of the transformation was then studied. First, we evaluated a range of aromatic and aliphatic thiols in combination with vinyl cyclic carbonate **II.5a**. In line with the relatively mild reaction characteristics of the developed allylic substitution reaction, the decarboxylative thiolation allowed the synthesis of a diverse array of (*Z*)-allylic thioethers **II.7a-II.7l** with high stereoselectivity (*Z*/*E* ratios typically >90:10) and satisfactory yields (Scheme II-3).



Scheme II-3. Scope in thiol reaction partners. [*a*] Reaction conditions: carbonate **II.5a** (0.20 mmol), thiol (1.5 equiv), ACN (0.20 mL), $Pd(dba)_2$ (3 mol%), **L1** (5 mol%), 70 °C, 12 h. [*b*] Thiol (0.20 mmol), carbonate **II.5a** (0.22 mmol).

The gathered results testified that a number of thiophenol substrates were tolerated under the optimized conditions. Electron-donating (**II.7b**, **II.7c**, **II.7f**, **II.7g** and **II.7j**) and electron-withdrawing groups (**II.7d**, **II.7e** and **II.7h**) in the *para*-, *meta*- and *ortho*- position of the aryl substituent are compatible with the formation of the allylic thioether product. Moreover, variation of the thiol partner allowed us to include synthetically useful aryl halides (**II.7e**), benzoic acid fragments (**II.7h**), and even a free phenol function (**II.7j**). Notably, the use of a pyridyl-substituted thiophenol gave smooth access to (*Z*)-allylic thioether **II.7i** in high yield and excellent stereoselectivity, despite the potential of heteroaromatic substituents to coordinate the palladium catalyst.

Apart from aryl-substituted thiols, alkyl thiols also proved to be feasible nucleophiles leading to their respective allylic thioethers in high stereoselectivity (**II.7k** and **II.7l**, *Z/E* >92:8). It is worth noting that for some particular challenging substrates the procedure was optimized by using a slight excess of vinyl cyclic carbonate **II.5a** (*cf.*, Table II-1, entry 19).

The (*Z*) configuration of the major isomer in all cases was supported by 2D NMR experiments (NOESY) and for **II.7a** also further evidence for the proposed *Z*-configuration was obtained from X-ray diffraction analysis (Figure II.3).

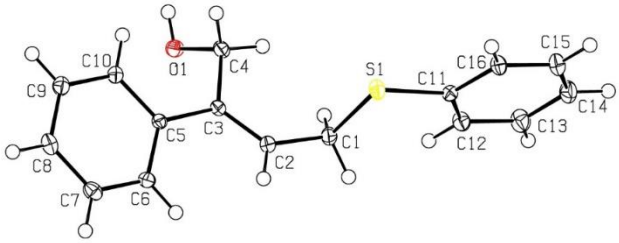
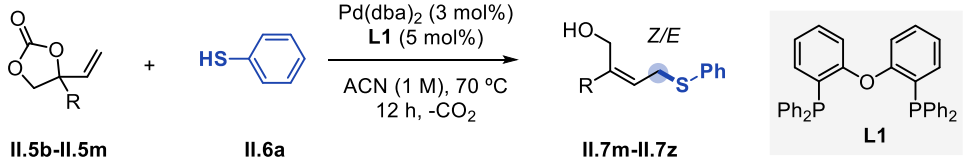


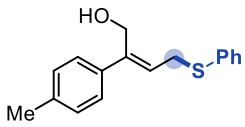
Figure II-3. X-ray analysis of (*Z*)-allylic thioether **II.7a**.

Next, we focused on the scope of the allylic partner and as such a variety of vinyl cyclic carbonates **II.5b**-**II.5m** were prepared. Allylic thiolation of the latter compounds was conducted using the optimized protocol giving access to an even wider range of highly functionalized allylic thioethers **II.7m**-**II.7x** (Scheme II-4). Moderate to excellent yields (up to 97%) and high stereocontrol (*Z/E* ratios typically >80:20) were observed in most cases.

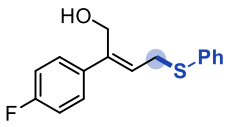
Both aryl and alkyl substituents in the carbonate reagent were tolerated. In addition, different functionalities such as benzoic ester (**II.7q**), nitrile (**II.7r**) and furyl (**II.7u)** groups were readily introduced further amplifying product diversity. However, upon use of more sterically demanding vinyl carbonates that incorporate naphthyl or cyclohexyl substituents, the catalytic procedure was less productive (**II.7s** and **II.7v**; 51% and 48% yield, respectively).



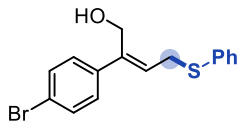
II.5b-II.5m **II.6a** **II.7m-II.7z**



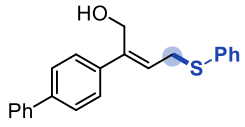
II.7m: 70%
94:6 *Z/E*



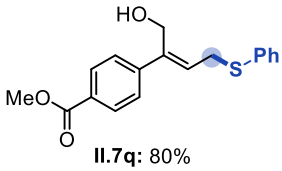
II.7n: 84%
83:17 *Z/E*



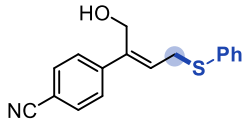
II.7o: 88%
87:13 *Z/E*



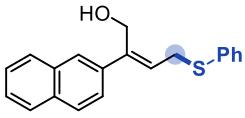
II.7p: 97%
94:6 *Z/E*



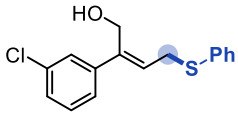
II.7q: 80%
84:16 *Z/E*



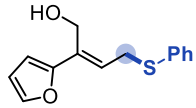
II.7r: 91%
67:33 *Z/E*



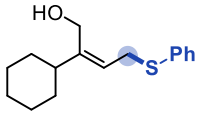
II.7s: 51%
89:11 *Z/E*



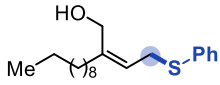
II.7t: 71%
80:20 *Z/E*



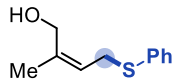
II.7u: 99%
>99:1 *E/Z*



II.7v: 48%[b]
84:16 *Z/E*



II.7w: 87%[b]
70:30 *Z/E*



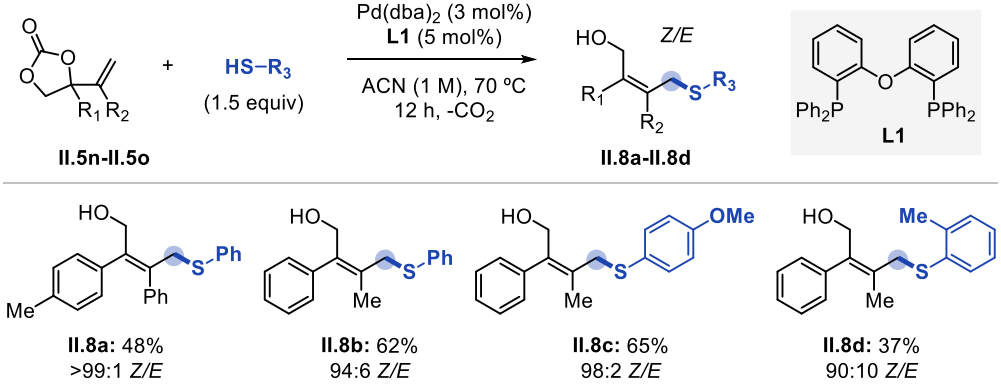
II.7x: 40%
80:20 *Z/E*

Scheme II-3. Scope in vinyl cyclic carbonate partners. [*a*] Reaction conditions unless otherwise stated: carbonate **II.5b-II.5m** (0.20 mmol), thiol **II.6a** (1.5 equiv), ACN (0.20 mL), $Pd(dba)_2$ (3 mol%), **L1** (5 mol%), 70 °C, 12 h. [*b*] Thiol **II.6a** (0.20 mmol), carbonate **II.5b-II.5m** (0.22 mmol). Note that formally compound **II.7u** has an (*E*)-configuration, but its formation follows a similar stereocontrolled thiolation pathway as observed for other reported compounds.

Thioethers **II.7r** and **II.7w** were obtained in lower *Z/E* ratios. These observations may be the result of the oxa-palladacycle intermediate being in equilibrium with a non-cyclic intermediate at 70 °C (see Chapter I, Scheme I-15).[23] If there were such equilibrium, the carbonate R substituent in the acyclic species can affect the olefin geometry prior to attack of the

thiol nucleophile through possible π-σ-π alkene isomerization.[26] Therefore, a higher tendency to form such a non-cyclic palladium intermediate might result in loss of stereocontrol. On the other hand, when the reaction was conducted using a vinyl cyclic carbonate bearing a less sterically demanding methyl substituent, product **II.7x** was formed along with a significant amount of the corresponding branched isomer, which affected the yield of the linear derivative (**II.7x**: 40%).

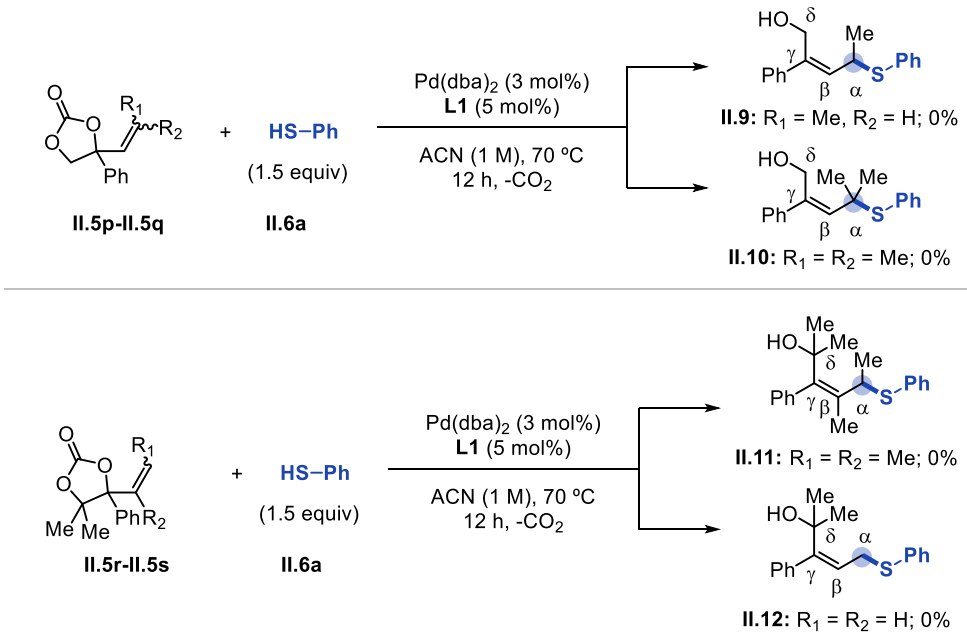
In view of the limited potential to stereoselectively introduce four different substituents in an olefinic unit,[19] we challenged the developed catalytic procedure by attempting the synthesis of elusive stereodefined, tetrasubstituted allylic thioethers (Scheme II-4). Gratifyingly, the installation of an additional alkyl or aryl substituent at the *β*-position of the allylic scaffold is feasible while maintaining excellent stereoselectivity (**II.8a-II.8d**; *Z/E* >90:10).



Scheme II-4. Preparation of elusive tetrasubstituted thioethers. [*a*] Reaction conditions unless otherwise stated: carbonate **II.5l-II.5q** (0.20 mmol), thiol (1.5 equiv), ACN (0.20 mL), $Pd(dba)_2$ (3 mol%), **L1** (5 mol%), 70 °C, 12 h.

The limitations of the developed method were identified as well (Scheme II-5). Preparation of *α*-functionalized allylic thioethers **II.9** and **II.10**, derived from internal olefin substrates (**II.5r** and **II.5s**) failed to produce the desired product under the optimized catalytic conditions. Similarly, the attempted synthesis of *δ*-functionalized allylic thioethers **II.11** and **II.12** was also not successful, as the desired product could not be observed even at temperatures of up to 100 °C with quantitative recovery of the carbonate substrates (**II.5t** and **II.5u**). Thus, these outcomes indicate some steric limitations pertinent to the current catalytic methodology.

26 Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747-760.



Scheme II-5. Attempted preparation of α- and δ-functionalized allylic thioethers.

II.2.3 One-pot (*Z*)-allylic sulfones synthesis

Allylic sulfone scaffolds are frequently observed in relevant pharmaceutical compounds[27] and have found versatile applications in organic synthesis. Therefore, their synthesis is of significant importance.[10, 11]

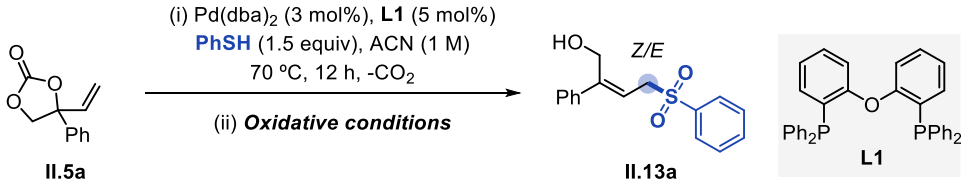
We thus set out to extend our methodology towards the stereoselective synthesis of highly substituted allylic sulfones by combining the Pd-catalyzed allylic thioether formation and an *in situ* oxidation. After a rapid screening of various conditions using vinyl cyclic carbonate **II.5a** and thiophenol **II.6a** as model substrates (Table II-2),[28] we were pleased to find that a one-pot thiolation/oxidation reaction in the presence of $(NH_4)_6Mo_7O_2{\cdot}4H_2O$ and H_2O_2 as oxidant[28b]

27 For applications of (allylic) sulfones in pharmaceutical compounds, see: (a) Chen, X.; Hussain, S.; Parveen, S.; Zhang, S.; Yang, Y.; Zhu, C. *Curr. Med. Chem*. **2012**, *19*, 3578-3604. (b) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem*. **2005**, *48*, 499-506. (c) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. *Chem. Rev*. **2009**, *109*, 2315-2349. (d) Alba, A.-N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev*. **2010**, *39*, 2018-2033.

28 (a) Trost, M. B.; Curran, D. P. *Tetrahedron Lett*. **1981**, *22*, 1287-1290. (b) Jeyakumar, K.; Chakravarthy, D. R.; Chand, D. K. *Catal. Commun*. **2009**, *10*, 1948-1951.

provided 90% isolated yield of the corresponding (*Z*)-sulfone **II.13a** with excellent stereocontrol (*Z*/*E* = 94:6). Notably, no epoxide by-product was detected under these conditions.

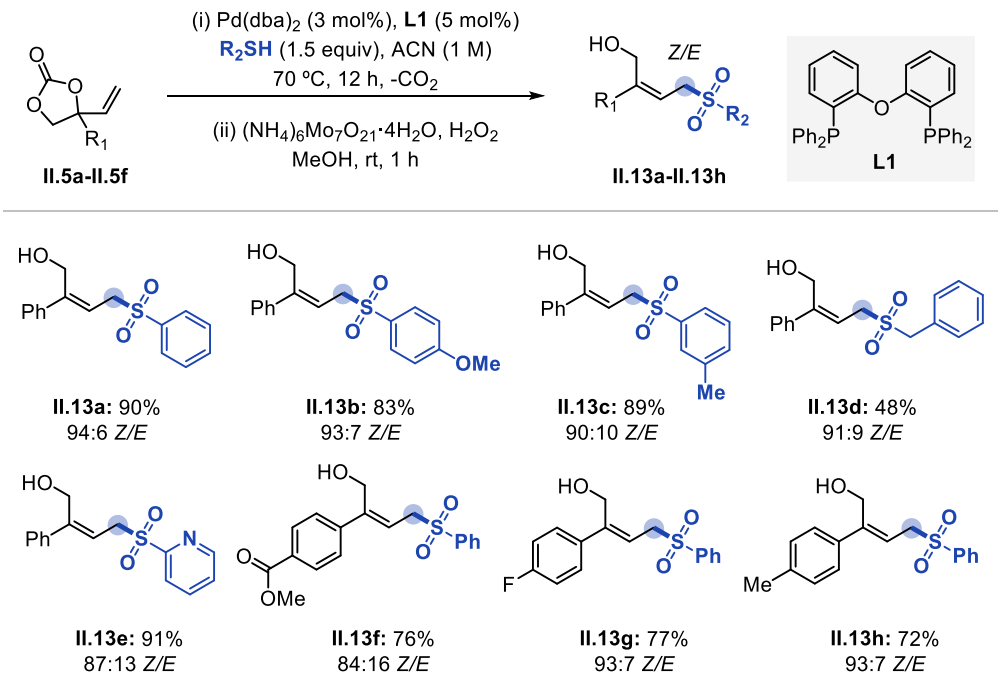
Table II-2. Optimization of the oxidation conditions towards allylic sulfone (*Z*)-**II.13a**.[a]



Entry	Oxidant	Solvent	T [ºC]	Time	Yield [%][b]	*Z*/*E*[c]
1	m-CPBA	DCM	0	1 h	77[d]	94/6
2	Oxone®	ACN/H_2O (1:1)	rt	1 h	35[e]	94/6
3	**$(NH_4)_6Mo_7O_{21}{\cdot}4H_2O$, H_2O_2**	**MeOH**	**rt**	**1 h**	**90[f]**	**94/6**

[*a*] Reaction conditions unless otherwise stated: (i) carbonate **II.5a** (0.20 mmol), **II.6a** (1.5 equiv), ACN (0.20 mL), $Pd(dba)_2$ (3 mol%), **L1** (5 mol%), 70 °C, 12 h. (ii) *Entry 1*: *m*-CPBA (2.5 equiv), DCM (0.2 mL), 0 ºC, 1 h; *Entry 2*: Oxone (3.0 equiv), ACN/H_2O (0.2 mL), rt, 1 h; *Entry 3*: $(NH_4)_6Mo_7O_{21}{\cdot}4H_2O$ (10 mol %), H_2O_2 (4.0 equiv, 30 wt % aqueous solution), MeOH (0.2 mL), rt, 1 h. [*b*] Isolated yield. [*c*] Based on ^{1}H NMR integration. [*d*] 13% of epoxide byproduct observed. [*e*] 55% of epoxide byproduct observed. [*f*] Epoxidation byproduct was not observed.

This one-pot strategy was then used to investigate the product scope in detail. The substituents of both the allylic surrogate and the thiol pro-nucleophile were systematically varied and provided an entry into a series of highly functionalized sulfones (Scheme II-6). Satisfyingly, the oxidation step did not interfere with the presence of internal alkene and primary alcohol groups or with other functionalities such as pyridyl (**II.13e**), methyl ester (**II.13f**) or aryl fluoride (**II.13g**). As such, good to excellent yields were obtained and the same degree of stereocontrol (*cf.*, allylic thioether formation) was attained in these sulfone syntheses showing that the oxidation step does not interfere with preferred (*Z*) product formation.



Scheme II-6. One-pot synthesis of highly substituted sulfones. [*a*] Reaction conditions unless otherwise stated: (i) carbonate **II.5a-II.5c** or **II.5f** (0.20 mmol), thiol (1.5 equiv), ACN (0.20 mL), $Pd(dba)_2$ (3 mol%), **L1** (5 mol%), 70 °C, 12 h. (ii) $(NH_4)_6Mo_7O_{21}\cdot 4H_2O$, H_2O_2 (4 equiv, 30 wt % in H_2O), MeOH (0.20 mL), rt, 1 h. [*b*] Thiol (0.20 mmol), carbonate **II.5a** (0.22 mmol).

In addition to this, X-ray analysis of sulfone **II.13a** unambiguously confirmed the (*Z*)-configuration of the final product (Figure II-4), which was additionally supported by NOESY experiments.

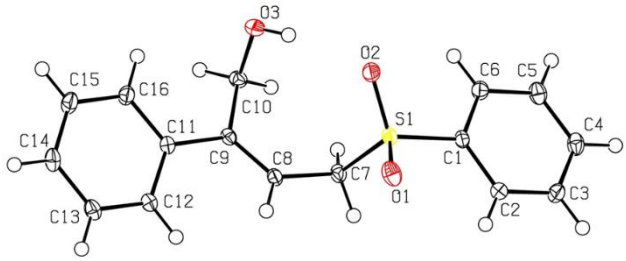
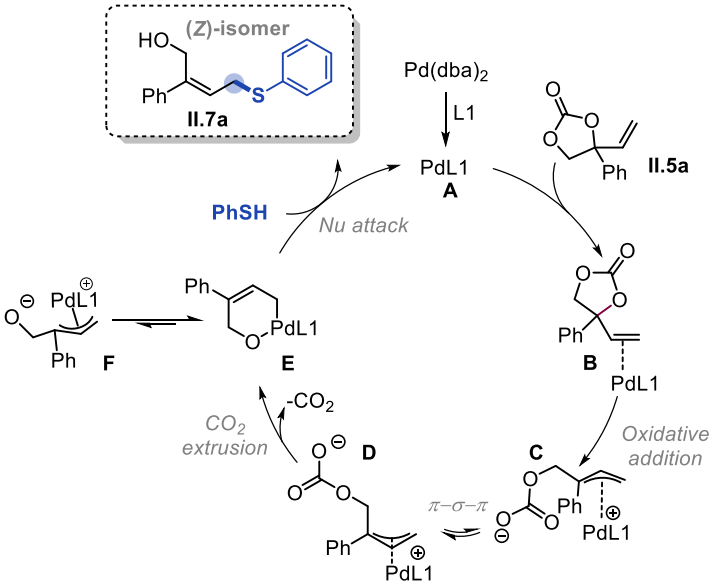


Figure II-4. X-ray analysis of (*Z*)-allylic sulfone **II.13a**.

II.2.4 Mechanistic considerations

Scheme II-7 shows a mechanistic hypothesis accounting for the palladium catalyzed allylic thiolation of vinyl cyclic carbonates. This reaction mechanism is based on a similar pathway as the one postulated in the previously reported stereoselective amination study, which revealed by DFT calculations the occurrence of a six-membered palladacycle as key intermediate able to direct the preferred formation of a (*Z*)-configured allylation product (see Chapter I, Scheme I-15).[23]



Scheme II-7. Proposed reaction manifold for the formation of allylic thioether **II.7a**.

It is proposed that the reaction initiates with the Pd(0) intermediate **A**, which is obtained upon ligand exchange of the initial $Pd(dba)_2$ precursor in the presence of the bidentate phosphine ligand **L1** (DPEPhos). Subsequently, the palladium complex is coordinated by the vinyl group of the VCC **II.5a** to give intermediate **B**, followed by an oxidative cleavage of the cyclic structure. In this step, there is a formal transfer of two electrons from the Pd center to the organic substrate, resulting in an intermediate **C** containing a η^3-allylic group attached to a linear carbonate, which is in dynamic equilibrium with intermediate **D**, through a π-σ-π interconversion. Although at this stage, it is far from obvious how stereocontrol can be achieved from this open chain species, according to the previous elucidated mechanism in allylic amination, intermediate **D** may evolve towards the formation of six-membered palladacyclic intermediate **E** (as supported by DFT calculations) through extrusion of carbon dioxide. The (*Z*)

configured double bond is already established in the six-membered ring,[23] and thus allows for the allylation to be set up for stereoselective formation of the final product (*Z*)-**II.7a** by nucleophilic attack of the thiophenol while regenerating the Pd(0) species for further catalytic turnover. The formation of intermediate **E** is thus key to the overall selectivity of the process. Notably, under the optimized conditions the equilibration of acyclic η^3-allyl-Pd species **F** to η^1-palladacyclic intermediate **E** is electronically biased as the presence of an aryl/vinyl substituent allows for hyperconjugation of the double bond in **E**. This in turn controls the (*Z*)-configuration of the palladacycle and thus the stereocontrol towards the thioether product **II.7a**. Therefore, a higher tendency to form such an acyclic allyl-palladium intermediate may give rise to loss of stereocontrol.

II.3. Conclusions

Significant progress has been observed in recent years in the synthesis of allylic thioethers and sulfones. However, most of these processes are effective toward the preparation of allylic thioethers or sulfones with limited potential to introduce three or four different substituents in the olefinic unit in a stereocontrolled fashion.

This chapter summarizes the development of a general catalytic route for the stereocontrolled preparation of tri- and tetrasubstituted (*Z*)-allylic thioethers. This methodology relies on a Pd-catalyzed allylic thiolation reaction of modular vinyl cyclic carbonates used as allylic surrogates. Using a catalytic system based on the combination of a Pd(0) pre-catalyst and DPEPhos ligand, the regio- and stereoselective course of this reaction can be controlled, providing good yields and high selectivities for (*Z*)-allylic thioethers. In addition, oxidation of the *in situ* prepared thioethers in a one-pot procedure has also been developed, giving access to the corresponding (*Z*)-allylic sulfones.

The mild reaction conditions of this protocol allow for broad functional group tolerance and the coupling of both alkyl and aryl thiols furnishing the products in good to high yields and high levels of stereocontrol. Notably, our protocol does not require any additives while it is also characterized by minimal waste release and operational simplicity, avoiding the need for special precautions with respect to air/moisture sensitivity.

Taking into account previous mechanistic investigations carried out in our group, the (*Z*)-selectivity in the present catalytic protocol is attributed to a nucleophilic attack of the thiol reagent onto an *in situ* generated (*Z*)-configured, six-membered palladacycle intermediate, which guides the stereoselective course of the developed process.

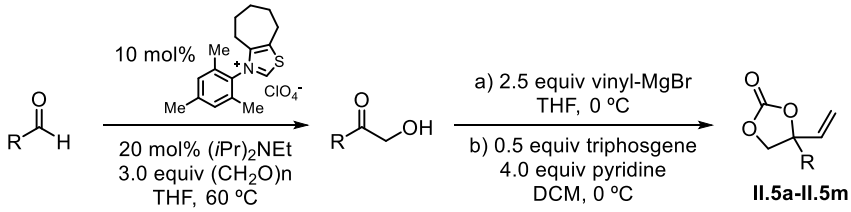
II.4. Experimental section

II.4.1 General information and instrumentation

Thiol reagents, solvents, palladium pre-catalysts and ligands were purchased from Aldrich or TCI, and used without further purification. In the screening phase, the internal standard toluene was added after the reaction mixture that had been stirred at 70 ºC for 12 h. After that, an aliquot of the resulting mixture was taken and the yield was determined by means of ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. *Z/E* ratios were calculated from the corresponding ^{1}H NMR spectra using signal integration. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and related 2D NMR spectra were recorded at room temperature on a Bruker AV-400 or AV-500 spectrometer and referenced to the residual deuterated solvent signals. All reported NMR values are given in parts per million (ppm). FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer. Mass spectrometric analyses and X-ray diffraction studies were performed by the Research Support Group at ICIQ.

II.4.2 General procedure for the synthesis of vinyl cyclic carbonates

The vinyl cyclic carbonates **II.5a-II.5m** were prepared according to previous reported procedures with minor modifications (Scheme II-8).[23,24,29]



Scheme II-8. General procedure for the preparation of vinyl cyclic carbonates.

Synthesis of α-hydroxylmethyl ketones:[30] In an oven-dried Schlenk-flask sealed with a rubber septum and equipped with a magnetic stirring bar, thiazolium salt (10 mol%), paraformaldehyde (3.0 equiv) and the corresponding aldehyde (1.0 equiv) were added. The Schlenk flask was then subjected to three cycles of pressurization/depressurization using dry N_2.

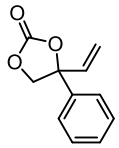
29 (a) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 11257-11260. (b) Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 6439-6452.

30 Kuhl, N.; Glorius, F. *Chem. Commun*. **2011**, *47*, 573-575.

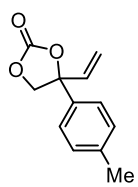
After that, under the protection of dry N_2, anhydrous THF (5 mL) and (iPr)$_2$NEt (20 mol%) were added and the resulting mixture was heated to 60°C. (Note: in the case of aliphatic aldehydes, the aldehyde was added after stirring the other reactants for 5 min at room temperature). After a maximum reaction time of 24 h, the solvent was evaporated and the crude product was purified by flash chromatography.

Step (a): To a solution of the respective pure hydroxy methyl ketone (5 mmol, 1.0 equiv) in THF (20 mL) was added vinylmagnesium bromide (1.0 M in THF, 2.5 equiv) at 0 ºC. The reaction was stirred under an N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated affording the crude product, which was directly used in the next step.

Step (b): To a solution of the corresponding crude diol (1.0 equiv) and pyridine (4.0 equiv) in DCM (20 mL) was added triphosgene (0.5 equiv, 1.0 M in DCM) at 0 ºC. The reaction was stirred under an N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica to afford the corresponding vinyl cyclic carbonates **II.5a-II.5m**.

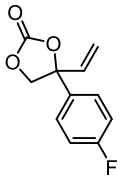


4-Phenyl-4-vinyl-1,3-dioxolan-2-one (II.5a). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 80%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45-7.34 (m, 5H), 6.16 (dd, J = 17.1; 10.8 Hz, 2H), 5.44 (s, 1H), 5.41 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 8.4 Hz, 1H), 4.58 (d, J = 8.4 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.1. 138.4, 136.5, 129.0, 128.9, 124.9, 117.6, 85.5, 74.5.

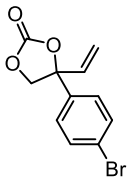


4-(*p*-Tolyl)-4-vinyl-1,3-dioxolan-2-one (II.5b). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 71%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.11 (m, 4H), 6.15 (dd, J = 17.2; 10.7 Hz, 2H), 5.42 (d, J = 2.4 Hz, 1H),

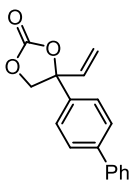
5.40 (d, *J* = 4.0 Hz, 1H), 4.62 (d, *J* = 8.4 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.3, 139.1, 136.8, 135.6, 129.8, 125.0, 117.6, 85.7, 74.7, 21.3.



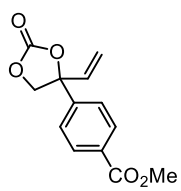
4-(4-Fluorophenyl)-4-vinyl-1,3-dioxolan-2-one (II.5c). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 91%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.9; 5.1 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 6.14 (dd, *J* = 17.2; 10.7 Hz, 2H), 5.45 (d, *J* = 10.7 Hz, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 4.64 (d, *J* = 8.5 Hz, 1H), 4.55 (d, *J* = 8.5 Hz, 1H). **^{19}F NMR** (500 MHz, $CDCl_3$) δ -112.4. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.8 (d, $^{1}J_{CF}$ = 249.1 Hz), 153.8, 136.3, 134.1, 127.0 (d, $^{3}J_{CF}$ = 8.4 Hz), 118.0, 116.1 (d, $^{2}J_{CF}$ = 21.9 Hz), 85.1, 74.5.



4-(4-Bromophenyl)-4-vinyl-1,3-dioxolan-2-one (II.5d). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 93%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.12 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.40 (dd, *J* = 17.2; 10.7 Hz, 2H), 4.64 (d, *J* = 8.5 Hz, 1H), 4.53 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.9, 137.6, 136.2, 132.4, 126.8, 123.4, 118.3, 85.2, 74.5.

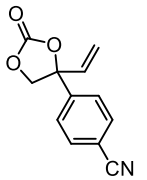


4-([1,1'-Biphenyl]-4-yl)-4-vinyl-1,3-dioxolan-2-one (II.5e). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. White solid, yield: 84%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.60-7.54 (m, 2H), 7.49-7.35 (m, 5H), 6.20 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.58-5.35 (m, 2H), 4.68 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.2, 142.1, 140.2, 137.4, 136.6, 130.5, 129.1, 128.0, 127.9, 127.3, 125.6, 117.9, 85.6, 74.7.

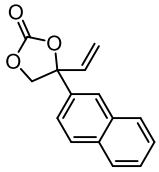


4-Methyl-(2-oxo-4-vinyl-1,3-dioxolan-4-yl) benzoate (II.5f). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 87%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.15

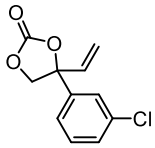
(dd, *J* = 10.7; 17.1 Hz, 2H), 5.46 (d, *J* = 9.2 Hz, 1H), 5.42 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 8.5 Hz, 1H), 4.56 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.4, 153.8, 143.3, 136.0, 130.9, 130.4, 125.1, 118.2, 85.2, 74.3, 52.4.



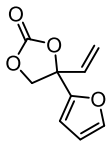
4-(4-Isocyanophenyl)-4-vinyl-1,3-dioxolan-2-one (II.5g). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 30%. The NMR spectroscopic data correspond to those previously reported in the literature. [23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.13 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.68-5.36 (m, 2H), 4.70 (d, *J* = 8.6 Hz, 1H), 4.53 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 153.4, 143.6, 135.6, 133.0, 125.9, 118.9, 118.1, 113.3, 84.9, 74.3.



4-(Naphthalen-2-yl)-4-vinyl-1,3-dioxolan-2-one (II.5h). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. White solid, yield: 65%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05-7.84 (m, 1H), 7.78 (dd, *J* = 7.4; 1.2 Hz, 1H), 7.56-7.40 (m, 2H), 6.40 (dd, *J* = 17.2; 10.7 Hz, 2H), 5.55- 5.24 (m, 2H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.8, 136.8, 134.5, 130.1, 129.7, 128.8, 126.7, 126.1, 125.4, 124.5, 123.4, 120.1, 86.1, 74.9.

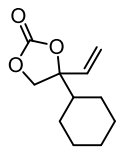


4-(3-Chlorophenyl)-4-vinyl-1,3-dioxolan-2-one (II.5i). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 70%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.35 (m, 3H), 7.23-7.26 (m, 1H), 6.13 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.46 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 14.5 Hz, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.55 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.8, 140.6, 136.1, 135.3, 130.5, 129.3, 125.4, 123.2, 118.4, 85.0, 74.5.

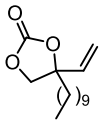


4-(Furan-2-yl)-4-vinyl-1,3-dioxolan-2-one (II.5j). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 56%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61-7.40 (m, 2H), 6.41 (dd, *J* = 1.7; 1.2 Hz, 1H), 6.13 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.59-5.33

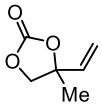
(m, 2H), 4.51 (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.1, 144.8, 140.7, 135.2, 124.3, 118.5, 108.4, 81.7, 74.2.



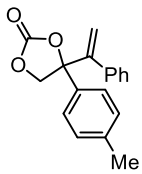
4-Cyclohexyl-4-vinyl-1,3-dioxolan-2-one (II.5k). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 62%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.61-5.27 (m, 2H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 1.91-1.61 (m, 7H), 1.40-0.93 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.7, 134.8, 116.9, 87.3, 72.2, 45.6, 26.7, 26.5, 26.2, 26.1, 25.8.



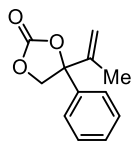
4-Decyl-4-vinyl-1,3-dioxolan-2-one (II.5l). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 71%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.42 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 4.22 (q, *J* = 8.3 Hz, 2H), 1.84-1.73 (m, 2H), 1.39-1.25 (m, 16H), 0.88 (t, *J* = 9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6, 136.32, 116.5, 85.1, 73.4, 38.2, 32.0, 29.6, 29.6, 29.6, 29.4, 29.4, 23.1, 22.8, 14.2.



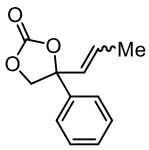
4-Methyl-4-vinyl-1,3-dioxolan-2-one (II.5m). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates. Yellow oil, yield: 42%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.2; 10.7 Hz, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 4.27 (d, *J* = 8.3 Hz, 1H), 4.18 (d, *J* = 8.3 Hz, 1H), 1.60 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.5, 137.0, 116.7, 82.7, 74.5, 24.3.



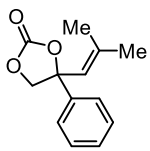
4-(1-Phenylvinyl)-4-(*p*-tolyl)-1,3-dioxolan-2-one (II.5n). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, using (1-phenylvinyl)magnesium bromide (1.0 M in THF, 2.5 equiv) instead of vinyl magnesium bromide. Brown solid, yield: 68%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.31 (m, 2H), 7.28-7.26 (m, 2H), 7.25-7.21 (m, 3H), 7.07-7.05 (m, 2H), 5.62 (s, 1H), 5.57 (s, 1H), 4.73-4.66 (m, 2H), 2.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.0, 147.6, 139.3, 137.6, 135.5, 129.7, 128.5, 128.3, 126.0, 117.7, 87.5, 73.5, 21.3.



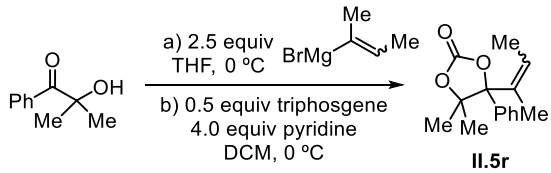
4-Phenyl-4-(prop-1-en-2-yl)-1,3-dioxolan-2-one (II.5o). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, using isopropenylmagnesium bromide (0.5 M in THF, 2.5 equiv) instead of vinyl magnesium bromide. White solid, yield: 65%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53-7.31 (m, 5H), 5.25-5.03 (m, 2H), 4.79 (d, *J* = 8.6 Hz, 1H), 4.63 (d, *J* = 8.6 Hz, 1H), 1.73 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.0, 142.8, 138.4, 128.9, 125.0, 114.0, 88.0, 73.1, 18.4.



4-Phenyl-4-(prop-1-en-1-yl)-1,3-dioxolan-2-one (II.5p). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, using 1-propenylmagnesium bromide (0.5 M in THF, 2.5 equiv) instead of vinyl magnesium bromide. White solid, yield: 62%. *The carbonate is a mixture of two stereoisomers with ratio of 40:60*. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44-7.32 (m, 5H), 5.96-5.83 (m, 1H), 5.79-5.72 (m, 1H), 4.64-4.59 (m, 1H), 4.56-4.53 (m, 1H), 1.77-1.59 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.5, 154.4, 140.3, 139.2, 132.9, 130.4, 130.1, 129.5, 129.1, 128.9, 128.9, 128.8, 125.0, 125.0, 85.8, 85.4, 77.4, 17.8, 15.0.

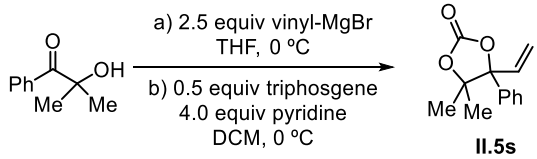


4-(2-Methylprop-1-en-1-yl)-4-phenyl-1,3-dioxolan-2-one (II.5q). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, using 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 2.5 equiv) instead of vinyl magnesium bromide. White solid, yield: 71%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 5.70-5.68 (m, 1H), 4.55 (d, *J* = 8.3 Hz, 1H), 4.45 (d, *J* = 8.3 Hz, 1H), 1.83 (d, *J* = 1.4 Hz, 3H), 1.54 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.8, 143.6, 141.1, 129.0, 128.6, 125.1, 124.2, 85.4, 78.1, 26.7, 20.1.



II.5r

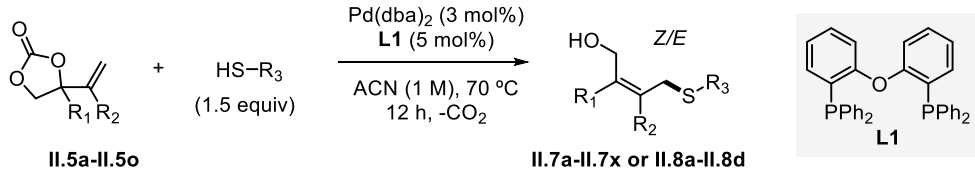
4-(But-2-en-2-yl)-5,5-dimethyl-4-phenyl-1,3-dioxolan-2-one (II.5r). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, starting from 2-hydroxy-2-methyl-1-phenylpropan-1-one, and using but-2-en-2-ylmagnesium bromide (1.0 M in THF, 2.5 equiv). White solid, yield: 62%. *Note: mixture of two stereoisomers with ratio of 40:60*. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7 7.50-7.35 (m, 5H), 5.79-5.56 (m, 1H), 1.90-1.26 (m, 12H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.9, 137.4, 137.0, 133.2, 131.2, 129.0, 128.7, 128.3, 128.2, 127.37, 127.1, 126.6, 125.9, 94.8, 94.2, 88.8, 88.3, 26.2, 25.7, 24.4, 24.2, 24.1, 16.2, 14.2, 13.7.



II.5s

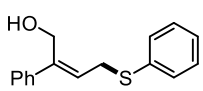
4,4-Dimethyl-5-phenyl-5-vinyl-1,3-dioxolan-2-one (II.5s). The title compound was prepared following the general procedure for the preparation of vinyl cyclic carbonates, starting from 2-hydroxy-2-methyl-1-phenylpropan-1-one. White solid, yield: 71%. The NMR spectroscopic data correspond to those previously reported in the literature.[23, 24, 29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 6.30-6.24 (m, 1H), 5.50 (d, *J* = 16.9 Hz, 1H), 5.37 (d, *J* = 10.9 Hz, 1H), 1.63 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.4, 136.7, 135.1, 128.9, 128.5, 124.6, 116.7, 89.7, 87.8, 25.1, 23.1.

II.4.3 General procedure for the preparation of allylic thioethers

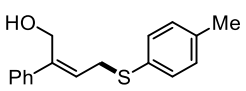


Scheme II-9. General approach towards the preparation of allylic thioethers.

A screw-capped vial was charged with the respective vinyl cyclic carbonate (0.2 mmol, 1.0 equiv), thiol derivative (0.3 mmol, 1.5 equiv), the $Pd(dba)_2$ pre-catalyst (0.003 g, 3 mol%), phosphine **L1** (0.005 g, 5 mol%) and ACN (200 μL). The reaction mixture was stirred at 70 °C for 12 h. The reaction mixture was purified by flash column chromatography on silica gel to afford the corresponding allylic thioether product. All purified products were fully characterized by ^{1}H, ^{13}CNMR, IR spectra and HRMS analysis; ^{19}F NMR and related 2D NMR experiments were carried out when necessary. **Note**: Only the data for the main component, *i.e.* the (*Z*)-isomer is listed.

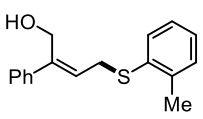


(*Z*)-2-Phenyl-4-(phenylthio)-but-2-en-1-ol (II.7a). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 90%, *Z/E* = 94:6. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.40-7.39 (m, 2H), 7.35-7.28 (m, 6H), 5.99 (t, *J* = 8.1 Hz, 1H), 4.35 (s, 2H), 3.76 (d, *J* = 8.1 Hz, 2H), 1.12 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.2, 140.2, 135.1, 132.2, 129.1, 128.6, 127.7, 127.5, 126.5, 126.4, 59.5, 33.2. **IR** (ATR): ν = 3368, 3055, 2923, 1582, 1438, 1006, 738, 691 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 279.0808 $(M + Na)^+$, found: 279.0814.

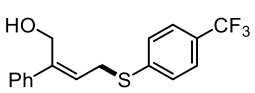


(*Z*)-2-Phenyl-4-(*p*-tolylthio)but-2-en-1-ol (II.7b). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 73%, *Z/E* = 92:8. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41-7.32 (m, 6H), 7.29-7.28 (m, 1H), 7.14-7.13 (m, 2H), 5.98 (t, *J* = 8.1 Hz, 1H), 4.30 (d, *J* = 6.0 Hz, 2H), 3.71 (d, *J* = 8.1 Hz, 2H), 2.33 (s, 3H), 1.04 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.9, 140.3, 137.9, 133.0, 131.1,

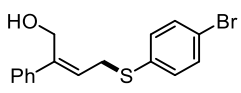
129.9, 128.6, 127.7, 126.6, 126.5, 59.4, 33.8, 21.2. **IR** (ATR): ν = 3431, 2930, 1490, 1432, 1089, 1014, 802, 767, 669 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 253.1047 $(M - OH)^+$, found: 253.1045.



(*Z*)-2-Phenyl-4-(*o*-tolylthio)but-2-en-1-ol (II.7c). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 93%, *Z/E* = 92:8. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 3H), 7.35-7.32 (m, 2H), 7.29-7.28 (m, 1H), 7.24-7.22 (m, 1H), 7.19-7.17 (m, 2H), 6.01 (t, *J* = 8.1 Hz, 1H), 4.34 (s, 2H), 3.72 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H), 1.28 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 140.3, 139.8, 134.4, 132.0, 130.4, 128.6, 127.7, 127.4, 126.6, 126.5, 126.1, 59.5, 32.3, 20.7. **IR** (ATR): ν = 3370, 3056, 2922, 1492, 1466, 1065, 1007, 743, 696 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 253.1045 $(M - OH)^+$, found: 253.1045.

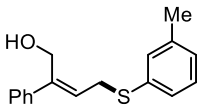


(*Z*)-2-Phenyl-4-((4-(trifluoromethyl)phenyl)thio)but-2-en-1-ol (II.7d). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). White solid, yield: 70%, *Z/E* = 83:17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.45-7.30 (m, 7H), 5.99 (t, *J* = 8.1 Hz, 1H), 4.53 (s, 2H), 3.87 (d, *J* = 8.1 Hz, 2H), 1.58 (br. s, 1H). **^{19}F NMR** (376 MHz, CDCl3) δ -62.18. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0, 141.3, 139.9, 129.0, 128.7, 128.4 (q, $^2J_{CF}$ = 33 Hz), 128.0, 126.5, 125.8 (q, $^3J_{CF}$ = 4 Hz), 125.4, 124.1 (q, $^1J_{CF}$ = 272 Hz), 59.7, 31.4. **IR** (ATR): ν = 3385, 1602, 1324, 1164, 1093, 1011, 822 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 307.0773 $(M - OH)^+$, found: 307.0763.

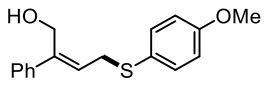


(*Z*)-4-((4-Bromophenyl)thio)-2-phenylbut-2-en-1-ol (II.7e). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). White solid, yield: 76%, *Z/E* = 80:20. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.40-7.38 (m, 2H), 7.36-7.33 (m, 3H), 7.31-7.27 (m, 2H), 5.96 (t, *J* = 8.1 Hz, 1H), 4.41 (s, 2H), 3.76 (d, *J* = 8.1 Hz, 2H), 1.39 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.5, 140.0, 134.5, 132.9, 132.1, 128.7, 127.9, 126.5, 126.0, 121.2,

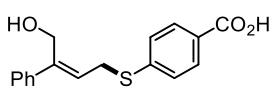
59.6, 32.9. **IR** (ATR): ν = 3426, 2930, 1471, 1432, 1087, 1003, 809, 767, 690 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 317.0003 $(M - OH)^+$, found: 316.9994.



(*Z*)-2-Phenyl-4-(*m*-tolylthio)but-2-en-1-ol (II.7f). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Orange solid, yield: 95%, *Z/E* = 90:10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.40 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.25 (m, 3H), 7.23-7.21 (m, 1H), 7.08-7.07 (m, 1H), 5.99 (t, *J* = 8.1 Hz, 1H), 4.35 (s, 2H), 3.75 (d, *J* = 8.1 Hz, 2H), 2.33 (s, 3H), 1.22 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 140.3, 138.9, 134.7, 132.7, 129.0, 128.9, 128.6, 128.2, 127.7, 126.5, 126.5, 59.5, 33.1, 21.3. **IR** (ATR): ν = 3366, 3028, 2920, 1591, 1474, 1007, 765, 689 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 253.1043 $(M - OH)^+$, found: 253.1045.

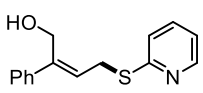


(*Z*)-4-((4-Methoxyphenyl)thio)-2-phenylbut-2-en-1-ol (II.7g). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Colorless oil, yield: 83%, *Z/E* = 93:7. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43-7.38 (m, 4H), 7.35-7.32 (m, 2H), 7.29-7.28 (m, 1H), 6.86-6.85 (m, 2H), 5.96 (t, *J* = 8.3 Hz, 1H), 4.24 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 3.64 (d, *J* = 8.3 Hz, 2H), 1.02 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 141.8, 140.4, 135.8, 135.8, 128.6, 127.7, 126.8, 126.5, 114.7, 59.4, 55.5, 34.8. **IR** (ATR): ν = 3371, 1590, 1491, 1461, 1242, 1172, 1025, 825, 696 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 269.1002 $(M - OH)^+$, found: 269.0995.

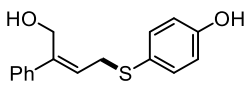


(*Z*)-4-((4-Hydroxy-3-phenylbut-2-en-1-yl)thio)benzoic acid (II.7h). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). White solid, yield: 98%, *Z/E* = 91:9. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.94-7.93 (m, 2H), 7.45-7.43 (m, 2H), 7.41-7.39 (m, 2H), 7.32-7.29 (m, 2H), 7.25-7.22 (m, 1H), 5.95 (t, *J* = 7.7 Hz, 1H), 4.50 (s, 2H), 3.97 (d, *J* = 7.7 Hz, 2H). **^{13}C NMR** (101 MHz, CD_3OD) δ 144.8, 144.0, 142.1, 131.1, 129.4, 129.3, 128.8, 128.4, 127.5, 126.7, 125.6, 59.5, 31.5. **IR** (ATR): ν = 3560, 3533, 3033, 2921, 2612, 2528,

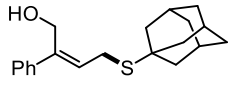
2022, 1667, 1590, 1404, 1278, 1008, 756, 697 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 299.0741 $(M - H)^-$, found: 299.0747.



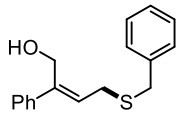
(*Z*)-2-Phenyl-4-(pyridin-2-ylthio)but-2-en-1-ol (II.7i). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Orange oil, yield: 93%, *Z/E* > 99:1. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36-8.34 (m, 1H), 7.50-7.44 (m, 3H), 7.32-7.29 (m, 2H), 7.26-7.18 (m, 2H), 7.01-6.98 (m, 1H), 5.92 (t, *J* = 7.8 Hz, 1H), 5.02 (br. s, 1H), 4.66 (s, 2H), 4.10 (d, *J* = 7.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.3, 149.0, 141.4, 141.3, 136.3, 128.4, 127.5, 127.4, 126.2, 123.0, 119.8, 60.8, 28.6. **IR** (ATR): *v* = 3319, 3051, 1577, 1453, 1413, 1123, 1012, 756, 696 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 258.0945 $(M + H)^+$, found: 258.0947.



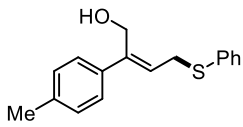
(*Z*)-4-((4-Hydroxy-3-phenylbut-2-en-1-yl)thio)phenol (II.7j). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). Yellow solid, yield: 87%, *Z/E* = 91:9. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.37-7.35 (m, 2H), 7.30-7.27 (m, 3H), 7.24-7.22 (m, 1H), 7.08-7.00 (m, 1H), 6.75-6.73 (m, 2H), 5.87 (t, *J* = 8.1 Hz, 1H), 4.07 (s, 2H), 3.63 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, CD_3OD) δ 159.0, 142.6, 142.4, 137.1, 129.2, 128.1, 128.0, 127.4, 116.8, 116.8, 59.1, 35.4. **IR** (ATR): *v* = 3169, 2923, 2922, 1595, 1581, 1491, 1426, 1218, 1168, 993, 825, 696 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 271.0797 $(M - H)^-$, found: 271.0798.



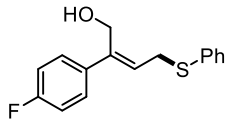
(*Z*)-4-(((3s,5s,7s)-Adamantan-1-yl)thio)-2-phenylbut-2-en-1-ol (II.7k). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 98%, *Z/E* > 99:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.35-7.32 (m, 2H), 7.28-7.25 (m, 1H), 6.04 (t, *J* = 8.1 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 3.45 (d, *J* = 8.1 Hz, 2H), 2.07(m, 3H), 1.93 (m, 6H), 1.71 (m, 6H), 1.29 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 140.7, 128.5, 127.5, 127.5, 126.3, 60.0, 45.5, 43.6, 36.4, 29.8, 23.8. **IR** (ATR): *v* = 3382, 2903, 2843, 1492, 1012 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 297.1665 $(M - OH)^+$, found: 297.1671.



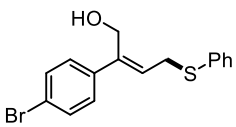
(*Z*)-4-(Benzylthio)-2-phenylbut-2-en-1-ol (II.7l). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 50%, *Z/E* = 92:8. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.37-7.28 (m, 8H), 5.97 (t, *J* = 8.1 Hz, 1H), 4.45 (s, 2H), 3.78 (s, 2H), 3.31 (d, *J* = 8.1 Hz, 2H), 1.62 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 140.3, 138.1, 129.0, 128.7, 128.7, 127.7, 127.3, 127.2, 126.4, 59.7, 36.0, 28.8. **IR** (ATR): *v* = 3378, 3026, 2916, 1493, 1452, 1007, 764, 696 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 253.1041 $(M - OH)^+$, found: 253.1045.



(*Z*)-4-(Phenylthio)-2-(*p*-tolyl)but-2-en-1-ol (II.7m). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 70%, *Z/E* = 94:6. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7 7.46-7.44 (m, 2H), 7.34-7.23 (m, 5H), 7.16-7.14 (m, 2H), 5.97 (t, *J* = 8.1 Hz, 1H), 4.33 (s, 2H), 3.75 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H), 1.17(br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0, 137.5, 137.2, 135.1, 132.1, 129.3, 129.1, 127.4, 126.3, 125.5, 59.4, 33.2, 21.2. **IR** (ATR): *v* = 3416, 2922, 1581, 1478, 1473, 999, 819, 689 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 293.0971 $(M + Na)^+$, found: 293.0971.

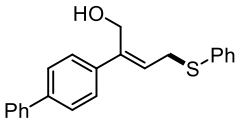


(*Z*)-2-(4-Fluorophenyl)-4-(phenylthio)but-2-en-1-ol (II.7n). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). White solid, yield: 84%, *Z/E* = 83:17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.38-7.30 (m, 4H), 7.28-7.27 (m, 1H), 7.03-6.99 (m, 2H), 5.94 (t, *J* = 8.1 Hz, 1H), 4.31 (s, 2H), 3.74 (d, *J* = 8.1 Hz, 2H), 1.14 (br. s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.86. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (d, $^{1}J_{CF}$ = 247 Hz), 141.2, 132.2, 129.1, 128.9, 128.2, 128.1, 127.5, 126.5 (d, $^{3}J_{CF}$ = 9 Hz), 115.5 (d, $^{2}J_{CF}$ = 21 Hz), 59.5, 33.1. **IR** (ATR): *v* = 3438, 1506, 1580, 1221, 1023, 833, 732, 1007, 696 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 297.0718 $(M + Na)^+$, found: 297.0720.

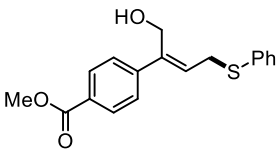


(*Z*)-2-(4-Bromophenyl)-4-(phenylthio)but-2-en-1-ol (II.7o). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained

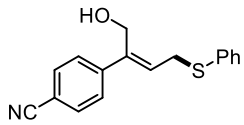
after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 88%, *Z/E* = 87:13. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45-7.43 (m, 4H), 7.33-7.30 (m, 2H), 7.28-7.27 (m, 2H), 7.25-7.24 (m, 1H), 5.98 (t, *J* = 8.1 Hz, 1H), 4.29 (s, 2H), 3.73 (d, *J* = 8.1 Hz, 2H), 1.16 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 139.2, 134.8, 132.2, 131.6, 129.1, 128.14, 127.6, 126.9, 121.7, 59.2, 33.2. **IR** (ATR): *v* = 3360, 1564, 1480, 1436, 1073, 1006, 739, 690 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 316.9993 $(M - OH)^+$, found: 316.9994.



(*Z*)-2-([1,1'-Biphenyl]-4-yl)-4-(phenylthio)but-2-en-1-ol (II.7p). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). White solid, yield: 97%, *Z/E* = 94:6. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.50-7.43 (m, 6H), 7.37-7.27 (m, 4H), 6.07 (t, *J* = 8.1 Hz, 1H), 4.38 (s, 2H), 3.78 (d, *J* = 8.1 Hz, 2H), 1.13 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 140.7, 140.6, 139.1, 135.0, 132.2, 129.1, 128.9, 127.5, 127.4, 127.3, 127.1, 126.9, 126.3, 59.4, 33.3. **IR** (ATR): *v* = 3356, 1560, 1476, 1438, 1015, 836, 763, 668 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 355.1113 $(M + Na)^+$, found: 355.1103.

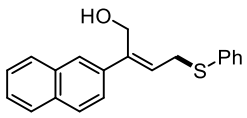


Methyl (*Z*)-4-(1-hydroxy-4-(phenylthio)but-2-en-2-yl)benzoate (II.7q). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 80%, *Z/E* = 84:16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98-7.97 (m, 2H), 7.46-7.43 (m, 3H), 7.32-7.29 (m, 2H), 7.27-7.22 (m, 1H), 7.15-7.13 (m, 1H), 6.07 (t, *J* = 8.1 Hz, 1H), 4.32 (s, 2H), 3.90 (s, 3H), 3.75 (d, *J* = 8.1 Hz, 2H), 1.38 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.9, 144.9, 141.2, 134.7, 132.4, 129.9, 129.2, 129.2, 128.3, 127.7, 126.4, 59.2, 52.2, 33.2. **IR** (ATR): *v* = 3417, 3066, 2949, 1715, 1606, 1436, 1275, 1107, 690 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 337.0856 $(M + Na)^+$, found: 337.0835.

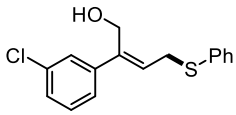


(*Z*)-4-(1-Hydroxy-4-(phenylthio)but-2-en-2-yl)benzonitrile (II.7r). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown oil, yield: 91%, *Z/E* = 67:33. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61-7.60 (m, 2H), 7.50-7.49 (m, 2H), 7.46-7.45 (m, 1H), 7.34-7.32 (m, 2H), 7.25-7.24 (m, 1H), 7.17-7.16 (m, 1H), 6.08 (t, *J* =

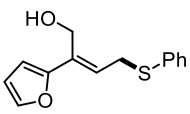
8.1 Hz, 1H), 4.30 (s, 2H), 3.75 (d, *J* = 8.1 Hz, 2H), 1.04 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 140.5, 134.5, 132.6, 132.3, 129.3, 129.2, 127.9, 127.1, 118.9, 111.2, 59.0, 33.3. **IR** (ATR): *v* = 3412, 3068, 2924, 2226, 1604, 1438, 1004, 836, 690 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 264.0835 $(M - OH)^+$, found: 264.0841.



(*Z*)-2-(Naphthalen-2-yl)-4-(phenylthio)but-2-en-1-ol (II.7s). The tittle compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 51%, *Z/E* = 89:11. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85-7.83 (m, 1H), 7.79-7.77 (m, 1H), 7.67-7.65 (m, 1H), 7.53-7.52 (m, 2H), 7.48-7.47 (m, 1H), 7.45-7.36 (m, 4H), 7.33-7.31 (m, 1H), 7.25-7.20 (m, 1H), 5.80 (t, *J* = 8.1 Hz, 1H), 4.39 (s, 2H), 3.87 (d, *J* = 8.1 Hz, 2H), 1.27 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.8, 139.0, 135.2, 133.8, 131.9, 131.6, 129.2, 129.1, 128.4, 127.9, 127.3, 126.2, 126.1, 125.9, 125.6, 125.3, 61.6, 32.7. **IR** (ATR): *v* = 3371, 3054, 2924, 1479, 1438, 1394, 1013, 777, 690 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 329.0965 $(M + Na)^+$, found: 329.0971.

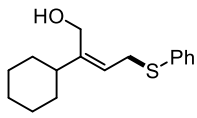


(*Z*)-2-(3-Chlorophenyl)-4-(phenylthio)but-2-en-1-ol (II.7t). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown oil, yield: 71%, *Z/E* = 80:20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.38 (s, 1H), 7.34-7.31 (m, 2H), 7.29-7.27 (m, 2H), 7.25 (s, 2H), 6.00 (t, *J* = 8.1 Hz, 1H), 4.29 (d, *J* = 5.2 Hz, 2H), 3.74 (d, *J* = 8.1 Hz, 2H), 1.10 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 140.9, 134.8, 134.5, 132.4, 129.8, 129.9, 127.7, 127.7, 127.6, 126.7, 124.6, 59.3, 32.2. **IR** (ATR): *v* = 3350, 3069, 2926, 1562, 1475, 997, 737, 669 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 273.0496 $(M - OH)^+$, found: 273.0499.

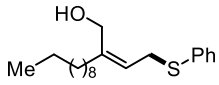


(*E*)-2-(Furan-2-yl)-4-(phenylthio)but-2-en-1-ol (II.7u). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 99%, *E/Z* > 99:1. *Note that formally compound **II.7u** has an (E)-configuration, but its formation follows a similar stereocontrolled thiolation pathway as for the other reported compounds*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.43-7.42 (m, 2H), 7.37 (s, 1H), 7.32-7.29 (m, 2H),

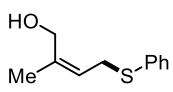
7.27-7.25 (m, 1H), 6.55-6.50 (m, 1H), 5.95 (t, *J* = 8.1 Hz, 1H), 4.19 (s, 2H), 3.72 (d, *J* = 8.1 Hz, 2H), 1.08 (br. s, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 139.8, 135.1, 133.4, 132.1, 129.1, 127.5, 125.5, 123.5, 108.0, 59.3, 32.9. **IR** (ATR): *v* = 3360, 1581, 1478, 1438, 1162, 1013, 871, 736, 688 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 245.0626 $(M - H)^+$, found: 245.0631.



(*Z*)-2-Cyclohexyl-4-(phenylthio)but-2-en-1-ol (II.7v). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 48%, *Z/E* = 84:16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.31-7.29 (m, 2H), 7.25-7.22 (m, 1H), 5.46 (t, *J* = 8.1 Hz, 1H), 3.94 (s, 2H), 3.60 (d, *J* = 8.1 Hz, 2H), 2.03-1.98 (m, 1H), 1.77-1.76, (m, 2H), 1.74-1.68 (m, 2H), 1.28-1.22 (m, 3H), 1.18-1.11 (m, 3H) 0.85 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 135.5, 132.0, 129.0, 127.2, 121.9, 59.5, 43.4, 32.7, 32.6, 26.8, 26.3. **IR** (ATR): *v* = 3278, 2922, 2850, 1452, 689 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 245.1365 $(M - OH)^+$, found: 245.1358.

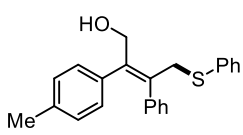


(*Z*)-2-(2-(Phenylthio)ethylidene)dodecan-1-ol (II.7w). The title compound was prepared following the general procedure for the preparation of allylic thioethers by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Colorless oil, yield: 87%, *Z/E* = 70:30. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.36-7.34 (m, 1H), 7.31-7.28 (m, 2H), 5.46 (t, *J* = 8.1 Hz, 1H), 3.96 (d, *J* = 5.2 Hz, 2H), 3.58 (d, *J* = 8.1 Hz, 2H), 2.08 (t, *J* = 7.6 Hz, 2H), 1.26 (m, 16H), 0.90 (br. s, 1H), 0.88 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 131.6, 130.1, 129.0, 127.1, 122.8, 60.1, 35.2, 32.4, 32.0, 29.7, 29.6, 29.5, 29.4, 28.2, 22.8, 14.2. **IR** (ATR): *v* = 3388, 3276, 1486, 1431, 778, 690 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 303.2136 $(M - OH)^+$, found: 303.2141.

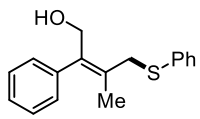


(*Z*)-2-Methyl-4-(phenylthio)but-2-en-1-ol (II.7w). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown oil, yield: 40%, *Z/E* = 80:20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.36-7.28 (m, 3H), 5.46 (t, *J* = 8.1 Hz, 1H), 3.94 (s, 2H), 3.56 (d, *J* = 8.1 Hz, 2H), 1.79 (s, 3H), 0.89 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ

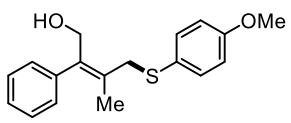
139.0, 131.5, 130.2, 129.0, 127.0, 122.8, 61.3, 32.3, 21.4. **IR** (ATR): ν = 3356, 2918, 2851, 1479, 1437, 737 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 177.0732 (M - OH)$^+$, found: 177.0733.



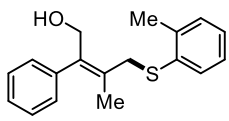
(*Z*)-3-Phenyl-4-(phenylthio)-2-(*p*-tolyl)but-2-en-1-ol (II.8a). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 48%, *Z/E* > 99:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.33-7.28 (m, 3H), 7.12-7.09 (m, 5H), 6.94-6.88 (m, 4H), 4.37 (s, 2H), 4.11 (s, 2H), 2.23 (s, 3H), 1.59 (br. s, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5, 141.2, 137.0, 136.5, 135.7, 135.6, 131.7, 129.6, 129.4, 129.0, 128.8, 127.9, 127.3, 126.7, 63.4, 39.5, 21.2. **IR** (ATR): ν = 3339, 3064, 3020, 2921, 1510, 1480, 1439, 1072, 996, 733, 697 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 369.1280 (M + Na)$^+$, found: 369.1284.



(*Z*)-3-Methyl-2-phenyl-4-(phenylthio)but-2-en-1-ol (II.8b). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). White solid, yield: 62%, *Z/E* = 94:6. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.36-7.32 (m, 6H), 7.11-7.08 (m, 2H), 4.07 (d, J = 5.0 Hz, 2H), 3.73 (s, 2H), 1.75 (s, 3H), 1.08 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 139.3, 135.3, 132.8, 131.2, 129.0, 128.8, 128.4, 127.7, 127.0, 62.8, 39.1, 19.9. **IR** (ATR): ν = 3197, 3055, 2903, 2866, 1585, 1480, 1437, 1009, 700 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 293.0979 (M + Na)$^+$, found: 293.0971.

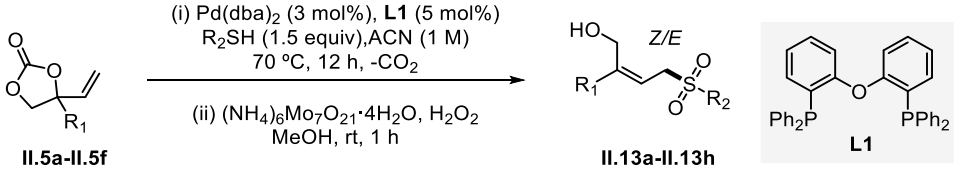


(*Z*)-4-((4-Methoxyphenyl)thio)-3-methyl-2-phenylbut-2-en-1-ol (II.8c). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow oil, yield: 65%, *Z/E* = 98:2. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.24 (m, 1H), 7.09-7.07 (m, 2H), 6.90-6.88 (m, 2H), 3.95 (d, *J* = 5.0 Hz, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 1.73 (s, 3H), 0.95 (br. s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 141.1, 139.0, 136.3, 131.6, 128.8, 128.4, 127.0, 125.2, 114.6, 62.8, 55.5, 40.4, 19.8. **IR** (ATR): ν = 3258, 2917, 1493, 1245 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 283.1149 (M - OH)$^+$, found: 283.1151.



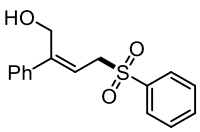
(*Z*)-3-Methyl-2-phenyl-4-(*o*-tolylthio)but-2-en-1-ol (II.8d). The title compound was prepared following the general procedure for the preparation of allylic thioethers, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown oil, yield: 37%, *Z/E* = 90:10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 1H), 7.36-7.32 (m, 2H), 7.28-7.20 (m, 4H), 7.12-7.10 (m, 2H), 4.05 (d, *J* = 5.0 Hz, 2H), 3.66 (s, 2H), 2.49 (s, 3H), 1.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 140.4, 139.3, 134.7, 133.1, 131.2, 130.4, 128.8, 128.4, 127.8, 127.0, 126.6, 62.8, 38.2, 20.8, 20.2. **IR** (ATR): *v* = 3390, 3066, 2920, 2862, 1467, 1440, 1377, 1064, 995, 701 cm^{-1}. **HRMS** (APCI+, MeOH): *m/z* calcd. 267.1200 $(M - OH)^+$, found: 267.1202.

II.4.4 General procedure for the one-pot preparation of allylic sulfones



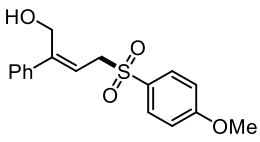
Scheme II-10. General procedure for the preparation of allylic sulfones.

A screw-capped vial was charged with the respective vinyl cyclic carbonate (0.2 mmol, 1.0 equiv), thiol derivative (0.3 mmol, 1.5 equiv), the $Pd(dba)_2$ pre-catalyst (0.003 g, 3 mol%), phosphine **L1** (0.005 g, 5 mol%) and ACN (200 μL). The reaction mixture was stirred at 70 ºC for 12 h. The solvent was removed and the crude product was dissolved in MeOH (200 μL). Afterwards $(NH_4)_6Mo_7O_24{\cdot}4H_2O$ (0.025 g, 10 mol %) and H_2O_2 (0.8 mol, 4 equiv, 30 wt% aqueous solution) were added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was purified by flash column chromatography on silica gel to afford the corresponding allylic sulfone product. All purified products were fully characterized by ^{1}H, ^{13}C NMR, IR spectra and HRMS analysis; ^{19}F NMR and related 2D NMR experiments were carried out when necessary. **Note**: Only the data for the main component, *i.e.* the (*Z*)-isomer is listed.

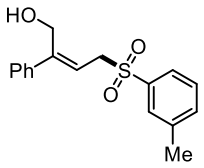


(*Z*)-2-Phenyl-4-(phenylsulfonyl)but-2-en-1-ol (II.13a). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). White solid, yield:

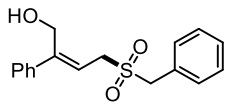
90%, *Z/E* = 94:6. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93-7.92 (m, 2H), 7.71-7.68 (m, 1H), 7.61-7.58 (m, 2H), 7.44-7.42 (m, 2H), 7.37-7.32 (m, 3H), 5.71 (t, *J* = 8.4 Hz, 1H), 4.43 (s, 2H), 4.15 (d, *J* = 8.4 Hz, 2H), 2.52 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.2, 140.0, 138.8, 134.2, 129.5, 128.7, 128.5, 128.4, 126.5, 115.1, 60.4, 56.1. **IR** (ATR): *v* = 3491, 3055, 1448, 1290, 1137, 705, 609 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 311.0723 $(M + Na)^+$, found: 311.0712.



(*Z*)-4-((4-Methoxyphenyl)sulfonyl)-2-phenylbut-2-en-1-ol (II.13b). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). White solid, yield: 83%, *Z/E* = 93:7. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.44-7.42 (m, 2H), 7.35-7.31 (m, 3H), 7.02-7.00 (m, 2H), 5.71 (t, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 4.11 (d, *J* = 8.4 Hz, 2H), 3.88 (s, 3H), 2.74 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.1, 148.9, 140.1, 130.6, 130.2, 128.6, 128.3, 126.5, 115.5, 114.6, 60.3, 56.3, 55.8. **IR** (ATR): *v* = 1593, 1577, 1496, 1260, 1133, 1085, 732 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 341.0830 $(M + Na)^+$, found: 341.0831.

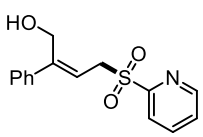


(*Z*)-2-Phenyl-4-(*m*-tolylsulfonyl)but-2-en-1-ol (II.13c). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). Colorless oil, yield: 89%, *Z/E* = 90:10. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.48-7.42 (m, 4H), 7.37-7.32 (m, 3H), 5.72 (t, *J* = 8.4 Hz, 1H), 4.44 (s, 2H), 4.14 (d, *J* = 8.4 Hz, 2H), 2.57 (br. s, 1H), 2.45 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.3, 140.0, 139.8, 138.7, 135.0, 129.3, 128.8, 128.7, 128.4, 126.6, 125.6, 115.2, 60.4, 56.1, 21.4. **IR** (ATR): ν = 3487, 2924, 1297, 1132, 1062, 696 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 301.0902 $(M - H)^-$, found: 301.0904.

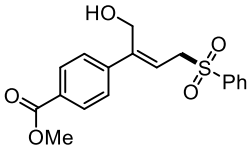


(*Z*)-4-(Benzylsulfonyl)-2-phenylbut-2-en-1-ol (II.13d). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). White solid, yield: 48%, *Z/E* = 91:9. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49-7.35 (m, 10H), 5.83 (t, *J* = 8.4 Hz, 1H), 4.48 (d, *J* = 6.5 Hz, 2H), 4.31 (s, 2H), 3.92 (d, *J* = 8.4 Hz, 2H), 2.75 (t, *J* = 6.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.5, 139.9, 130.6, 129.3, 129.2, 128.6, 128.4, 127.5, 126.5, 114.1,

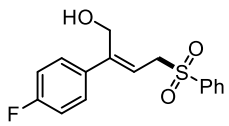
60.5, 59.4, 51.2. **IR** (ATR): ν = 3483, 1302, 1114, 1010, 696 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 325.0866 $(M + Na)^+$, found: 325.0855.



(*Z*)-2-Phenyl-4-(pyridin-2-ylsulfonyl)but-2-en-1-ol (II.13e). The title compound was prepared following the general procedure for the preparation of allylic sulfones by using a slight excess of vinyl carbonate substrate (0.22 mmol), and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). Brown oil, yield: 91%, *Z/E* = 87:13. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.78-8.77 (m, 1H), 8.08-8.06 (m, 1H), 7.99-7.95 (m, 1H), 7.59-7.57 (m, 1H), 7.41-7.39 (m, 2H), 7.32-7.30 (m, 3H), 5.77 (t, *J* = 8.4 Hz, 1H), 4.53 (s, 2H), 4.49 (d, *J* = 8.4 Hz, 2H), 2.77 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.1, 150.3, 149.5, 140.0, 138.5, 128.6, 128.4, 127.8, 126.6, 122.6, 114.5, 60.5, 51.9. **IR** (ATR): ν = 3496, 1427, 1307, 1106, 749, 701 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 312.0654 $(M + Na)^+$, found: 312.0665.

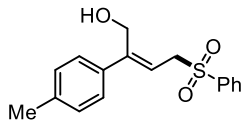


Methyl (*Z*)-4-(1-hydroxy-4-(phenylsulfonyl)but-2-en-2-yl)benzoate (II.13f). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). Yellow oil, yield: 76%, *Z/E* = 84:16. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2H), 7.92-7.90 (m, 2H), 7.71-7.68 (m, 1H), 7.61-7.57 (m, 2H), 7.51-7.49 (m, 2H), 5.79 (t, *J* = 8.4 Hz, 1H), 4.44 (d, *J* = 6.5 Hz, 2H), 4.16 (d, *J* = 8.4 Hz, 2H), 3.91 (s, 3H), 2.73 (t, *J* = 6.5 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.8, 148.5, 144.5, 138.7, 134.3, 129.9, 129.5, 128.5, 128.4, 126.5, 116.9, 60.1, 56.1, 52.3. **IR** (ATR): ν = 3367, 1715, 1438, 1277, 1084, 1015, 732 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 369.0783 $(M + Na)^+$, found: 369.0767.



(*Z*)-2-(4-Fluorophenyl)-4-(phenylsulfonyl)but-2-en-1-ol (II.13g). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). White solid, yield: 77%, *Z/E* = 93:7. **^{1}H NMR** (500 MHz, $CDCl_3$) δ .93-7.91 (m, 2H), 7.72-7.68 (m, 1H), 7.62-7.58 (m, 2H), 7.44-7.41 (m, 2H), 7.06-7.01 (m, 2H), 5.67 (t, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 6.5 Hz, 2H), 4.13 (d, *J* = 8.4 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.61. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{CF}$ = 249 Hz), 148.4, 138.8,

136.1, 134.3, 129.5, 128.5, 128.4 (d, $^3J_{CF}$ = 8.2 Hz), 115.7 (d, $^2J_{CF}$ = 21.5 Hz), 114.9, 60.4, 56.1. **IR** (ATR): ν = 2921, 2851, 1508, 1447, 1305, 1140, 1082, 827, 686 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 329.0626 $(M + Na)^+$, found: 329.0618.



(*Z*)-4-(Phenylsulfonyl)-2-(*p*-tolyl)but-2-en-1-ol (II.13h). The title compound was prepared following the general procedure for the preparation of allylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 2/1). Colorless oil, yield: 72%. *Z/E* = 93:7. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.70-7.66 (m, 1H), 7.60-7.56 (m, 2H), 7.33-7.31 (m, 2H), 7.16-7.15 (m, 2H), 5.68 (t, *J* = 8.4 Hz, 1H), 4.40 (s, 2H), 4.14 (d, *J* = 8.4 Hz, 2H), 2.35 (s, 3H), 2.32 (br. s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.0, 138.8, 138.4, 137.0, 134.2, 129.4, 129.4, 128.5, 126.4, 114.2, 60.3, 56.2, 21.2. **IR** (ATR): ν = 3495, 2921, 1447, 1303, 1138, 1083, 1010, 730, 697 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 325.0865 $(M + Na)^+$, found: 325.0869.

II.4.5 Crystallographic data

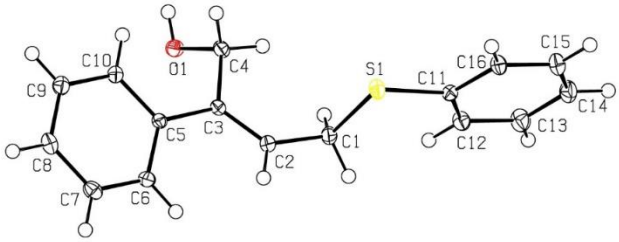


Table II-3. Crystal data and structure refinement for **II.7a** (CCDC-1504675).

Empirical formula	$C_{16}H_{16}OS$
Formula weight	256.35
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P*2(1)
Unit cell dimensions	a = 7.5678(6)Å α = 90°
	b = 5.1454(4)Å β = 98.7561(18)°
	c = 16.9271(14)Å γ = 90°
Volume	651.45(9) $Å^3$
Z	2
Density (calculated)	1.307 Mg/m^3
Absorption coefficient	0.233 mm^{-1}
F(000)	272
Crystal size	0.40 × 0.10 × 0.10 mm^3
Theta range for data collection	1.217 to 33.772°
Index ranges	-11<=h<=11,-7<=k<=8,-12<=l<=26
Reflections collected	7181
Independent reflections	4205 [*R*(int) = 0.0241]
Completeness to theta =33.772°	94.4%
Absorption correction	Multi-scan
Max. and min. transmission	0.977 and 0.771
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4205/ 1 / 164
Goodness-of-fit on F^2	1.049
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0377, *wR*2 = 0.0992
R indices (all data)	*R*1 = 0.0390, *wR*2 = 0.1038
Flack parameter	x = -0.08(5)
Largest diff. peak and hole	0.506 and -0.394 $e·Å^{-3}$

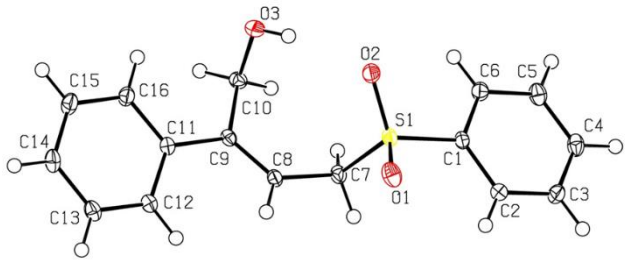


Table II-4. Crystal data and structure refinement for **II.13a** (CCDC-1504676).

Empirical formula	$C_{16}H_{16}O_3S$	
Formula weight	288.35	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*2(1)/n	
Unit cell dimensions	*a* = 7.9679(3)Å	α = 90°.
	b = 11.4739(5)Å	β = 93.3560(10)°.
	c = 14.9692(6)Å	γ = 90°.
Volume	1366.18(10) Å^3	
Z	4	
Density (calculated)	1.402 Mg/m^3	
Absorption coefficient	0.241 mm^{-1}	
F(000)	608	
Crystal size	0.30 × 0.20 × 0.20 mm^3	
Theta range for data collection	2.238 to 33.212°	
Index ranges	-11<=h<=12,-10<=k<=17,-21<=l<=23	
Reflections collected	17748	
Independent reflections	5025 [*R*(int) = 0.0194]	
Completeness to theta =33.212°	95.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.953 and 0.894	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5025/ 0 / 182	
Goodness-of-fit on F^2	1.044	
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0349, *wR*2 = 0.0948	
R indices (all data)	*R*1 = 0.0399, *wR*2 = 0.0983	
Largest diff. peak and hole	0.464 and -0.460 e·Å^{-3}	

UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE SYNTHESIS OF SULFONES AND AMINO ACIDS FROM FUNCTIONALIZED HETEROCYCLES
José Enrique Gómez Pulido

Chapter III

Copper-Catalyzed Enantioselective Construction of Tertiary Propargylic Sulfones

The results described in this chapter have been published in:

Gómez, J. E.; Cristòfol, À.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2019**, *58*, 3903-3907

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III.1. Introduction

III.1.1 Sulfur-containing quaternary stereocenters

The selective formation of carbon-sulfur (C–S) bonds constitute a significant topic within synthetic organic chemistry because organosulfur compounds are widely present in bioactive natural products, as well as being valuable chemical intermediates in synthesis.[1] In addition to this, organosulfur fragments are present in many synthetic drugs as previously introduced in Chapter II. Interestingly, the majority of these organosulfur compounds are enantiomerically pure having carbon-based stereogenic centers.[2]

Sulfur compounds containing quaternary stereocenters are prominent and common structural motifs with unique synthetic challenges.[3] The importance of optically active sulfur compounds featuring quaternary centers is exemplified by various bioactive compounds depicted in Figure III-1 including Spirobrassinin,[4] bis-*N*-norgliovictin,[5] thiolactomycin[6] and Tazobactam

1 For reviews on C–S bond formation, see: (a) Kondo, T.; Mitsudo, T.-A. *Chem. Rev*. **2000**, *100*, 3205-3220. (b) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem*. **2008**, *80*, 993-1003. (c) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev*. **2014**, *114*, 8807-8864. (d) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev*. **2015**, *44*, 291-314. (e) Qian, Z.; Jiang, X. *Org. Biomol. Chem*. **2017**, *15*, 1942-1946. For a review on enzymatic C–S bond formation, see: (f) Dunbar, K. L.; Scharf, D. H.; Litomska, A.; Hertweck, C. *Chem. Rev*. **2017**, *117*, 5521-5577.

2 For the importance of optically active sulfur-containing compounds see: (a) Damani, L. A. *Sulphur-Containing Drugs and Related Organic Compounds*. Wiley, New York, **1989**. (b) Toru, T.; Bolm, C. *Organosulfur Chemistry in Asymmetric Synthesis*. Wiley-VCH, Weinheim, **2008**. (c) Liu, H.; Jiang, X. *Chem. Asian J*. **2013**, *8*, 2546-2563. (d) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ*. **2010**, *87*, 1348-1349. (e) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 2832-2842. (f) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem*. **2016**, *16*, 1200-1216. (g) Scott, K. A.; Njardarson, J. T. *Top. Curr. Chem*. **2018**, *376*, 5. (h) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev*. **2007**, *107*, 5133-5209.

3 Reviews on catalytic enantioselective synthesis of sulfur-containing tetrasubstituted carbon stereocenters: (a) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem*. **2011**, *7*, 582-595. (b)Yu, J.-S.; Huang, H.-M.; Ding, P.-G.; Hu, X.- S.; Zhou, F.; Zhou, J. *ACS Catal*. **2016**, *6*, 5319-5344.

4 (a) Pedras, M. S. C.; Hossain, M.; Sarwar, M. G.; Montaut, S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 5469-5471. (b) Suchý, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentová, E. *J. Org. Chem*. **2001**, *66*, 3940-3947.

5 Song, Y.; Dou, H.; Gong, W.; Liu, X.; Yu, Z.; Li, E.; Tan, R.; Hou, Y. *Eur. J. Pharmacol*. **2013**, *705*, 49-60.

6 (a) Nishida, I.; Kawaguchi, A.; Yamada, M. *J. Biochem*. **1986**, *99*, 1447-1454. (b) Slayden, R. A.; Lee, R. E.; Armour, J. W.; Cooper, A. M.; Orme, I. M.; Brennan, P. J.; Besra, G. S. *Antimicrob. Agents Ch*. **1996**, *40*, 2813-2819. (c) Heath, R. J.; White, S. W.; Rock, C. O. *Prog. Lipid Res*. **2001**, *40*, 467-497. (d) Campbell, J. W.; Cronan, J. E. *Annu. Rev. Microbiol*. **2001**, *55*, 305-332.

among others.[7] Moreover, compounds such as chiral tertiary thiol **III.1** has been patented as flavoring agents.[8]

Noticeably, the biological activities and properties displayed by these compounds may be greatly influenced by the absolute configuration and substituents of the sulfur-containing, carbon stereocenter. For example, the (*R*)-enantiomer of spirothiazolidinone **III.2** is almost 10 times biologically more active than its opposite enantiomer (Figure III-1).[9] Consequently, the pursuit of new catalytic strategies that enable the formation of a C–S bond with simultaneous generation of a sterically hindered stereocenter and with sufficient structural diversity remains crucial within organic chemistry. Thus, new methods for their construction might facilitate the synthesis and modification of bioactive compounds to build up more extensive synthetic libraries, which in turn can accelerate drug discovery programs.[3]

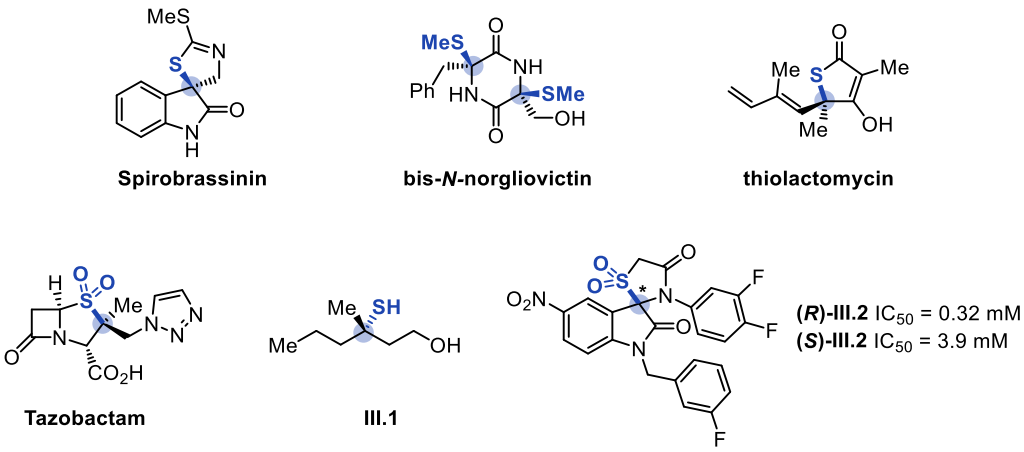


Figure III-1. Selected drugs and bioactive compounds featuring S-containing quaternary stereocenters.

However, the synthesis of sulfur compounds containing quaternary stereocenters in a catalytic and enantioselective manner is a huge challenge, especially for acyclic systems. Besides the general challenges associated with the synthesis of fully substituted carbon stereocenters (such as the relatively low reactivity of precursors and difficulties in enantiofacial control of the

7 Micetich, R. G.; Maiti, S. N.; Spevak, P.; Hall, T. W.; Yamabe, S.;Ishida, N.; Tanaka, M.; Yamazaki, T.; Nakai, A.; Ogawa, K. *J. Med. Chem.* **1987**, *30*, 1469-1474.
8 Gonzalo, A.; Markus, G.; Frank, K.; Joachim, S.; Janos, Z. *Eur. Patent Appl.* 1055667, **2000**.
9 Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5902-5905.

prochiral carbons),[10] the coordinating properties of sulfur species may pose additional difficulties.[11] The interaction between a metal complex and a sulfur species, in particular when using thiols and disulfides, might influence catalyst turnover or even shut down catalysis completely. The relatively strong nucleophilicity of sulfur compounds might cause undesired side reactions under metal-free (*i.e*., organocatalytic) conditions. An ever-increasing attention is paid to the catalytic asymmetric synthesis of S-containing tetrasubstituted carbon stereocenters. In recent decades, different catalytic systems have been developed to forge such stereocenters, but their efficient and selective construction remains non-trivial.

III.1.2 Tertiary propargylic sulfones

The sulfonyl group (-SO_2-) is considered as a strong electron-withdrawing group employed as a temporary modulator of chemical reactivity and often used as versatile fragment in organic synthesis. Therefore, a variety of different transformations are feasible with this functional group.[2, 12] In addition, sulfur compounds containing a sulfonyl functional group have found various applications in fields as diverse as agrochemistry, pharmaceutical industry and in polymer science.[2, 12, 13] Hence, chemists have developed numerous strategies for the preparation of sulfonyl compounds including the catalytic synthesis of enantioenriched sulfones.[1, 12] In this context, whilst chiral secondary sulfone derivatives have been the subject of many investigations,[14] tertiary sulfones have remained mostly unexplored owing to the lack of efficient

10 (a) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*. Wiley-VCH, Weinheim, **2005**. (b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181-191. (c) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev*. **2017**, *117*, 12564-12580.

11 (a) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*. Marcel Dekker, New York, **1984**. (b) Hutton, A. T.; Wilkinson, G.; Gillard, R. D.; McCleverty, J. A. *Comprehensive Coordination Chemistry*. Pergamon: Oxford, U.K., **1984**.

12 For related reviews: (a) Whitham, G. H. *Organosulfur Chemistry*. Oxford University Press: Oxford, New York, **1995**. (b) Oae, S. *Organic Chemistry of Sulfur*. Plenium Press, New York, **1977**. (c) Stirling, C. J. M. *Organic sulphur chemistry: Structure, mechanism, and synthesis*. Butterworths: London, Boston, **1975**. (d) Patai, S.; Rappoport, Z.; Stirling, C. J. M. *The Chemistry of Sulphones and Sulphoxides*. Wiley-VCH, New York, **1988**. (d) Simpkins, N. S. *Sulfones in Organic Synthesis* Pergamon, New York, **1993**. (e) Vogel, P.; Turks, M.; Bouchez, L.; Markovic, D.; Varela-Álvarez, A.; Sordo, J. Á. *Acc. Chem. Res***. 2007**, *40*, 931-942. (f) Wilden, J. D. *J. Chem. Res.* **2010**, *34*, 541-548. (g) Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis* **2016**, *13*, 1939-1973.

13 (a) Teall, M.; Oakley, P.; Harrison, T.; Shaw, D.; Kay, E.; Elliott, J.; Gerhard, U.; Castro, J. L.; Shearman, M.; Ball, R. G.; Tsou, N. N. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2685-2688. (b) Yamada, M.; Ichikawa, T.; Ii, M.; Itoh, K.; Tamura, N.; Kitazaki, T. *Bioorg. Med. Chem*. **2008**, *16*, 3941-3958.

14 Representative examples of asymmetric synthesis of secondary sulfones: (a) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc*. **1995**, *117*, 9662-9670. (b) Gais, H.-J.; Jagusch, T.;

methodologies for their preparation in optically pure form. Enantioenriched tertiary propargylic sulfones **III.3** remain interesting though challenging targets (Figure III-2).

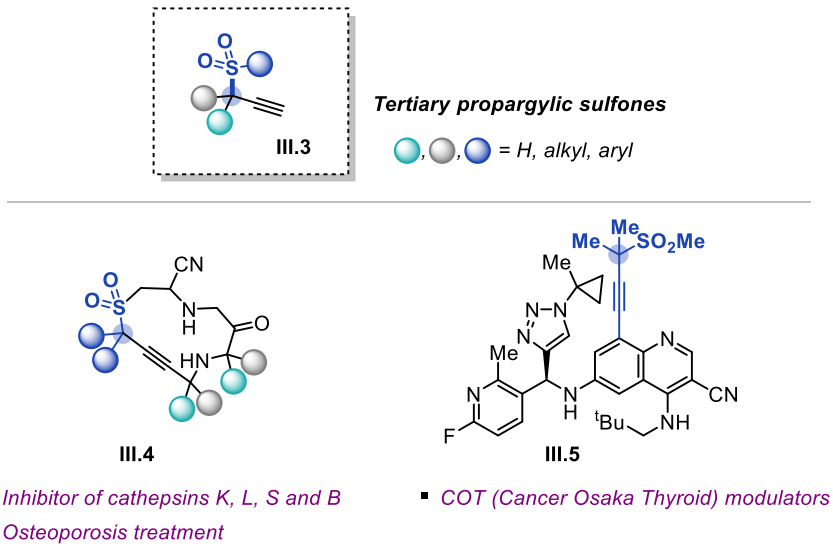


Figure III-2. Propargyl sulfone moiety and its occurrence in biologically active molecules.

Tertiary propargylic sulfones represent an important and structurally interesting class of compounds. Besides the tremendous progress that has been made in harnessing sulfones as valuable electrophilic cross-coupling partners,[12, 15] the pendant alkyne group in propargylic architectures can provide an additional synthetic handle for subsequent chemical transformations.[16] Thus, it is not surprising that these commodities have been exploited in synthetic chemistry and material sciences, as well as being incorporated in the structure of

Spalthoff, N.; Gerhards, F.; Frank, Raabe, G. M. *Chem. Eur. J.* **2003**, *9*, 4202-4221. (c) Ueda, M.; Hartwig, J. *Org. Lett.* **2010**, *12*, 92-94. (d) Najib, A.; Hirano K.; Miura, M. *Chem. Eur. J.* **2018**, *24*, 6525-6529. (e) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. *J. Am. Chem. Soc.* **2018**, *140*, 7056-7060.

15 For recent examples: (a) Ariki, Z. T.; Maekawa, Y.; Nambo, M.; Crudden, C. M. *J. Am. Chem. Soc.* **2018**, *140*, 78-81. (b) Yim, J. C.; Nambo, M.; Crudden, C. M. *Org. Lett.* **2017**, *19*, 3715-3718. (c) Nambo, M.; Keske, E. C.; Rygus, J. P. G.; Yim, J. C. H.; Crudden, C. M. *ACS Catal.* **2017**, *7*, 1108-1112. (d) Nambo, M.; Crudden, C. M. *ACS Catal.* **2015**, *5*, 4734-4742. (e) Nambo, M.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 742-746. (f) Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.-H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S. *Science* **2018**, *360*, 75-80. (g) Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. *J. Am. Chem. Soc.* **2018**, *140*, 880-883. (h) Gong, L.; Sun H- B.; Deng L- F.; Zhang X. Liu J.; Yang S.; Niu D. *J. Am. Chem. Soc.* **2019**, *141*, 7680-7686.

16 (a) Stang, P. J.; Diederich, F. *Modern Acetylene Chemistry.* Wiley-VCH, Weinheim, **1995**. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

pharmaceutically active agents[17] such as the inhibitors of cathepsins **III.4**,[18] cancer Osaka thyroid modulators **III.5** (Figure III-2)[19] and DNA cleaving agents.[20]

Despite the versatile potential of these sulfone scaffolds (**III.3**) in synthetic chemistry,[21] the current methodologies available for accessing chiral tertiary propargylic sulfones are unfortunately limited, and a catalytic asymmetric synthesis of such compounds remains to date unknown.

Racemic versions for preparing relatively non-functionalized propargylic sulfones have been reported. The most widely utilized approach is a Williamson-type reaction between propargylic bromides, iodides, or mesylates and thiols in the presence of inorganic bases.[17a,b, 22] However, these traditional approaches leading to tertiary propargylic sulfones rely on multistep synthetic sequences starting from propargylic alcohols **III.6**, involving hydroxyl group activation, substitution and oxidation and requiring several purification steps (Scheme III-1a). Furthermore, the key step involving C–S bond construction requires the use of odorous thiols as reagents and is carried out through an S_N2 substitution process. Importantly, such an approach is limited by the use of primary and secondary alcohols. Tertiary propargylic alcohols are difficult to access due to competitive E1 elimination or rearrangement *via* carbocation intermediates.

In a different approach, propargylic sulfones **III.10** containing a quaternary center can be prepared starting form sulfonylallenes **III.8**.[23] The allenyl functionality possessing a sulfonyl electron-withdrawing group at the α-position is sufficiently acidic to be γ-deprotonated by a mild base. Hence, the generated allenic/propargylic anions **III.9a** and **III.9b** can be intramolecularly

17 (a) García-Rubia, A. Romero-Revilla, J. A.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc*. **2015**, *137*, 6857-6865. (b) Moure, A. L.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. *Org. Lett*. **2013**, *15*, 2054-2057. (c) Liu, J.; Liu, Z.; Liao, P.; Bi, X. *Org. Lett*. **2014**, *16*, 6204-6207.

18 Oballa, R.; Bayly, C.; Truchon, J.-F.; Li, C. S.; Leger, S. *U.S. Patent Appl*. 0063013, **2010**.

19 Bacon, E. M.; Balan, G.; Chou, C.-H.; Clark, C. T.; Kim, M.; Kirschberg, T. A.; Phillips, G.; Schroeder, S. D.; Aquires, N. H.; Stevens, K. L.; Taylor, J. G.; Watkins, W. J.; Wright, N. E.; Zipeel, S. M. *PCT Int. Appl. WO* 2017007689A1, **2017**.

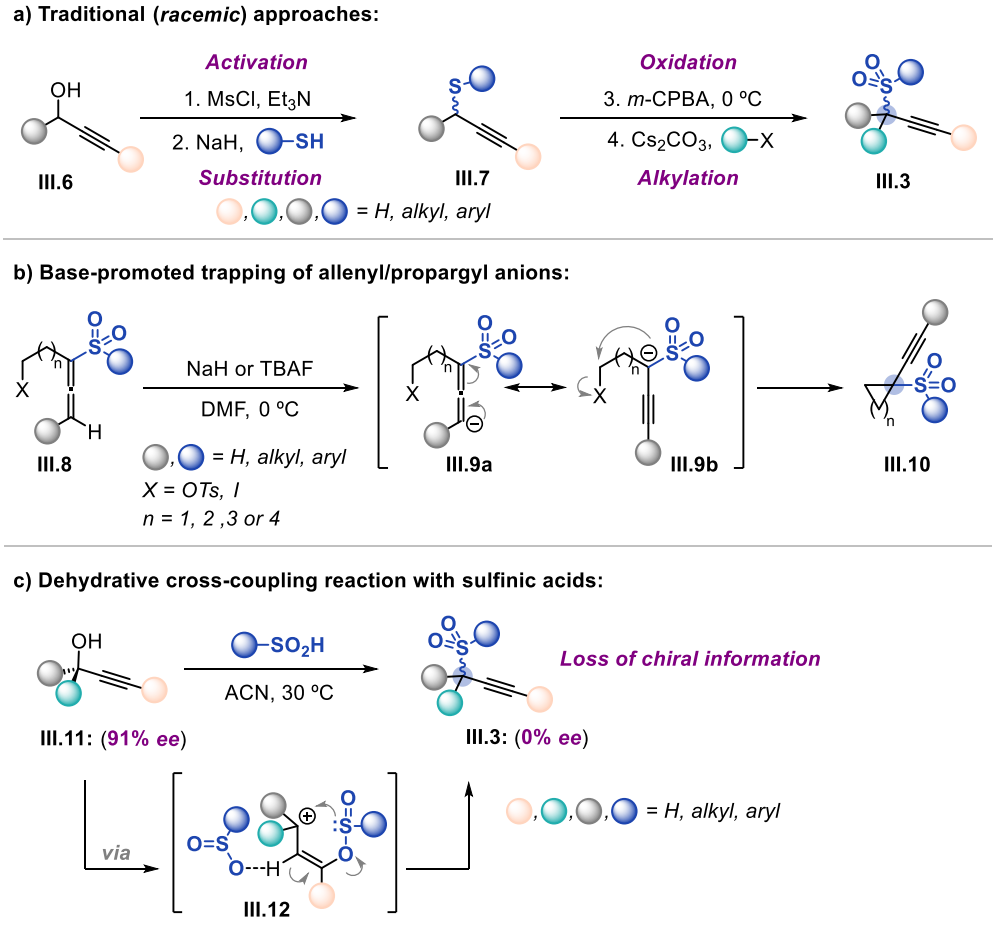
20 Haruna, K.-i.; Kanezaki, H.; Tanabe, K.; Dai, W.-M.; Nishimoto, S.-i. *Bioorg. Med. Chem*. **2006**, *14*, 4427-4432. (b) Haruna, K.-i.; Tanabe, K.; Ishii, A.; Min-Dai, W.; Hatta, H.; Nishimoto, S.-i. *Bioorg. Med. Chem*. **2003**, *11*, 5311-5316. (c) McPhee, M. M.; Kerwin, S. M. *Bioorg. Med. Chem*. **2001**, *9*, 2809-2818. (d) McPhee, M. M.; Kern, J. T.; Hoster, B. C.; Kerwin, S. M. *Bioorg. Chem*. **2000**, *28*, 98-118. (e) Muehlebach, M.; Lutz, W.; Wenger, J.; Finney, J.; Mathews, C. J.; Fawke, D. *PCT Int. Appl. WO* 2008110308A2, **2008**.

21 Vizer, S. A.; Sycheva, E. S.; Al Quntar, A. A. A.; Kurmankulov, N. B.; Yerzhanov, K. B.; Dembitsky, V. M. *Chem. Rev*. **2015**, *115*, 1475-1502.

22 Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett* **2005**, 3067-3070.

23 (a) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett*. **2007**, *9*, 2549-2552. (b) Kitagaki, S.; Teramoto, S.; Ohta, Y.; Kobayashi, H.; Takabe, M.; Mukai, C. *Tetrahedron* **2010**, *66*, 3687-3694. For a related intermolecular approach: (c) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Briére, J.-F.; Perrio, S. *Adv. Synth. Catal*. **2017**, *359*, 96-106.

trapped allowing for a carbon-carbon bond formation and delivering the desired tertiary (Scheme III-1b). Still, these methods require the C–S bond to be pre-installed prior to sulfone formation and they have the inherent drawback of using highly specific allene substrates **III.8** that fairly limit the product scope of these approaches.[23]



Scheme III-1. Reported approaches for the synthesis of tertiary propargylic sulfones.

Fortunately, more recent advances targeting the synthesis of tertiary propargylic sulfones **III.3** demonstrated a more convenient and practical synthetic method for tertiary sulfone preparation. Loh and co-workers reported in 2018 a regiospecific, dehydrative cross-coupling reaction between sulfinic acids and propargyl alcohols **III.11** to deliver a wide range of propargylic sulfones with highly congested carbon centers **III.3** (Scheme III-1c).[24] Remarkably,

24 Liu, Y.; Xie, P.; Sun, Z.; Wo, X.; Gao, C.; Fu, W.; Loh, T.-P. *Org. Lett.* **2018**, *20*, 5353-5356.

the scope of this transformation can be extended to tertiary alcohols, resulting in otherwise difficult to prepare tertiary sulfones. Although attractive, this approach is limited to the preparation of racemic sulfones, even in the case when the reaction is conducted in the presence of an enantioenriched propargyl alcohol **III.11**. Under the optimized reaction conditions, the corresponding product **III.3** is racemized due to a sigmatropic rearrangement process of the sulfinic ester intermediate **III.12** that delivers **III.3** as a racemic mixture (Scheme III-1c).[25]

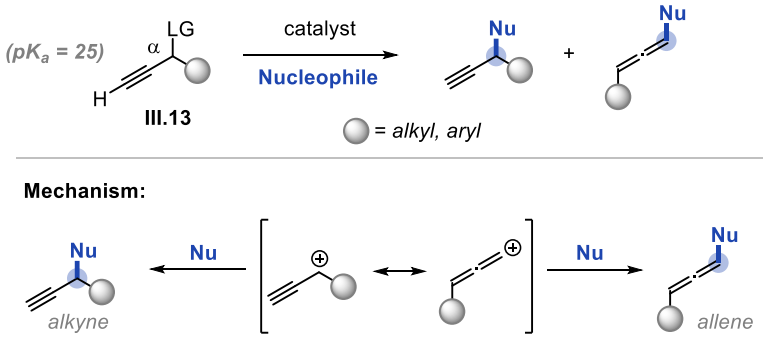
Whilst some methodologies for the synthesis of racemic propargylic tertiary sulfones **III.3** exist, unfortunately to date no general catalytic approach for the *asymmetric* synthesis of propargylic sulfones incorporating tetrasubstituted carbons has been established. Likely, the constrains associated with the stereoselective construction of sulfur-containing quaternary stereogenic centers as previously mentioned,[10, 11] are the main reason why an efficient catalytic asymmetric synthesis of propargylic sulfones has not been realized yet. Therefore, the development of a general and practical strategy that can overcome these limitations would be warranted to further widen the synthetic potential of these propargylic scaffolds.

In this context, the copper-catalyzed asymmetric propargylic substitution (APS) reaction has emerged as a powerful tool to convert propargylic alcohol derivatives into various enantioenriched alkyne-containing products. Thus, this stereoconvergent approach can be envisaged as attractive synthetic alternative to achieve the asymmetric synthesis of tertiary propargylic sulfones starting from a suitable racemic propargylic substrate.

25 Acid-catalyzed rearrangement from sulfinic esters to sulfones: Stirling, C. J. M. *Chem. Commun.* **1967**, 3, 131.

III.1.3 Cu-catalyzed asymmetric propargylic substitution (APS) reactions

The direct propargylic substitution reaction of a propargylic alcohol **III.13** or derivatives thereof with nucleophiles is an important and versatile reaction in organic synthesis. It features mild reaction conditions, a tolerance of a diverse range of functional groups, and importantly it allows the construction of both carbon-carbon and carbon-heteroatom bonds.[26] Regioselectivity in propargylic substitution reactions is of utmost importance since either alkyne or allene products can be generated. Therefore, fine-tuning of catalyst, nucleophile and propargylic substrate is necessary to substitute site-selectively the α-position of the propargylic moiety in order to obtain the desired alkyne-substituted products (Scheme III-2).[26]



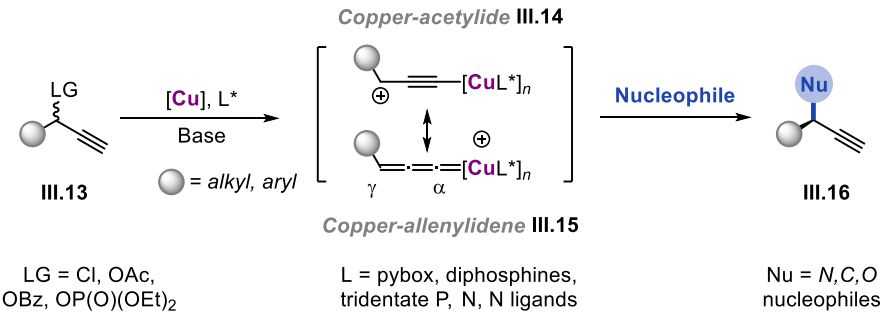
Scheme III-2. Alkyne *versus* allene formation in catalytic propargylic substitution reactions.

To date, transition metals such as ruthenium, rhenium, palladium, gold and copper have been successfully employed in propargylic substitution reactions of propargylic alcohols and their derivatives.[26] Without a doubt, the copper-catalyzed propargylic substitution reaction has attracted most of the attention due to its intrinsic advantages such as low cost and toxicity, mild reaction conditions and excellent selectivity. In particular, recent progress and the broad scope of asymmetric transformations has demonstrated that Cu-catalyzed propargylic substitution reactions are superior to protocols that depend on the use of other transition metals. [27]

26 For reviews, see: (a) Nishibayashi, Y.; Uemura, S. *Curr. Org. Chem*. **2006**, *10*, 135-150. (b) Nishibayashi, Y.; Uemura, S. *In Comprehensive Organometallic Chemistry III*. Elsevier, Amsterdam, **2007**. (c) Ljungdahl, N.; Kann, N. *Angew. Chem. Int. Ed*. **2009**, *48*, 642-644. (d) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342-356. (e) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. **2009**, 6263-6276. (f) Debleds, O.; Gayon, E.; Vrancken, E.; Campagne, J.-M. *Beilstein J. Org. Chem*. **2011**, *7*, 866-877. (g) Ding, C.-H.; Hou, X.-L. *Chem. Rev*. **2011**, *111*, 1914-1937. (h) Bauer, E. B. *Synthesis* **2012**, *44*, 1131-1151. (i) Roy, R.; Saha, S. *RSC Adv*. **2018**, *8*, 31129-31193.

27 For a general overview: Zhang D.-Y.; Hu, X.-P. *Tetrahedron Lett*. **2015**, *56*, 283-295.

Mechanistically, these reactions are presumed to occur via a copper-allenylidene intermediate **III.15**, which is then trapped by the nucleophile to form the C–Nu bond (Scheme III-3). This unique mechanistic feature brings two practical advantages. First, intermediate **III.15** reacts with nucleophiles principally at the γ-position, hence furnishing the terminal alkyne product **III.16** with high regioselectivity. Second, both enantiomers of **III.13** participate in the reaction and are transformed to the same copper-allenylidene intermediate **III.15** to give the desired product **III.16** in a stereoconvergent fashion. Thus, the use of chiral ligands typically leads to enantioenriched products by controlling the facial selectivity of the C–Nu bond-forming event.



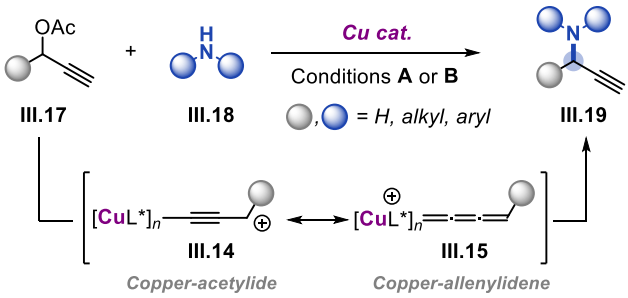
Scheme III-3. The copper-catalyzed asymmetric propargylic substitution (APS) reaction.

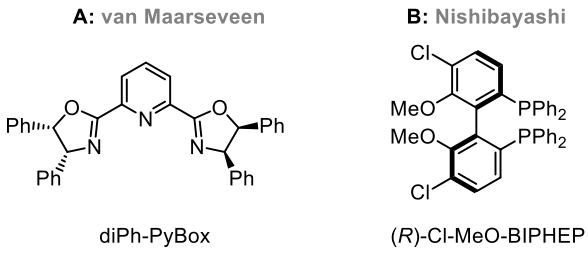
Initial studies and scope

Pioneering studies performed by Murahashi and co-workers in 1994 on the racemic amination of propargylic esters **III.17** represents among the earliest examples of copper-catalyzed propargylic substitution reactions.[28] Later in 2008, the groups of van Maarseveen[29] and Nishibayashi[30] independently reported the first asymmetric version of this copper-catalyzed propargylic substitution reaction (Scheme III-4). These methods provided optically active propargylic amines **III.19** with appreciable enantioselectivities. The major difference between van Maarseveen's and Nishibayashi's methods is the chiral ligand that was employed. In van Maarseveen's method, a chiral 2,6-bis(oxazolinyl)pyridine (PyBOX) type ligand in combination with CuI was used as the catalyst (conditions **A**, Scheme III-4), and primary amines proved to

28 Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282-2284.
29 Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780.
30 Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem. Int. Ed*. **2008**, *47*, 3781-3783.

be more suitable nucleophiles. In comparison, Nishibayashi employed CuOTf·½C_6H_5 ligated by an atropoisomeric diphosphine ligand such as (*R*)-Cl-MeO-BIPHEP as the catalyst (conditions **B**, Scheme III.4), and only secondary amines worked as suitable nucleophiles.



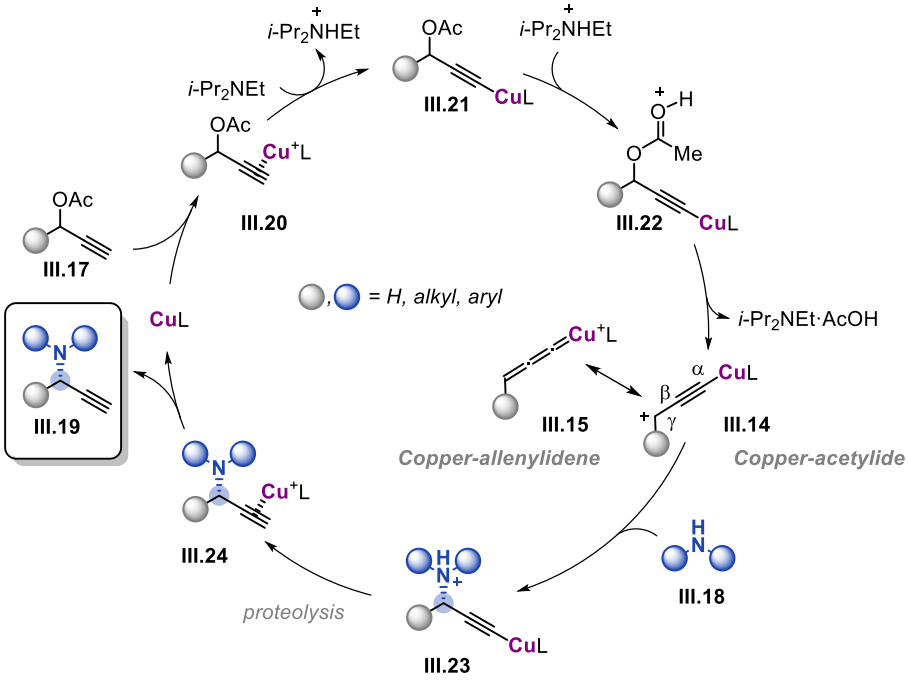


Conditions				Yield (%)	*ee* (%)
A	Ph	H	2-MeOC_6H_4	97	85
A	1-naphthyl	H	2-MeOC_6H_4	91	85
A	Ph	Me	Ph	90	60
B	Ph	Me	Ph	96	85
B	3-thienyl	Me	4-$CF_3C_6H_4$	87	92
B	Ph	H	Ph	90	53

Scheme III-4. First examples of copper-catalyzed asymmetric propargylic reactions by van Maarseveen and Nishibayashi. Conditions **A**: CuI (10 mol%)/ Pybox (12 mol%), *i*Pr_2NEt, MeOH, -20 ºC. Conditions **B**: CuOTf·½C_6H_5 (5 mol%)/(*R*)-Cl-MeO-BIPHEP (10 mol%), *i*Pr_2NEt, MeOH, 0 ºC.

Although both catalytic systems are different, Nishibayashi and co-workers made an extensive effort to get more insight into the reaction mechanism and proposed a reaction pathway similar to the one initially suggested by van Maarseveen. The experimental results revealed that

an achiral copper-allenylidene complex **III.15** should be a key intermediate.[31] This conclusion was also supported by density functional theory (DFT) calculations, and the proposed overall mechanism is depicted in Scheme III-5.

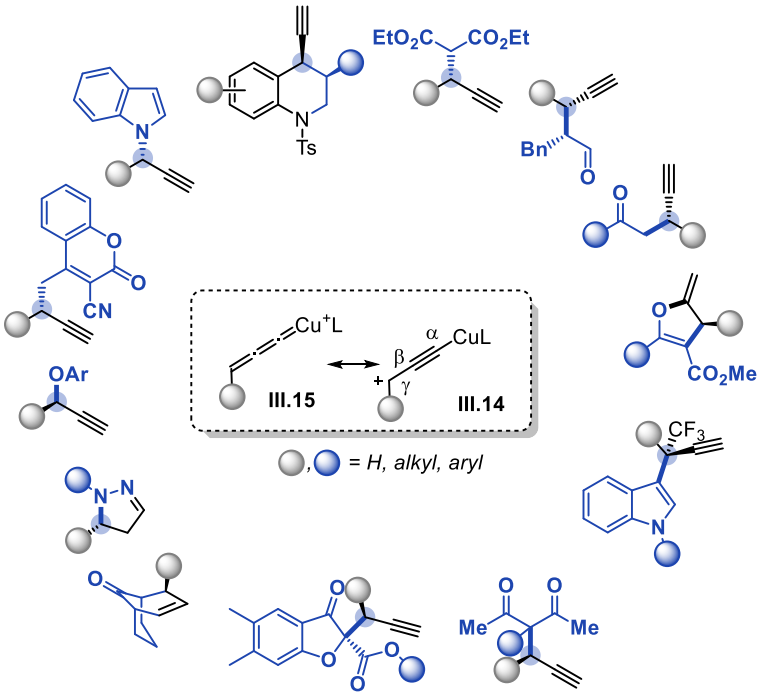


Scheme III-5. Proposed catalytic cycle for the copper-catalyzed propargylic amination reaction.

The copper-allenylidene complex (**III.15**) is formed by elimination of an acetyl moiety from the copper-acetylide complex (**III.22**; the protonated species of **III.21**), while **III.21** is formed from the copper-π-alkyne complex (**III.20**) resulting from **III.17** and the initial chiral copper complex. *N*,*N*-Diisopropylethylamine (*i*Pr$_2$NEt) promotes the deprotonation and protonation steps from **III.20** towards the copper-allenylidene complex **III.15**. The copper-acetylide complex bearing a cationic γ-carbon (**III.14**) exists as a resonance structure of **III.15**. The amine nucleophile **III.18** then regioselectively attacks the Cu-allenylidene complex **III.15**, whereas blocking of one side of the cationic intermediate by the chiral ligand ensures asymmetric induction during the C–N bond formation. After proteolysis, the product **III.19** is released to complete the catalytic cycle. The attack of the amine to the γ-carbon atom of the allenylidene

31 (a) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc*. **2010**, *132*, 10592-10608. (b) Sakata, K.; Nishibayashi, Y. *Catal. Sci. Technol*. **2018**, *8*, 12-25.

complex **III.15** is the key step in determining both the regio- and stereoselectivity of the process. This mechanism also explains why the reaction requires the use of propargyl substrates having a terminal acetylene unit.



Scheme III-6. Selection of products synthesized *via* Cu-catalyzed APS reactions with nucleophiles.

Since the initial studies by the groups of Murahashi,[28] van Maarseveen[29] and Nishibayashi,[30] remarkable progress has been made in the copper-catalyzed asymmetric propargylation reaction with various reagents including different N-,[29,30,31] O-,[32] and C-based nucleophiles.[33] The high versatility of this reaction has led to the preparation of an extensive

32 For oxygen-centered nucleophiles: (a) Shao, L.; Zhang, D.-Y.; Wang Y.-H.; Hu, X.-P. *Adv. Synth. Catal*. **2016**, *358*, 2558-2563. (b) Li, R.-Z.; Tang, H.; Wan, L.; Zhang, X.; Fu, Z.; Liu, J.; Yang, S.; Jia, D.; Niu, D. *Chem* **2017**, *3*, 834-845.

33 For carbon-centered nucleophiles: (a) Fang P.; Hou, X.-L. *Org. Lett*. **2009**, *11*, 4612-4615. (b) Zhu, F.-L.; Zou, Y.; Zhang, D.-Y.; Wang, Y.-H.; Hu, X.-H.; Chen, S.; Xu J.; Hu, X.-P. *Angew. Chem. Int. Ed.* **2014**, *53*, 1410-1414; (c) Zhu, F.-L.; Wang, Y.-H.; Zhang D.-Y.; Hu, X.-P. *Angew. Chem. Int. Ed.* **2014**, *53*, 10223-10227. (d) Shao, W.; Li, H.; Liu, C.; Liu, C.-J.; You, S.-L. *Angew. Chem. Int. Ed*. **2015**, *54*, 7684-7687 (e) Huang, G.; Cheng, C.; Ge, L.; Guo, B.; Zhao L.; Wu, X. *Org. Lett.* **2015**, *17*, 4894-4897. (f) Tsuchida, K.; Senda, Y.; Nakajima K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 9728-9732. (g) Xu, H.; Laraia, L.; Schneider, L.; Louven, K.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11232-11236. (h) Shemet, A.;

diversity of chiral propargylic products in high yield and enantiopurity (Scheme III-6).[34] Likewise, the versatility of this reaction is also illustrated by its application in the total synthesis[33h, 35] and the direct functionalization of natural products.[33i,j] However, the potential of the Cu-catalyzed APS reaction has yet to be fully explored.

III.1.4 Aim of the project

Whereas significant advances have been achieved in Cu-catalyzed APS reactions with various reagents including N-, O- and C-based nucleophiles, less progress has been made with S-centered nucleophiles.[36] For instance, no successful asymmetric methods while using sulfur-centered nucleophiles have been disclosed. Additionally, extension of the Cu-catalyzed APS reactions to substrates that allow for the successful construction of quaternary centers with high levels of enantioinduction remain rarely explored.[33f,h,j] Presumably, the difficulties associated with this approach are (1) achieving a high degree of enantiofacial discrimination upon substituting a sterically hindered center, and (2) the widespread belief that organosulfur compounds are catalyst poisons that preclude a successful development of an asymmetric methodology for the preparation of propargylic sulfur derivatives.[10, 11]

Therefore, inspired by these important limitations, our ongoing interest in the challenging synthesis of sterically congested quaternary stereocenters,[37] and the high value of sulfones in synthetic chemistry, in the present chapter efforts are described *to develop the first Cu-catalyzed*

Carreira, E. M. *Org. Lett*. **2017**, *19*, 5529-5532. (i) Zhang, K.; Lu, L.-Q.; Yao, S.; Chen, J.-R.; Shi, D.-Q.; Xiao, W.-J. *J. Am. Chem. Soc*. **2017**, *139*, 12847-12854. (j) Fu, Z.; Deng, N.; Su, S.-N.; Li, H.; Li, R.-Z.; Zhang, X.; Liu, J.; Niu, D. *Angew. Chem. Int. Ed*. **2018**, *57*, 15217-15221.

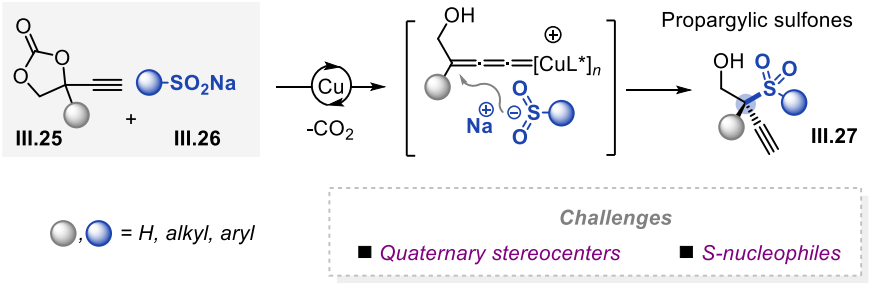
34 For selected examples: (a) Wang, Q.; Li, T.-R.; Lu, L.-Q.; Li, M.-M.; Zhang, K.; Xiao, W.-J. *J. Am. Chem. Soc*. **2016**, *138*, 8360-8363. (b) Li, T.-R.; Lu, L.-Q.; Wang, Y.-N.; Wang, B.-C.; Xiao, W.-J. *Org. Lett*. **2017**, *19*, 4098-4101. (c) Shao, W.; You, S.-L. *Chem. Eur. J*. **2017**, *23*, 12489-12493. (d) Song, J.; Zhang, Z.-J.; Gong, L.-Z. *Angew. Chem. Int. Ed*. **2017**, *56*, 5212-5216. (e) Lu, X.; Ge, L.; Cheng, C.; Chen, J.; Cao, W.; Wu, X. *Chem. Eur. J*. **2017**, *23*, 7689-7693. (f) Chen, H.; Lu, X.; Xia, X.; Zhu, Q.; Song, Y.; Chen, J.; Cao, W.; Wu, X. *Org. Lett*. **2018**, *20*, 1760-1763. (g) Ji, D.; Wang, C.; Sun, J. *Org. Lett*. **2018**, *20*, 3710-3713. (h) Jiang, F.; Feng, X.; Wang, R.; Gao, X.; Jia, H.; Xiao, Y.; Zhang, C.; Guo, H. *Org. Lett*. **2018**, *20*, 5278-5281.

35 Jeso, V.; Nicolaou, K. C. *Tetrahedron Lett*. **2009**, *50*, 1161-1163.

36 Propargylic substitution reactions using thiols in the presence of various transition-metal complexes have been investigated to afford the corresponding *racemic* propargylic sulfides: (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. J. *J. Am. Chem. Soc*. **2000**, *122*, 11019-11020. (b) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. J. *J. Am. Chem. Soc*. **2002**, *124*, 15172-15173. (c) Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T. *J. Am. Chem. Soc*. **2002**, *124*, 12960-12961. (d) Zhan, Z.-P.; Yang, W.-Z.; Yang, R.-F.; Yu, J.-I.; Li, J. P.; Liu, H.- J. *Chem. Commun*. **2006**, 3352-3354. (e) Zhan, Z.-P.; Yu, J.-I.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem*. **2006**, *71*, 8298-8301. (f) Hui, H.-H.; Zhao, Q.; Yang, M.-Y.; She, D.-B.; Chen, M.; Huang, G.-S. *Synthesis* **2008**, 191-196.

37 For a review: Guo, W.; Gómez, J. E.; Cristòfol, À.; Xie, J.; Kleij, A. W. *Angew. Chem. Int. Ed*. **2018**, *57*, 13735-13747.

asymmetric propargylic substitution reaction with S-centered nucleophiles towards the synthesis of tertiary propargylic sulfones. To achieve this goal, we focused on a Cu-catalyzed APS reaction enabled by coupling of sulfinate salts and alkyne-substituted cyclic carbonates (Scheme III-7). A successful development of such a methodology would represent a significant step forward in the practical synthesis of a wide scope of propargylic sulfones under high enantiocontrol from readily available and modular starting materials. The synthetic versatility of the resultant sulfonylated scaffolds should allow for an easy entry towards the preparation of other enantioenriched products, as will be discussed towards the end of this chapter.

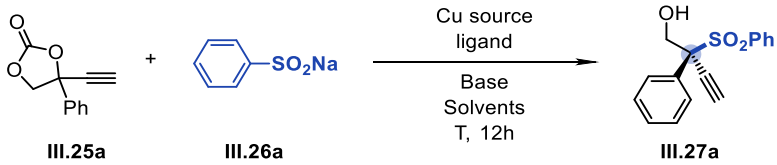


Scheme III-7. Cu-catalyzed APS reaction using sodium sulfinates as nucleophiles.

III.2. Results and discussion

III.2.1 Screening Studies

The feasibility of our copper-catalyzed propargylic sulfonylation strategy was initially studied using a racemic alkyne-substituted cyclic carbonate (**III.25a**) and sodium benzenesulfinate (**III.26a**) as benchmark substrates (Scheme III-8). The use of alkyne-substituted cyclic carbonates as propargylic surrogates [37] allows for the formation of a sulfur-containing quaternary stereocenter along with a useful β-hydroxyl functionality in a single step. Enantioenriched β-hydroxysulfone fragments are prominent motifs in bioactive compounds and building blocks in organic synthesis.[38] On the other hand, sodium sulfinates have been demonstrated to be versatile nucleophiles in transition-metal catalyzed substitution reactions to generate sulfone derivatives via C–S bond formation. Moreover, sulfinate salts are either commercially or readily available, bench-stable, non-hygroscopic and easy to handle.[39]



III.25a **III.26a** **III.27a**

Scheme III-8. Initial model reaction for the screening phase of the project.

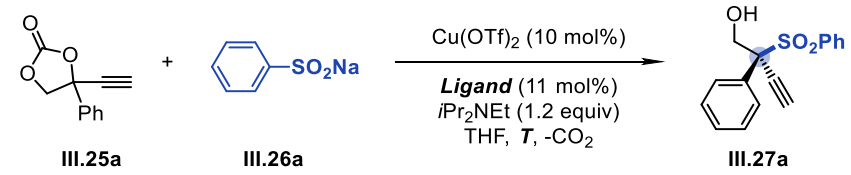
Copper complexes with chiral nitrogen ligands are found to be efficient catalysts for asymmetric propargylic substitution reactions.[26, 27] Thus, we commenced our optimization studies by screening different chiral ligands (**L1-L8**) in the presence of $Cu(OTf)_2$ (10 mol%) and *i*Pr_2NEt in THF to identify an optimal ligand able to impart enantiocontrol for the propargylic sulfonylation (Table III-1). When chiral PyBox ligand **L1** was used at 0 ºC, the desired sulfone product **III.27a** was isolated in good yield though without any enantiocontrol (Table III-1, entry 1). Unfortunately, the evaluation of another PyBox ligand **L2** did not provide any improvement

38 (a) Eto, H.; Kaneko, Y.; Takeda, S.; Tokizawa, M.; Sato, S.; Yoshida, K.; Namiki, S.; Ogawa, M.; Maebashi, K.; Ishida, K.; Matsumoto, M.; Asaoka, T. *Chem. Pharm. Bull*. **2001**, *49*, 173-182. (b) Oida, S.; Tajima, Y.; Konosu, T.; Nakamura, Y.; Somada, A.; Tanaka, T.; Habuki, S.; Harasaki, T.; Kamai, Y.; Fukuoka, T.; Ohya, S.; Yasuda, H. *Chem. Pharm. Bull*. **2000**, *48*, 694-707. (c) Robin, S.; Huet, F.; Fauve, A.; Veschambre, H. *Tetrahedron: Asymmetr*. **1993**, *4*, 239-246.

39 Sodium sulfinates are known to be versatile nucleophiles in transition-metal catalyzed substitution reactions. For a review: Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. *Org. Biomol. Chem*. **2014**, *12*, 9743-9759, and references therein.

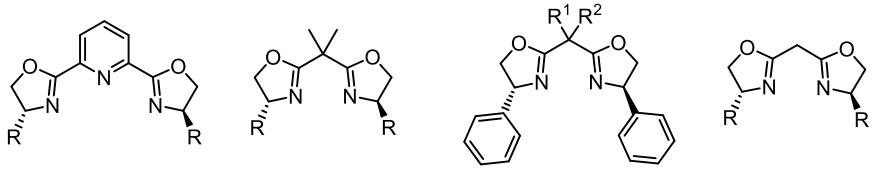
of the enantioselectivity (Table III-1, entry 2). Upon switching to commercially available bis(oxazoline) (BOX) ligands **L3-L7** (Table III-1, entries 3 to 8), slight improvement in the enantiocontrol was noted with (+)-2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline] **L4** (Table III-1, entry 4) providing a lead for further optimization. By further decreasing the reaction temperature, the enantiocontrol slightly improved although longer reaction times were needed (Table III-1, entry 9).

Table III-1. Effect of ligands on the asymmetric copper-catalyzed tertiary sulfone formation.[a]



III.25a **III.26a** **III.27a**

Entry	Ligand	T [ºC]	Time [h]	Yield [%][b]	*er*[c]
1	**L1**	0	12	82	52:48
2	**L2**	0	12	45	52:48
3	**L3**	0	12	46	53:47
4	**L4**	0	12	90	60:40
5	**L5**	0	12	90	57:43
6	**L6**	0	12	80	57:43
7	**L7**	0	12	80	59:41
8	**L8**	0	12	30	54:46
9	**L4**	**-10**	**24**	**90**	**72:28**



L1, R = Ph
L2, R = *i*Pr

L3, R = *t*Bu
L4, R = Ph
L5, R = *i*Pr

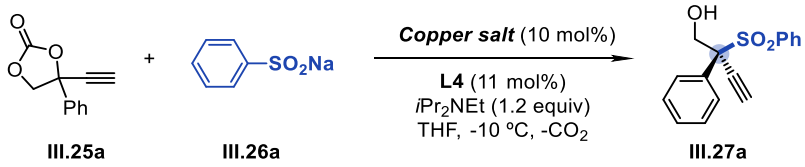
L6, R_1 = Me; R_2 = Bn
L7, $R_1 = R_2$ = 4-*t*Bu$C_6H_4CH_2$-

L8, R = Ph

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **ligand** (11 mol%), THF (0.20 mL), 12 h. [*b*] Isolated yield. [*c*] Determined by UPC2.

Further screening of the reaction conditions using **L4** at -10 ºC revealed that other copper salts gave similar results in terms of yield, albeit the enantioselectivity did not improve (Table III-2). Therefore, these results prompted us to continue our optimization studies using $Cu(OTf)_2$ as the copper source (*vide infra*).

Table III-2. Effect of the copper salt on the asymmetric copper-catalyzed tertiary sulfone formation.[a]



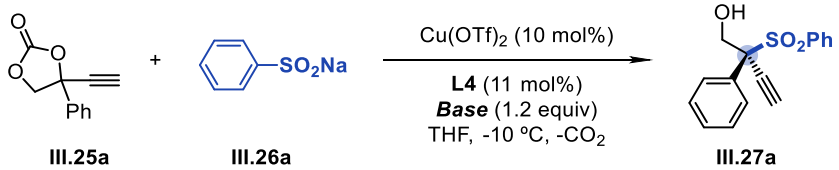
III.25a **III.26a** **III.27a**

Entry	Copper salt	Time [h]	Yield [%][b]	*er*[c]
1	**$Cu(OTf)_2$**	**24**	**90**	**72:28**
2	$(CuOTf)_2$·Tol	24	90	67:33
3	$(CuOTf)_2$·Ph	24	90	66:34
4	$Cu(ACN)_4(OTf)$	24	90	67:33
5	$Cu(ACN)_4(PF_6)$	24	90	68:32
6	$Cu(py)_4(OTf)_2$	24	90	52:48

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), **copper salt** (10 mol%), **L4** (11 mol%), THF (0.20 mL), -10 ºC, 24 h. [*b*] Isolated yield. [*c*] Determined by UPC2.

In the absence of a base, no reaction was observed and hence the addition of a base seemed to be crucial in terms of reactivity (Table III-3). Moreover, the nature of the base had a profound effect on the enantiocontrol. In fact, tertiary non-cyclic amines worked most effective to promote the catalytic reaction (Table III-3, entries 2 and 3). Specifically, with *i*Pr$_2$NEt the best yield and enantiocontrol was achieved (Table III-3, entry 2).

Table III-3. Effect of the base on the asymmetric copper-catalyzed tertiary sulfone formation.[a]



III.25a **III.26a** **III.27a**

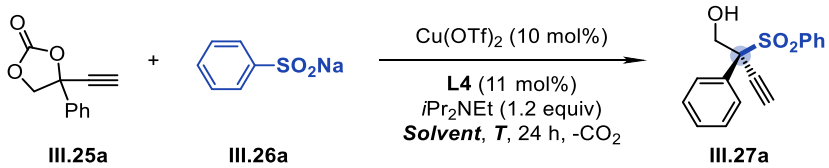
Entry	Base	Time [h]	Yield [%][b]	*er*[c]
1	-	24	n.r	-
2	***i*Pr$_2$NEt**	**24**	**90**	**72:28**
3	NEt$_3$	24	90	70:30
4	NMM	24	91	65:35
5	DABCO	24	50	63:37
6	NMP	24	77	65:35
7	Cs_2CO_3	24	<10	-

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), **base** (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), THF (0.20 mL), -10 ºC, 24 h. [*b*] Isolated yield. [*c*] Determined by UPC2. NMM = *N*-methylmorpholine. DABCO = 1,4-diazabicyclo[2.2.2]octane. NMP = *N*-methyl-4-piperidone.

The reaction medium and temperature turned out to be crucial for the overall reaction efficiency (Table III-4). The reaction in some common organic solvents provided the desired sulfone in good yields, although with low enantiomeric ratios (Table III-4, entries 1 to 4). Whereas the reaction proceeded smoothly in THF at -10 ºC (Table III-4, entry 4), it became very slow at -20 ºC. Low yields were obtained for **III.27a** even at prolonged reaction times (Table III-4, entry 5). Nonetheless, high reaction rates were observed upon switching to a polar, protic solvent such as MeOH at -20 ºC, although with a negative influence on the enantiocontrol (Table III-4, entry 6). Thus, the applicability of solvent mixtures was subsequently studied. Gratifyingly, a combination of THF and MeOH (1:1) promoted the formation of the propargylic target in good yield and with appreciable enantiocontrol (Table III-4, entry 7). Moreover, by fine-tuning the solvent ratio, concentration and temperature, the enantioinduction of the process was further enhanced (Table III-4, entries 8 and 9). The effect of other polar protic solvents on the enantioselectivity was also scrutinized (Table III-4, entries 10 and 11), and the copper-catalyzed propargylic sulfonylation gave the best result when a 3:1 mixture of THF/HFIP (HFIP

= 1,1,1,3,3,3-hexafluoro-2-propanol) at -30 ºC was used, providing the desired product **III.27a** in 93% yield and 96.5:3.5 *er* (Table III-4, entry 11).

Table III-4. Effect of the solvent and temperature on the asymmetric copper-catalyzed tertiary sulfone formation.[a]



III.25a **III.26a** **III.27a**

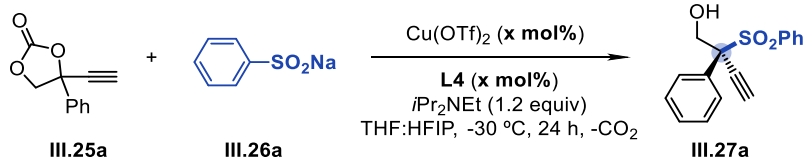
Entry	Solvent	T [ºC]	Yield [%][b]	*er*[c]
1	THF	-10	90	72:28
2	Toluene	-10	81	65:35
3	Dioxane	-10	79	68:32
4	DCM	-10	52	67:33
5	THF	-20	<10	-
6	MeOH	-20	97	56:44
7	THF/MeOH (1/1)	-20	93	80:20
8[d]	THF/MeOH (3/1)	-20	93	87:13
9[d]	THF/MeOH (3/1)	-30	93	92:8
10[d]	THF/TFE (3/1)	-30	93	94:6
11[d]	**THF/HFIP (3/1)**	**-30**	**93**	**96.5:3.5**

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), **solvent** (0.20 mL), **T**, 24 h. [*b*] Isolated yield. [*c*] Determined by UPC2. [*d*] Solvent volume: 0.60 mL.

Finally, in an attempt to improve our protocol, different catalyst loadings were examined (Table III-5). However, lowering the amount of catalyst led to reduced yields and longer reaction times. Therefore, the screening and optimization studies revealed that the best conditions toward the asymmetric formation of the desired tertiary propargylic sulfone **III.27a** were the use of Cu(OTf)$_2$ (10 mol%), ligand **L4** (11 mol%) and 1.2 equivalents of *i*Pr$_2$NEt in THF/HFIP (3:1) at -30 °C (Table III-5, entry 1). The X-ray analysis of the crystals obtained for the major enantiomer

of **III.27a** further revealed that the absolute configuration of propargylic sulfone **III.27a** is (*S*) (Section III.4.6).

Table III-5. Effect of catalyst loading on the asymmetric copper-catalyzed tertiary sulfone formation.[a]

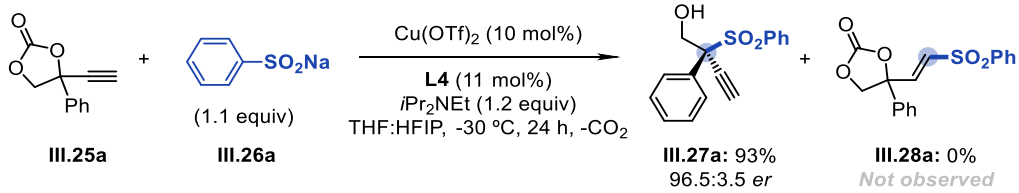


III.25a **III.26a** **III.27a**

Entry	$Cu(OTf)_2$	**L4**	Yield [%][b]	*er*[c]
1	**10 mol%**	**11 mol%**	**93**	**96.5:3.5**
2[d]	8 mol%	9 mol%	80	96.5:3.5
3[d]	3 mol%	4 mol%	<10	-

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), $Cu(OTf)_2$, **L4**, THF:HFIP (3:1) (0.60 mL), -30 ºC, 24 h. [*b*] Isolated yield. [*c*] Determined by UPC2. [*d*] 48h.

It should be mentioned that no *syn*-selective hydrosulfonylation product derived from **III.25a** in the presence of sodium sulfinates was observed during the optimization of the reaction conditions, despite that recently such potential byproducts were reported using copper catalysis to afford (*E*)-alkenyl sulfones (Scheme III-9).[40] It is also noteworthy that a possible *retro*-aldol/aldol reaction of the *β*-hydroxysulfone product **III.27a** was not detected in the crude mixtures, as it may have an impact on the enantioselectivity of the isolated products.[41]



III.25a **III.26a** **III.27a:** 93% 96.5:3.5 *er* **III.28a:** 0% *Not observed*

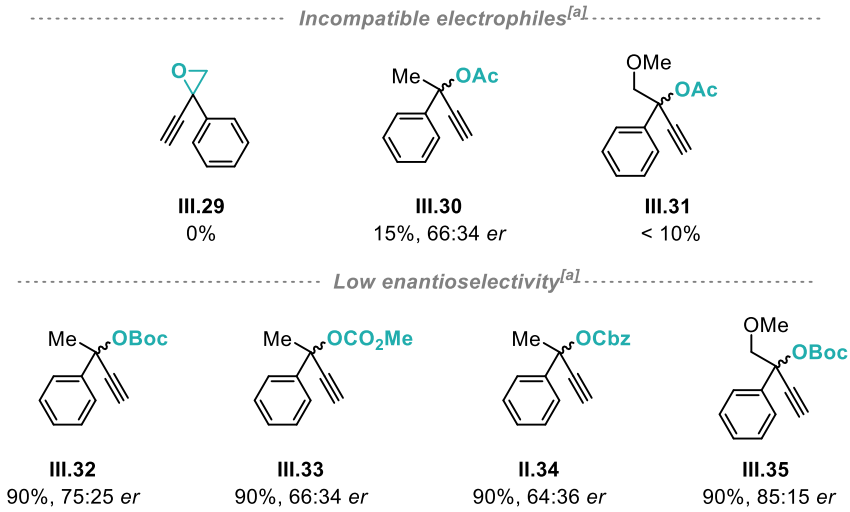
Scheme III-9. Possible copper-catalyzed hydrosulfonylation side-reaction.

40 Taniguchi, N. *Tetrahedron* **2014**, *70*, 1984-1990.

41 For related examples of retro-aldol/aldol reaction: (a) Lewis, F. W.; McCabe, T. C.; Grayson, D. H. *Tetrahedron* **2011**, *67*, 7517-7528. (b) Chang, M.-Y.; Chen, Y.-C.; Chan, C.-K. *Synlett* **2014**, *25*, 1739-1744.

III.2.2 Investigation of the effect of the leaving group

In order to extend our substrate survey, we investigated whether other propargylic surrogates possessing (*rac*)-quaternary centers and widely employed in Cu-catalyzed APS reaction, could undergo similar asymmetric sulfonylation (Scheme III-10).



Scheme III-10. Screening of electrophiles for asymmetric copper-catalyzed tertiary sulfone formation. [*a*] Reaction conditions: **III.29**-**III.35** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), THF:HFIP (3:1, 0.60 mL), -30 ºC, 24 h. The *er* values were determined by UPC2.

When a propargylic epoxide (**III.29**)[42] was employed as an alternative electrophile, the formation of a propargylic ether was observed resulting from a nucleophilic attack of the protic solvent on the copper-allenylidene intermediate and this product was isolated in 86% yield.[32] The formation of the latter prevented the isolation of any sulfonylated species. This result underlines the importance of the nature of the substrate towards highly selective formation of the tertiary sulfone target **III.27a**, despite the fact that a rather similar copper-allenylidene intermediate may be formed starting either from the cyclic carbonate **III.25a** or the epoxide **III.29**. Attempts to transform more commonly employed quaternary propargylic acetates such

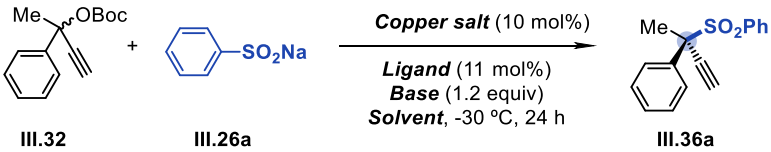
42 Hattori, G.; Yoshida, A.; Miyake, Y.; Nishibayashi, Y. *J. Org. Chem.* **2009**, *74*, 7603-7607.

as **III.30** or **III.31** failed and only trace amounts of the desired product was detected and thus indicate the difficulty of cleaving the acetate group under these experimental conditions.

Gratifyingly, upon changing the leaving group from acetate to linear carbonates **III.32**, **III.33**, **III.34** and **III.35**, the desired tertiary sulfone products were isolated in high yields under the optimized conditions though with moderate levels of asymmetric induction. Interestingly, upon using the acyclic propargylic carbonate bearing a hydroxy-protected functionality (**III.35**) under standard conditions, the corresponding sulfonylated product was formed with (slightly) higher enantioselectivity (Scheme III-10: **III.32**: 90% yield and 75:25 *er* vs. **III.35**: 90% yield and 85:15 *er*). At the moment there is no rational explanation for this observation, though it suggests that the presence of an oxygen atom at the β-position of the substrate plays an apparent role in this asymmetric transformation (*cf.*, **III.25a**: 93% yield and 96.5:3.5 *er*, and **III.35**: 90% yield and 85:15 *er*).

Non-cyclic propargylic carbonate **III.32** represents a useful extension of the substrate scope for our methodology (90% yield, 75:25 *er*). Therefore, we conducted additional screening experiments to see if higher enantioselectivity could be obtained for substrate **III.32**. However, after evaluating different reaction conditions with this acyclic substrate, including variation of the ligand, copper source, type of bases and solvent regrettably no improvement of the enantioselectivity of the reaction was observed (Table III-6). Therefore, these results evidence the fact that the nature of the propargylic electrophile in this Cu-catalyzed APS reaction is decisive to produce the tertiary sulfonylated products both in high yields and in high enantiomeric ratios. More extensive fine-tuning of the reaction conditions with this second model substrate might be necessary to potentially afford the corresponding sulfone **III.36a** with higher enantioselectivity.

Table III-6. Screening of quaternary propargylic linear carbonate **III.32**.[a]



III.32 **III.26a** **III.36a**

Entry	Copper salt	**Ligand**	Solvent (v/v)	Yield [%][b]	*er*[c]
1	$Cu(OTf)_2$	**L4**	THF	0	-
2[d]	$Cu(OTf)_2$	**L1**	THF/HFIP	30	50:50
3[d]	$Cu(OTf)_2$	**L2**	THF/HFIP	56	65:35
4[d]	$Cu(OTf)_2$	**L3**	THF/HFIP	<5	-
5[d]	**$Cu(OTf)_2$**	**L4**	**THF/HFIP**	**90**	**75:25**
6[d]	$Cu(OTf)_2$	**L5**	THF/HFIP	90	54:46
7[d]	$Cu(OTf)_2$	**L6**	THF/HFIP	92	53:47
8[d]	$Cu(OTf)_2$	**L7**	THF/HFIP	86	55:45
9[e]	$Cu(OTf)_2$	**L4**	2-MeTHF/HFIP	50	68:32
10[f]	$Cu(OTf)_2$	**L4**	Dioxane/HFIP	<5	-
11[g]	$Cu(OTf)_2$	**L4**	Toluene/HFIP	22	52:48
12[h]	$Cu(OTf)_2$	**L4**	DCM/HFIP	<5	-
13[d]	$(CuOTf)_2 \cdot Ph$	**L4**	THF/HFIP	90	71:29
14[d]	$Cu(py)_4(OTf)_2$	**L4**	THF/HFIP	0	-
15[d]	$Cu(OAc)_2$	**L4**	THF/HFIP	85	71:29
16[d,i]	$Cu(OTf)_2$	**L4**	THF/HFIP	90	74:26
17[d,j]	$Cu(OTf)_2$	**L4**	THF/HFIP	0	-

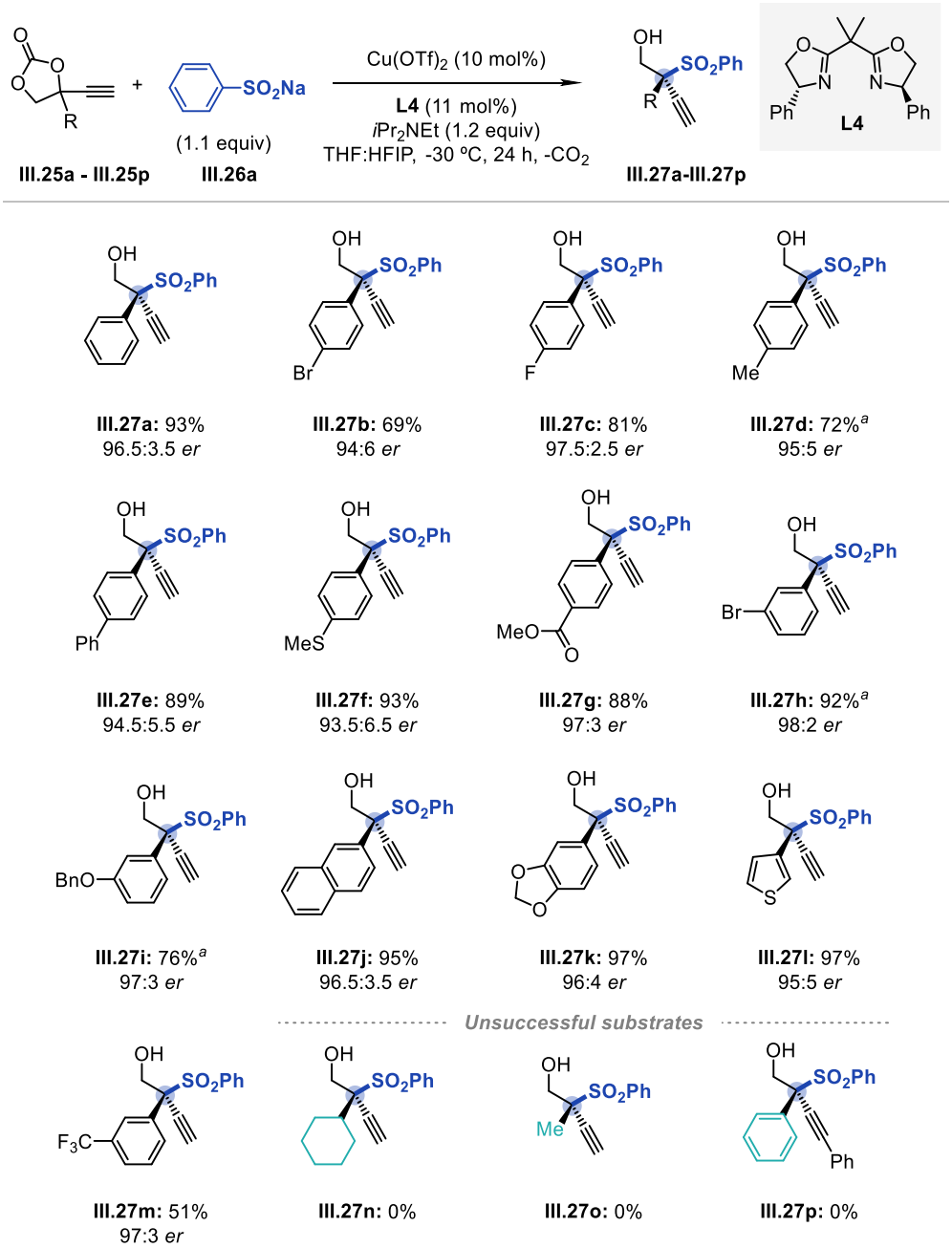
[*a*] Reaction conditions unless otherwise noted: **III.32** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), iPr$_2$NEt (0.24 mmol, 1.2 equiv), **copper salt** (10 mol%), **ligand** (11 mol%). [*b*] Isolated yield. [*c*] Determined by UPC2. [*d*] THF/HFIP (3:1, 0.6 mL). [*e*] 2-MeTHF/HFIP (3:1, 0.6 mL). [*f*] Dioxane/HFIP (3:1, 0.6 mL). [*g*] Toluene/HFIP (3:1, 0.6 mL). [*h*] DCM/HFIP (3:1, 0.6 mL). [*i*] Et_3N (0.24 mmol, 1.2 equiv). [*j*] DABCO (0.24 mmol, 1.2 equiv). DABCO = 1,4-diazabicyclo[2.2.2]octane.

III.2.3 Substrate scope of cyclic carbonates

Having identified the optimal reaction conditions for the asymmetric synthesis of **III.27a** (93% yield, 96.5:3.5 *er*), we then turned our attention to examine the scope and generality of this copper-catalyzed transformation by initially evaluating a range of propargylic cyclic carbonates **III.25b-III.25p** in combination with sodium benzenesulfinate **III.26a** (Scheme III-11).

As summarized in Scheme III-11, a wide range of aryl propargylic cyclic carbonates were feasible electrophiles for this copper-catalyzed asymmetric propargylation reaction. The developed protocol enabled the efficient synthesis of structurally diverse tertiary propargylic sulfones **III.27a-III.27m** with good yields and excellent enantiomeric ratios. Both electron-deficient and electron-rich aromatic propargylic cyclic carbonates with various substitutions on the benzene ring performed well under the standard reaction conditions, affording the corresponding products **III.27b-III.27i** and **III.27m** in good yields (51−93% yields) and excellent enantiomeric ratios (93.5:6.5−98:2 *er*). Prolonged reaction times were needed for substrates **III.25d** and **III.25h**. The asymmetric C–S bond formation was not affected by bulky naphthyl (**III.27j)** or heteroaryl groups (**III.27k**). Notably, the use of thiophene-substituted cyclic carbonate (**III.27l**) gave smooth access to the corresponding tertiary sulfone in high yield and enantioselectivity, despite its potential to shut down the reaction upon ligand coordination.

In contrast, it was found that this C–S bond formation was rather sensitive to electronic effects exerted by the electrophilic partner, as reflected by the fact that propargylic cyclic carbonates bearing *aliphatic* side chains (**III.27n** and **III.27o**) were much less reactive and the catalytic protocol failed even at higher temperatures and/or catalyst loadings. Instead, quantitative recovery of the corresponding alkyl-substituted carbonates was noted. These results indicate that the presence of an aryl moiety at the propargylic position is necessary to promote the catalytic sulfonylation. Likewise, no reaction occurred with the internal propargylic cyclic carbonate (**III.27p**), evidencing that the presence of a terminal acetylene appears to be a requisite for the copper-catalyzed propargylic substitution chemistry (Scheme III-11).



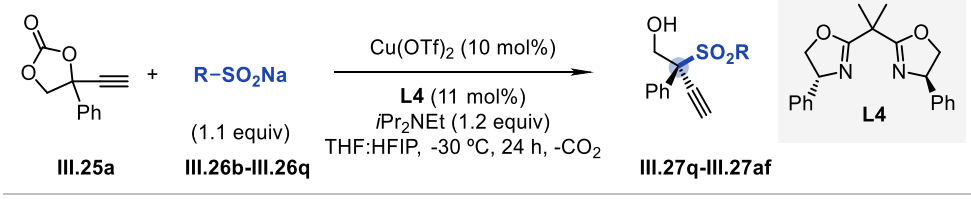
Scheme III-11. Substrate scope of the asymmetric propargylic sulfonylation of propargylic cyclic carbonates with sodium benzenesulfinate. Reaction conditions: **III.25a-III.25p** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), THF:HFIP (3:1, 0.60 mL), -30 ºC, 24 h. The *er* values were determined by UPC2. [*a*] Reaction time was 36 h.

III.2.4 Substrate scope of sodium sulfinates

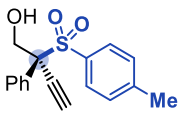
After surveying a broad range of electrophilic partners for the optimized Cu-catalyzed APS reaction, a variety of sulfinate salts were then assessed (Scheme III-12). Although some of the sulfinate salts are commercially available, these reagents are readily accessed from commodity chemicals (*i.e.*, sulfonyl chlorides and sodium sulfite) in a single step and are bench-top stable, crystalline solids.[39]

An array of sulfinate salts (**III.26b**-**III.26q**) were evaluated under the reaction conditions and a broad range of substituents were found to be tolerated (Scheme III-12). The method was quite efficient for the coupling of aryl sulfinate salts including those bearing aryl groups with *para* substitutions (**III.27q**–**III.27w**). Both electron-rich and electron-poor aryl sulfinates provided access to the tertiary propargylic sulfones in good to excellent yields and high enantioselectivities. *Meta*- and *ortho*-substitution on the aryl ring was also well tolerated (**III.27x-III.27z**, 77-88% yield), demonstrating tolerance to a certain degree of steric modulation.

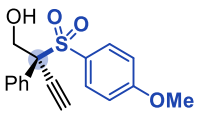
Bulky naphthyl and heterocyclic sulfinates proved also to be suitable reaction partners demonstrated by the synthesis of **III.27aa–III.27ad**. Notably, sulfinate salts equipped with 1,3-benzodioxole and 1,4-benzodioxane fragments were readily transformed into tertiary propargylic sulfones **III.27ac** and **III.27ad**. Such heteroaryl groups are often encountered in active pharmaceutical ingredients (APIs) and therefore provide interesting entries to compound collections used in drug discovery. To highlight the potential towards the synthesis of *aliphatic* sulfone products, the use of alkyl sulfinates **III.27ae** and **III.27af** was also investigated, and it was revealed in both cases that the targeted compounds can be obtained in excellent yields and high *er* values.



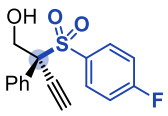
III.25a **III.26b-III.26q** **III.27q-III.27af**



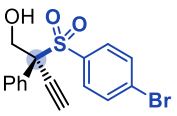
III.27q: 91%
96.5:3.5 *er*



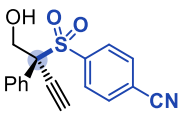
III.27r: 95%
96.5:3.5 *er*



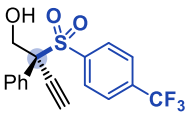
III.27s: 83%[b]
97:3 *er*



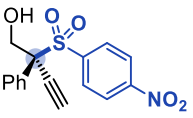
III.27t: 92%[b]
95:5 *er*



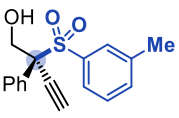
III.27u: 63%[b]
93:7 *er*



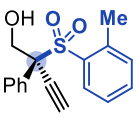
III.27v: 74%[b]
94:6 *er*



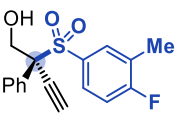
III.27w: 47%[b]
93:7 *er*



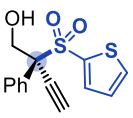
III.27x: 88%
96:4 *er*



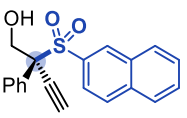
III.27y: 77%
95.5:4.5 *er*



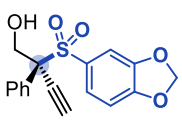
III.27z: 83%
96:4 *er*



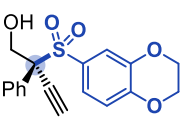
III.27aa: 58%[c]
94:6 *er*



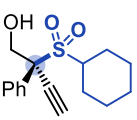
III.27ab: 69%[b]
96:4 *er*



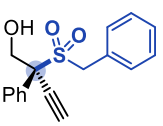
III.27ac: 73%
96:4 *er*



III.27ad: 81%[c]
89:11 *er*



III.27ae: 91%
91.5:8.5 *er*

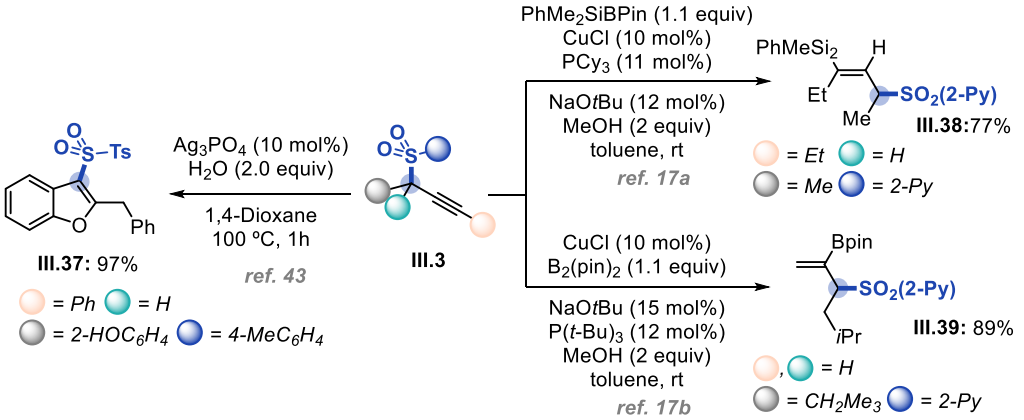


III.27af: 91%
92.5:7.5 *er*

Scheme III-12. Substrate scope of the asymmetric propargylic sulfonylation with different sodium sulfinates. Reaction conditions: **III.25a** (0.20 mmol), sodium sulfinates **III.26b-III.26q** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), THF:HFIP (3:1) (0.60 mL), -30 ºC, 24 h. The *er* values were determined by UPC2. [*a*] Reaction time was 36 h. [*b*] cyclic carbonate (0.22 mmol, 1.1 equiv), sulfinate salt (0.20 mmol). [*c*] The *er* value was determined from the corresponding acetate.

III.2.5 Synthetic transformations of tertiary propargylic sulfones

Propargylic sulfones are versatile building blocks in organic synthesis. For instance, Bi and co-workers reported that benzofuran skeletons **III.37** can be readily prepared in excellent yields from propargylic sulfones under silver catalysis.[43] Moreover, the Carretero group found that propargylic sulfones are versatile substrates to conveniently access either vinyl silanes **III.38**[17a] or vinyl boronates **III.39**[17b] in good yields and with excellent regio- and stereocontrol under copper catalysis (Scheme III-13).



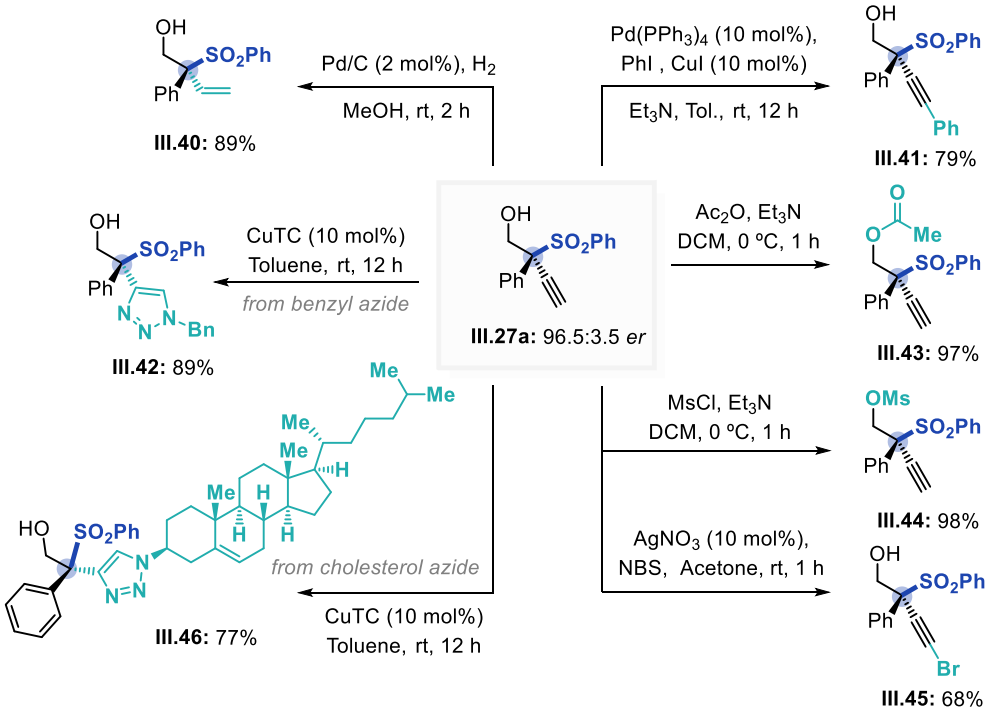
Scheme III-13. Known transformations of propargylic sulfones.

To show the synthetic utility of the enantioenriched tertiary propargylic sulfones prepared by the developed methodology in this chapter, we first conducted a larger-scale reaction (5.0 mmol scale, 1.13 g) to deliver the sulfone **III.27a** without any observable erosion of the enantioinduction of the process (82% yield, 96.5:3.5 *er*). Subsequently, we performed further derivatization reactions on this product. Sulfone **III.27a** was transformed into a series of derivatives that were shown to retain the chiral integrity of the starting propargylic sulfone and the results are summarized in Scheme III-14. For example, semi-hydrogenation of the pendant alkyne group in the presence of Pd/C using ambient pressure of H_2 delivered the allylic sulfone **III.40** in high yield (89%) and enantiopurity. Allyl sulfones are extremely versatile intermediates in organic synthesis because of the ability of the allylic sulfonyl group to act not only as a carbanion stabilizer but also as a nucleofuge. In particular, allyl sulfones with a chiral center at

43 Liu, J.; Liu, Z.; Liao, P.; Bi, X. *Org. Lett*. **2014**, *16*, 6204-6207.

the γ-position are of interest for the stereoselective alkylation of organometallic compounds and for the production of chiral allylic α-sulfonyl carbanions.[44] Notably, allylic products such as **III.40** are difficult to access through conventional methods.[14] Hence, our newly developed reaction is a useful approach to access allylic sulfones featuring quaternary stereocenters through a two-step sequence.

A Sonogashira coupling reaction between iodobenzene and **III.27a** delivers compound **III.41** in 79% yield. Using, a copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction with benzyl azide affords the corresponding triazole **III.42** in excellent yield (89%). Moreover, the versatile homopropargylic alcohol unit of sulfone **III.27a** could be easily protected affording the ester **III.43** (97%) and mesylated derivatives **III.44** (98%) through simple procedures. The terminal alkyne group introduced could also be conveniently brominated to prepare the corresponding haloalkyne **III.45** in good yield (68%). Lastly, to further illustrate the synthetic versatility and the successful application of the catalytic protocol using more complex substrates, **III.27a** was coupled with optically pure cholesterol azide via standard click chemistry to afford **III.46** in good yield while preserving the chiral nature of the tertiary sulfone (96:4 *dr*).



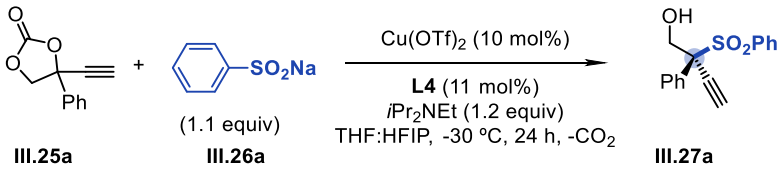
Scheme III-14. Synthetic use of tertiary propargylic sulfone **III.27a**.

44 Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051-2069, and references cited therein.

III.2.6 Mechanistic considerations

After having demonstrated the generality and utility of our protocol for the enantioconvergent synthesis of tertiary propargylic sulfones, we turned our attention to some of the mechanistic details of our copper-catalyzed asymmetric propargylation reaction. In order to gain insight into the active catalytic species, we examined the relationship between the *er* value of **L4** against the *er* value of the produced propargylic sulfone **III.27a** (Table III-7).

Table III-7. Positive nonlinear effect in the sulfonylation reaction. [a]



III.25a **III.26a** **III.27a**

Entry	*er* of **L4**[b]	*er* of **III.27a**[b]	Yield (%)[c]
1	100:0	96.5:3.5	93
2	90:10	96.5:3.5	93
3	80:20	93:7	81
4	70:30	89:11	45
5	60:40	79:21	18
6	50:50	50:50	0

[*a*] Reaction conditions unless otherwise stated: carbonate **III.25a** (0.20 mmol), sodium benzenesulfinate **III.26a** (0.22 mmol, 1.1 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol%), **L4** (11 mol%), THF:HFIP (3:1) (0.20 mL), -30 ºC, 24 h. [*b*] Determined by UPC2. [*c*] Isolated yield.

Both the enantioselectivity and the conversion to product are impacted by the enantiopurity of the ligand. A pronounced positive nonlinear effect (NLE) is clearly observed (Figure III-3a). This result may indicate the formation of higher order catalyst species involving multiple equivalents of ligand as key intermediates.[45] One model to explain the divergence from linearity between catalyst and product enantiopurity is based on a difference in thermodynamic stability of a *hetero*-chiral (*meso*) species and *homo*-chiral higher order species. Indeed, upon increasing

45 Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed*. **2009**, *48*, 456-494.

the *ee* of the ligand, the conversion to **III.27a** also increases (Figure III-3b) strongly indicating the formation of a less reactive copper complex in our catalytic system under scalemic conditions.

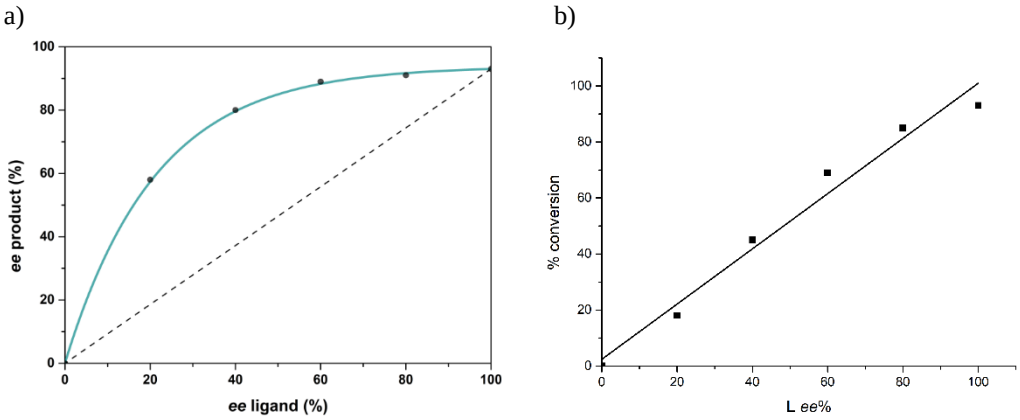
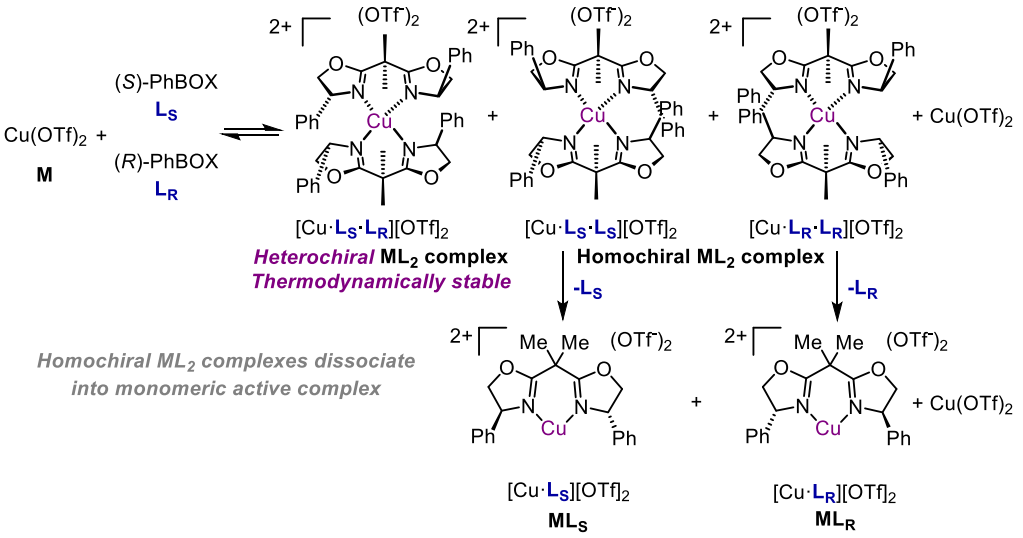


Figure III-3. (a) Plot of *er* of **L4** versus *er* of sulfone **III.27a**. (b) Plot of *er* of **L4** versus conversion of sulfone **III.27a**.

From the kinetic, catalytic and direct spectroscopic data in similar reported systems it is known that the formation of a heterochiral copper complex is a likely origin of a positive NLE.[46] For example, very recently Franz and co-workers described the use of a similar catalytic system towards an enantioselective Cu(II)-catalyzed spiroannulation of *N*-Boc-iminooxindoles with allylsilanes. As in our case, a significant positive nonlinear effect (NLE) was observed.[47] In their case, EPR spectroscopy indicated that an **ML$_2$** species is formed in scalemic ligand mixtures where the formation of the catalytically inactive heterochiral **ML$_2$** complex is thermodynamically more stable than the homochiral **ML$_2$** complex (Scheme III-15). Therefore, they proposed that an equilibrium between the **M**, **ML**, and **ML$_2$** complexes is present when scalemic mixtures of ligand are used, which would explain both the positive NLE as well as the reduced conversion to product also observed in our catalytic protocol. In the Franz process, the homochiral **ML$_2$** complex dissociates irreversibly and quantitatively into an active **ML** complex which subsequently binds/activates the substrate, leading to the spiroannulation product. The heterochiral **ML$_2$** complex does not participate in this monomer-dimer equilibrium (Scheme III-15). When more of the heterochiral **ML$_2$** complex is formed (which cannot dissociate to a

46 Blackmond, D. G. *Acc. Chem. Res*. **2000**, *33*, 402-411.
47 Armstrong, B. M.; Sayler, R. I.; Shupe, B. H.; Stich, T. A.; Britt, D. R.; Franz, A.K. *ACS Catal*. **2019**, *9*, 1224-1230.

monomeric species) the remaining ligand is enantioenriched and consequently a positive NLE is observed.

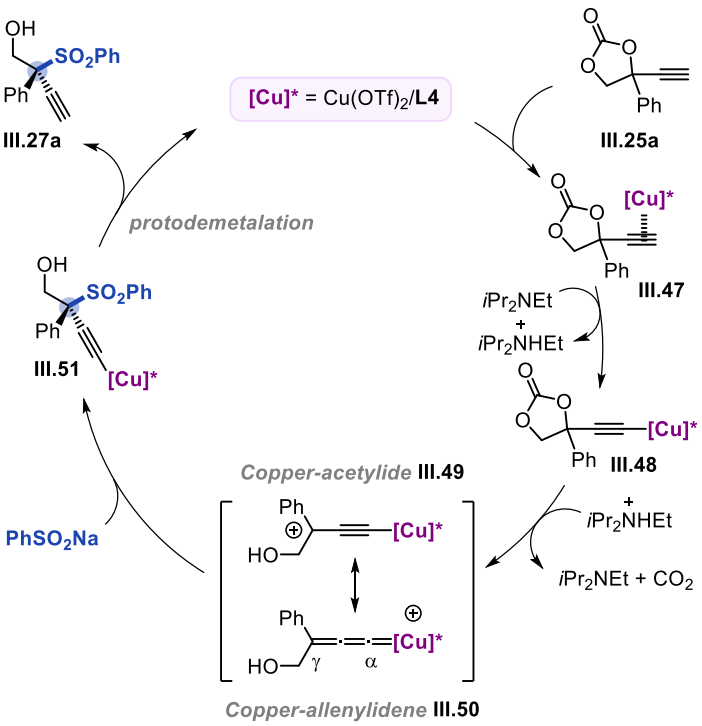


Scheme III-15. Proposed speciation of copper (II) complexes under scalemic reaction conditions according to Franz and co-workers.

Based on this precedent in the literature and considering our experimental observations, a mononuclear copper-allenylidene complex may be a key reactive intermediate in the developed propargylic sulfonylation reaction. However, when considering previous studies on the copper-catalyzed APS reaction, we cannot exclude the possibility of the presence of dinuclear copper complexes. Detailed mechanistic studies are still required to substantiate which of these two possibilities is more likely to advance the course of the propargylic sulfonylation reaction.

A plausible mechanism is proposed in Scheme III-16 according to previous mechanistic studies on related propargylic substitution reactions[31, 32, 33, 34] and our experimental data. First, an *in situ* formed copper-catalyst **[Cu]*** should react with propargylic substrate **III.25a** through a π-complex (**III.47**), which after base-assisted deprotonation forms a copper-acetylide species **III.48**. Subsequently, the decarboxylation reaction of **III.48** followed by a protonation process furnishes the copper-allenylidene intermediate **III.50** and its resonance structure (*viz.*, copper-acetylide intermediate **III.49**). This reactive species is intercepted by the sulfinate nucleophile affording the corresponding copper-acetylide complex **III.51**. The absolute configuration at the propargylic position in **III.27a** indicates that the attack of the sulfinate on the cationic γ-carbon in the copper-allenylidene complex occurs preferentially from the *Re* face of the

Cu(allenylidene) species **III.50**. Finally, protodemetalation renders the sulfone target **III.27a** as the free alcohol species in the presence of HFIP while regenerating the active copper catalyst.



Scheme III-16. Proposed mechanism towards the formation of tertiary propargylic sulfone **III.27a**.

III.3. Conclusions

In this chapter, we have presented a previously considered elusive copper-catalyzed asymmetric propargylic substitution reaction that enables the enantioselective preparation of propargylic sulfones with sterically congested quaternary stereocenters. Our newly developed C–S bond formation protocol is based on a copper-catalyzed sulfonylation reaction of propargylic cyclic carbonates with easily accessible sodium sulfinates. This practical method not only represents the first successful example of a transition-metal catalyzed APS reaction using sulfur-centered nucleophiles, but also complements previous accomplishments in the area that report the application of oxygen-, nitrogen- and carbon-based nucleophiles.

Furthermore, our protocol is characterized by good to high yields, high enantiomeric ratios (up to 98:2), wide functional group tolerance, and scalability. The substrate scope is not merely restricted to propargylic *cyclic* carbonates, also acyclic propargylic carbonates could be

sulfonylated, albeit with lower enantioselectivities. The fact that an additional hydroxyl functionality is retained in the final sulfone product after loss of carbon dioxide, provides a direct access to enantioenriched β-hydroxysulfone backbones, which are prominent motifs in bioactive compounds and valuable building blocks in organic synthesis. Thus, the resultant formal tertiary propargylic β-hydroxysulfones prepared by our new protocol were used as synthetic precursors to give rise to a variety of other enantioenriched building blocks.

Finally, we have proposed a mechanistic pathway based on a Cu(Box)-allenylidene species acting as a key reactive intermediate and was found to give the best results in terms of yield and selectivity. The optimal performance of the Box ligand in our system was not anticipated as conventional catalysts derived from Box ligands are typically not very good catalysts in related propargylic substitution reactions. However, the nature of the active species remains unclear at this stage, and detailed investigations are necessary to elucidate the involved mechanistic scenario.

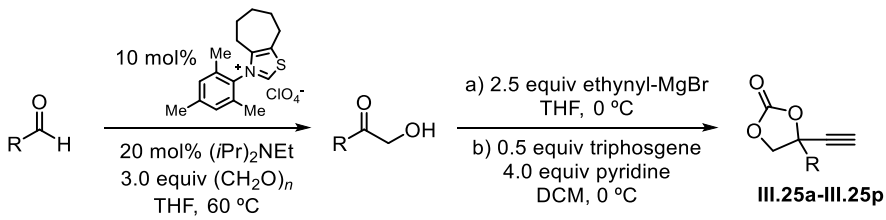
III.4. Experimental section

III.4.1 General information and instrumentation

Commercially available sulfonyl chlorides and solvents were purchased from Aldrich or TCI, and used without further purification. Copper salts were purchased from Aldrich. Ligands **L1-L8** were purchased from Aldrich and Strem. Functionalized cyclic carbonates **III.25a-III.25p** were prepared according to a procedure described below. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Bruker AV-500 spectrometer and referenced to the residual deuterated solvent signals. All reported NMR data are given in parts per million (ppm). FT-IR measurements were carried out using a Bruker Optics FTIR Alpha spectrometer. Optical rotations were measured with a Jasco P-1030 Polarimeter. Mass spectrometric analyses, UPC2 analyses, and X-ray diffraction analysis were performed by the Research Support Area (RSA) at ICIQ.

III.4.2 General procedure for the synthesis of cyclic carbonates

Cyclic carbonates were prepared according to the methods reported in the literature with some modifications (Scheme III-17).[48] A typical experimental procedure for the preparation of propargylic cyclic carbonates is described below:



Scheme III-17. General procedure for the preparation of propargylic cyclic carbonates.

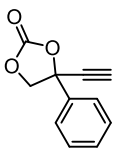
Synthesis of α-hydroxylmethyl ketones:[49] In an oven-dried Schlenk-flask sealed with a rubber septum and equipped with a magnetic stirring bar, thiazolium salt (10 mol%), paraformaldehyde (3.0 equiv) and the corresponding aldehyde (1.0 equiv) were added. The Schlenk flask was then subjected to three cycles of pressurization/depressurization using dry N_2.

48 Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc*. **2016**, *138*, 11970-11978.
49 Kuhl, N.; Glorius, F. *Chem. Commun*. **2011**, *47*, 573-575.

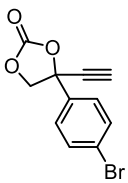
After that, under the protection of dry N_2, anhydrous THF (5 mL) and (iPr)$_2$NEt (20 mol%) were added and the resulting mixture was heated to 60°C. (Note: In the case of aliphatic aldehydes, the aldehyde was added after stirring the other reactants for 5 min at room temperature). After a maximum reaction time of 24 h, the solvent was evaporated and the crude product was purified by flash chromatography.

Step (a): To a solution of the respective pure hydroxy methyl ketone (5 mmol, 1.0 equiv) in THF (20 mL) was added ethynylmagnesium bromide (0.5 M in THF, 2.5 equiv) at 0 °C. The reaction was stirred under an N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated affording the crude product, which was directly used in the next step.

Step (b): To a solution of the corresponding crude diol (1.0 equiv) and pyridine (4.0 equiv) in DCM (20 mL) was added triphosgene (0.5 equiv, 1.0 M in DCM) at 0 °C. The reaction was stirred under an N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica to afford the corresponding propargylic cyclic carbonate **III.25a-III.25p**.



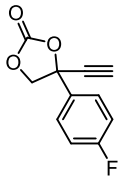
4-Ethynyl-4-phenyl-1,3-dioxolan-2-one (III.25a). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 91%. The NMR spectroscopic data correspond to those previously reported in the literature.[50] **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 4.79 (d, J = 8.5 Hz, 1H), 4.45 (d, J = 8.5 Hz, 1H), 3.00 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.6, 136.7, 130.0, 129.2, 126.2, 79.9, 79.1, 78.8, 77.3.



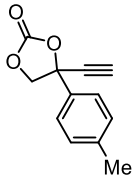
4-(4-Bromophenyl)-4-ethynyl-1,3-dioxolan-2-one (III.25b). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 85%. The NMR spectroscopic data correspond to those previously reported in the literature.[50] **^{1}H NMR** (500

50 Tian, L.; Gong, L.; Zhang, X. *Adv. Synth. Catal*. **2018**, *360*, 2055-2059.

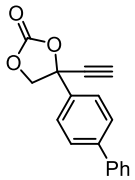
MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.45 (d, *J* = 8.5 Hz, 1H), 3.00 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.2, 135.8, 132.5, 126.9, 124.4, 79.4, 79.1, 78.6, 77.0.



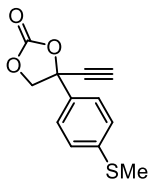
4-Ethynyl-4-(4-fluorophenyl)-1,3-dioxolan-2-one (III.25c). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 83%. The NMR spectroscopic data correspond to those previously reported in the literature.[50] **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.60-7.55 (m, 2H), 7.17-7.12 (m, 2H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.45 (d, *J* = 8.5 Hz, 1H), 3.01 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -110.92. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.6 (d, $^{1}J_{CF}$ = 247 Hz), 153.4, 132.7 (d, $^{4}J_{CF}$ = 3Hz), 127.5 (d, $^{3}J_{CF}$ = 9 Hz), 116.4 (d, $^{2}J_{CF}$ = 21 Hz), 79.7, 79.1, 78.7, 77.3.



4-Ethynyl-4-(*p*-tolyl)-1,3-dioxolan-2-one (III.25d). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 79%. The NMR spectroscopic data correspond to those previously reported in the literature.[50] **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 4.77 (d, *J* = 8.5 Hz, 1H), 4.49 (d, *J* = 8.5 Hz, 1H), 2.97 (s, 1H), 2.38 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.6, 140.1, 133.7, 129.8, 126.2, 80.0, 79.2, 78.6, 77.3, 21.2.

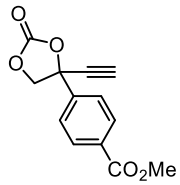


4-([1,1'-Biphenyl]-4-yl)-4-ethynyl-1,3-dioxolan-2-one (III.25e). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.69-7.64 (m, 4H), 7.60-7.58 (m, 2H), 7.48-7.45 (m, 2H), 7.41-7.38 (m, 1H), 4.83 (d, *J* = 8.5 Hz, 1H), 4.55 (d, *J* = 8.5 Hz, 1H), 3.02 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.5, 143.0, 139.9, 135.5, 129.1, 128.1, 127.9, 127.3, 126.7, 79.9, 79.1, 78.9, 77.2. **IR** (ATR): *v* = 3299, 3260, 2968, 2915, 2121, 1784, 1488, 1061, 690 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 287.0679 $(M + Na)^+$, found: 287.0679.

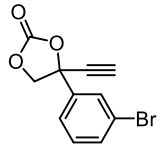


4-Ethynyl-4-(4-(methylthio)phenyl)-1,3-dioxolan-2-one (III.25f). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 73%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.73 (d, *J* = 8.5 Hz, 1H), 3.26 (s, 1H), 2.74 (s, 3H). **^{13}C NMR** (125

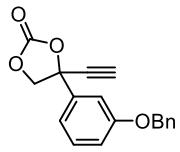
MHz, $CDCl_3$) δ 153.4, 141.5, 132.8, 126.3, 126.7, 79.6, 79.0, 78.9, 77.1, 15.3. **IR** (ATR): *v* = 3276, 3045, 2998, 2923, 2125, 1957, 1801, 1597, 1493, 1161, 673 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 257.0235 $(M + Na)^+$, found: 257.0243.



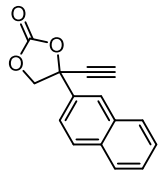
Methyl 4-(4-ethynyl-2-oxo-1,3-dioxolan-4-yl)benzoate (III.25g). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 69%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 4.82 (d, *J* = 8.5 Hz, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.02 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 153.2, 141.4, 131.7, 130.5, 126.5, 79.4, 79.2, 78.6, 77.0, 52.5. **IR** (ATR): ν = 3263, 3003, 2955, 2847, 2125, 1957, 1809, 1716, 1280, 1058, 785 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 269.0414 $(M + Na)^+$, found: 269.0420.



4-(3-Bromophenyl)-4-ethynyl-1,3-dioxolan-2-one (III.25h). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 75%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.72 (m, 1H), 7.58-7.57 (m, 1H), 7.50-7.49 (m, 1H), 7.35-7.32 (m, 1H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.46 (d, *J* = 8.5 Hz, 1H), 3.01 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.1, 139.0, 133.1, 130.8, 128.4, 123.7, 123.3, 79.4, 79.3, 78.2, 77.1. **IR** (ATR): *v* = 3268, 2126, 1807, 1571, 1474, 1181, 1060, 765 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 288.9484 $(M + Na)^+$, found: 288.9471.

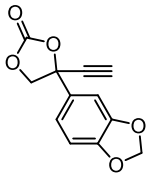


4-(3-(Benzyloxy)phenyl)-4-ethynyl-1,3-dioxolan-2-one (III.25i). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.45-7.33 (m, 6H), 7.20-7.19 (m, 1H), 7.16-7.14 (m, 1H), 7.05-7.02 (m, 1H), 5.09 (s, 2H), 4.77 (d, *J* = 8.5 Hz, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 2.97 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.3, 153.3, 138.3, 136.4, 130.5, 128.7, 128.3, 127.6, 117.4, 116.0, 112.1, 79.8, 78.9, 78.6, 77.2, 70.3. **IR** (ATR): *v* = 3283, 3033, 2125, 1805, 1585, 1444, 1182, 1060, 694 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 317.0785 $(M + Na)^+$, found: 317.0784.

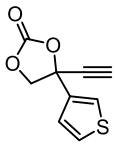


4-Ethynyl-4-(naphthalen-2-yl)-1,3-dioxolan-2-one (III.25j). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. The NMR spectroscopic data correspond to those previously reported in the literature.[50] Brown solid, yield: 88%. **^{1}H NMR**

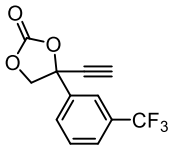
(500 MHz, $CDCl_3$) δ = 8.10 (m, 1H), 7.94-7.86 (m, 3H), 7.57-7.55 (m, 3H), 4.86 (d, *J* = 8.5 Hz, 1H), 4.59 (d, *J* = 8.5 Hz, 1H), 3.06 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.6, 133.7, 133.6, 132.7, 129.5, 128.5, 127.8, 127.5, 127.2, 126.0, 121.8, 79.9, 79.3, 79.0, 77.0.



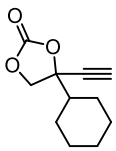
4-(Benzo[d][1,3]dioxol-5-yl)-4-ethynyl-1,3-dioxolan-2-one (III.25k). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Brown solid, yield: 68%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.10-7.08 (m, 1H), 7.02 (m, 1H), 6.85-6.84 (m, 1H), 6.02 (s, 2H), 4.74 (d, J = 8.5 Hz, 1H), 4.47 (d, J = 8.5 Hz, 1H), 2.98 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.5, 149.1, 148.6, 130.3, 119.5, 108.6, 105.9, 101.9, 79.9, 79.1, 78.7, 77.3. **IR** (ATR): *ν* = 3279, 2904, 2127, 1800, 1486, 1444, 1262, 1033, 764 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 255.0263 $(M + Na)^+$, found: 255.0264.



4-Ethynyl-4-(thiophen-3-yl)-1,3-dioxolan-2-one (III.25l). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 63%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.60-7.59 (m, 1H), 7.44-7.42 (m, 1H), 7.18-7.17 (m, 1H), 4.75 (d, *J* = 8.5 Hz, 1H), 4.56 (d, *J* = 8.5 Hz, 1H), 2.97 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.4, 137.7, 128.4, 124.9, 124.5, 79.6, 79.1, 78.1, 76.4. **IR** (ATR): *ν* = 3285, 2904, 3109, 1800, 2126, 1800, 1188, 1059, 851 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 216.9930 $(M + Na)^+$, found: 216.9930.



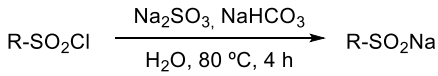
4-Ethynyl-4-(3-(trifluoromethyl)phenyl)-1,3-dioxolan-2-one (III.25m). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.84 (m, 1H), 7.78-7.76 (m, 1H), 7.73-7.71 (m, 1H), 7.64-7.60 (m, 1H), 4.84 (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 8.5 Hz, 1H), 3.04 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -62.88. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.1, 138.0, 131.9 (q, $^{2}J_{CF}$ = 33 Hz), 130.0, 127.1 (q, $^{1}J_{CF}$ = 271 Hz), 128.5 (q, $^{3}J_{CF}$ = 4 Hz), 127.0, 122.3 (q, $^{3}J_{CF}$ = 4 Hz), 79.5, 79.3, 78.4, 77.0. **IR** (ATR): *ν* = 3302, 3078, 2961, 2924, 2129, 1976, 1809, 1331, 1059, 668 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 279.0241 $(M + Na)^+$, found: 279.0239.



4-Cyclohexyl-4-ethynyl-1,3-dioxolan-2-one (III.25o). The title compound was prepared following the general procedure for the preparation of propargylic cyclic carbonates. Yellow oil, yield: 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 4.45 (d, *J* = 8.5 Hz, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 2.74 (s, 1H), 1.97-1.95 (m, 1H), 1.83-1.65

(m, 5H), 1,28-1.18 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.8, 81.6, 79.3, 77.6, 73.4, 46.0, 26.7, 26.6, 25.9, 25.6, 25.4. **IR** (ATR): *v* = 3263, 2930, 2857, 2122, 1797, 1451, 1175, 1062, 723 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 217.0825 $(M + Na)^+$, found: 217.0835.

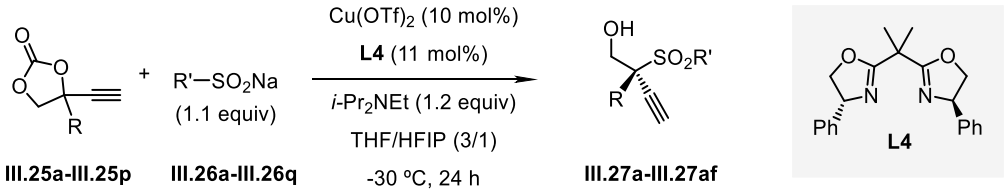
III.4.3 General procedure for the preparation of sodium sulfinates



Scheme III-18. General procedure for the preparation of sodium sulfinates.

Sodium sulfinates were prepared according to a method reported in the literature.[51] Sodium sulfite (30 mmol), sodium bicarbonate (30 mmol) and the corresponding sulfonyl chloride (15 mmol) was dissolved in 15 mL of H_2O. After stirring at 80 °C for 4 h, the water was removed by rotary evaporation. Then the remaining solid was extracted and recrystallized from ethanol to deliver the desired sodium sulfinate.

III.4.4 General procedure for the preparation of propargylic sulfones



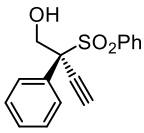
Scheme III-19. General procedure for the preparation of propargylic sulfones.

In a screw-capped vial, $Cu(OTf)_2$ (7.2 mg, 10 mol%) and **L4** (7.4 mg, 11 mol%) were combined with THF/HFIP (THF/HFIP = 3:1, 0.6 mL). The resultant solution was stirred for 30 min at room temperature. Then *i*Pr_2NEt (41.8 μL, 0.24 mmol, 1.2 equiv), sodium sulfinate (0.22 mmol, 1.1 equiv) and the corresponding cyclic carbonate (0.20 mmol, 1.0 equiv) were added successively. The reaction mixture was stirred at -30 ºC for 24 h (monitored by ^{1}H NMR), and then quenched by saturated NH_4Cl aqueous solution (5 mL). The organic components were extracted with DCM (3 × 5 mL), dried over anhydrous Na_2SO_4, following by filtration and concentration under vacuum. The resultant crude product was purified by flash chromatography to afford the corresponding pure propargylic sulfone. All purified products were fully

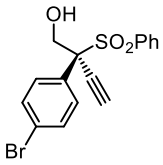
51 Du, B.; Qian, P.; Wang, Y.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* **2016**, *18*, 4144-4147.

characterized by ^{1}H, ^{13}C NMR, IR spectra and HRMS analysis, and ^{19}F NMR experiments where necessary.

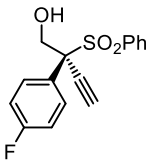
Scale-up Experiment: In a 100 ml round-bottom flask, $Cu(OTf)_2$ (180.8 mg, 10 mol%) and **L4** (183.9 mg, 11 mol%) were combined with THF/HFIP (THF/HFIP = 3:1, 15 mL). The resultant solution was stirred for 30 min at room temperature. Then *i*Pr_2NEt (1.1 mL, 6.0 mmol, 1.2 equiv), sodium benzenesulfinate **III.26a** (902.8 mg, 5.5 mmol, 1.1 equiv) and cyclic carbonate **III.25a** (940.3 mg, 5.0 mmol, 1.0 equiv) were added successively. The reaction mixture was stirred at -30 ºC (monitored by ^{1}H NMR), and then quenched by saturated NH_4Cl aqueous solution (20 mL). The organic components were extracted with DCM (3 × 20 mL), dried over anhydrous Na_2SO_4, following by filtration and concentration under vacuum. The resultant crude product was purified by flash chromatography (hexane/EtOAc= 4:1) to afford the pure sulfone **III.27a** (1.2 g, 82%, 96.5:3.5 *er*).



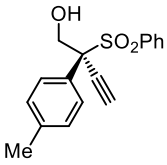
(*S*)-2-Phenyl-2-(phenylsulfonyl)but-3-yn-1-ol (III.27a). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 93%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (t, *J* = 7.6 Hz, 1H), 7.52-7.49 (m, 4H), 7.37-7.34 (m, 3H), 7.28 (t, *J* = 7.6 Hz, 2H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 2.88 (s, 1H), 2.40 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.8, 134.3, 131.1, 130.8, 129.6, 129.1, 128.5, 128.3, 80.7, 78.0, 72.8, 64.9. **IR** (ATR): *ν* = 3487, 3273, 2962, 1447, 1259, 1018, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 309.0562 $(M + Na)^+$, found: 309.0556. **UPC2**: IC column, isocratic CO_2/EtOH = 80:20, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +58.6 (c = 0.10, $CHCl_3$).



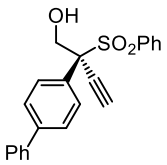
(*S*)-2-(4-Bromophenyl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27b). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 69%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.3 Hz, 1H), 7.57-7.53 (m, 2H), 7.46-7.39 (m, 6H), 4.71 (dd, *J* = 11.7, 5.6 Hz, 1H), 4.33 (dd, *J* = 11.7, 8.7 Hz, 1H), 2.88 (s, 1H), 2.56 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.7, 134.6, 131.7, 130.8, 130.3, 128.5, 124.3, 81.1, 77.6, 72.3, 64.9. **IR** (ATR): *ν* = 3287, 3094, 2916, 1488, 1305, 1145, 685 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 386.9652 $(M + Na)^+$, found: 386.9661. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 94:6, $[\alpha]_D^{25}$ = +35.2 (c = 0.12, $CHCl_3$).



(*S*)-2-(4-Fluorophenyl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27c). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.4 Hz, 1H), 7.56- 7.48 (m, 4H), 7.45- 7.35 (m, 2H), 7.05-6.95 (m, 2H), 4.75 (dd, *J* = 11.8, 5.9 Hz, 1H), 4.33 (dd, *J* = 11.8, 8.7 Hz, 1H), 2.89 (s, 1H), 2.53 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -111.40. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{CF}$ = 247 Hz), 134.7, 134.5, 131.2 (d, $^{4}J_{CF}$ = 3 Hz), 130.8, 128.4, 127.1 (d, $^{3}J_{CF}$ = 9 Hz), 115.6 (d, $^{2}J_{CF}$ = 21 Hz), 80.9, 77.9, 72.1, 65.0. **IR** (ATR): *v* = 3486, 3273, 2922, 1603, 1447, 1143, 1018, 685 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 327.0459 $(M + Na)^+$, found: 327.0462. **UPC2**: IA column, isocratic CO_2/MeOH = 85:15, 3 mL/min, 1500 psi, *er* = 97.5:2.5, $[\alpha]_D^{25}$ = +37.2 (c = 0.11, $CHCl_3$).

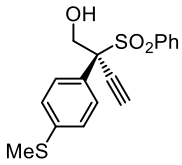


(*S*)-2-(Phenylsulfonyl)-2-(*p*-tolyl)but-3-yn-1-ol (III.27d). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 72%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.42-7.32 (m, 4H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 2.85 (s, 1H), 2.56 (m, 1H), 2.34 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.7, 134.9, 134.2, 130.8, 129.2, 129.0, 128.2, 127.9, 80.5, 72.5, 64.9, 21.2. **IR** (ATR): *v* = 3490, 3264, 1297, 1136, 1069, 593 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 323.0709 $(M + Na)^+$, found: 323.0712. **UPC2**: IC column, isocratic CO2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +47.3 (c = 0.12, $CHCl_3$).

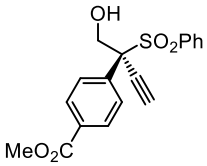


(*S*)-2-([1,1'-Biphenyl]-4-yl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27e). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61-7.53 (m, 9H), 7.46 (m, 2H), 7.40-7.37 (m, 3H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 2.90 (s, 1H), 2.57 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.4, 140.0, 134.9, 134.4, 130.9, 130.0, 129.6, 129.0, 128.3, 128.0, 127.2, 127.1, 80.7, 72.7, 65.0. **IR** (ATR): ν = 3508, 3306, 1486, 1446, 1142, 1079, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 385.0864 $(M + Na)^+$, found: 385.0869. **UPC2**: IC

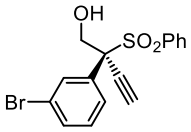
column, isocratic CO_2/MeOH = 70:30, 3 mL/min, 1500 psi *er* = 94.5:5.5, $[\alpha]_D^{25}$ = +148.9 (c = 0.10, $CHCl_3$).



(*S*)-2-(4-(Methylthio)phenyl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27f). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 93%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.46-7.35 (m, 4H), 7.15 (d, *J* = 8.6 Hz, 2H), 4.74 (dd, *J* = 11.7, 4.1 Hz, 1H), 4.32 (dd, *J* = 11.7, 7.6 Hz, 1H), 2.86 (s, 1H), 2.52 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.1, 134.9, 134.4, 130.9, 129.4, 128.3, 127.4, 125.8, 80.7, 77.9, 72.4, 65.0, 15.3. **IR** (ATR): $\underline{\nu}$ = 3496, 3275, 1493, 1446, 1303, 1143, 685 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 355.0415 $(M + Na)^+$, found: 355.0430. **UPC2**: IC column, isocratic CO_2/MeOH = 75:25, 3 mL/min, 1500 psi, *er* = 93.5:6.5, $[\alpha]_D^{25}$ = +124.8 (c = 0.10, $CHCl_3$).

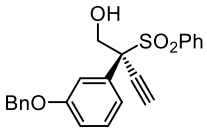


Methyl (*S*)-4-(1-hydroxy-2-(phenylsulfonyl)but-3-yn-2-yl)benzoate (III.27g). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.64-7.57 (m, 3H), 7.55-7.47 (m, 2H), 7.38 (dd, *J* = 8.4, 7.4 Hz, 2H), 4.79 (d, *J* = 11.8 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 3.93 (s, 3H), 2.92 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 136.1, 134.6, 134.6, 131.2, 130.8, 129.5, 129.2, 128.4, 81.2, 72.7, 65.0, 52.5. **IR** (ATR): ν = 3512, 3237, 1717, 1295, 1147, 1077 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 367.0616 $(M + Na)^+$, found: 367.0611. **UPC2**: IC column, isocratic CO_2/EtOH = 75:25, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +95.1 (c = 0.11, $CHCl_3$).

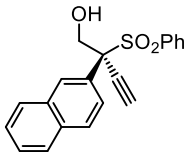


(*S*)-2-(3-Bromophenyl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27h). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 1.9 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.53-7.49 (m, 2H), 7.45-7.39 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 4.73 (dd, *J* = 11.8, 5.6 Hz, 1H), 4.35 (dd, *J* = 11.8, 8.6 Hz, 1H), 2.90 (s, 1H), 2.51 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.6, 134.5, 133.5, 132.7, 132.3, 130.8, 129.9, 128.4, 127.6, 122.5, 81.2,

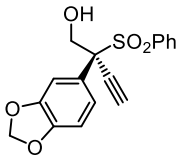
77.5, 72.3, 64.9. **IR** (ATR): ν = 3505, 3291, 1447, 1305, 1144, 684 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 386.9653 $(M + Na)^+$, found: 386.9661. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 98:2, $[\alpha]_D^{25}$ = +51.0 (c = 0.11, $CHCl_3$).



(*S*)-2-(3-(Benzyloxy)phenyl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27i). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 76%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 7.4 Hz, 1H), 7.55-7.46 (m, 2H), 7.44-7.29 (m, 7H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.17-7.07 (m, 2H), 6.96 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.07-4.95 (m, 2H), 4.75 (dd, *J* = 11.8, 6.1 Hz, 1H), 4.33 (dd, *J* = 11.8, 8.5 Hz, 1H), 2.86 (s, 1H), 2.51 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.6, 136.7, 134.9, 134.3, 132.6, 130.8, 129.5, 128.76, 128.3, 128.2, 127.6, 121.5, 116.1, 116.1, 80.7, 77.9, 72.7, 70.2, 65.0. **IR** (ATR): ν = 3497, 3280, 1582, 1446, 1306, 1145, 687 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 415.0955 $(M + Na)^+$, found: 415.0961. **UPC2**: IC column, isocratic CO_2/MeOH = 75:25, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +51.5, (c = 0.14, $CHCl_3$).

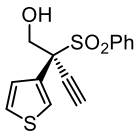


(*S*)-2-(Naphthalen-2-yl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27j). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 95%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.84-7.74 (m, 3H), 7.65 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.58-7.42 (m, 5H), 7.30 (dd, *J* = 8.4, 7.4 Hz, 2H), 4.88 (dd, *J* = 11.7, 5.2 Hz, 1H), 4.47 (dd, *J* = 11.7, 8.1 Hz, 1H), 2.95 (s, 1H), 2.63 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.7, 134.3, 133.5, 132.7, 130.8, 129.6, 128.6, 128.4, 128.3, 128.2, 127.6, 127.3, 126.6, 125.5, 80.9, 78.1, 72.9, 65.0. **IR** (ATR): ν = 3253, 3220, 1303, 1142, 1061, 711, 593 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 359.0702 $(M + Na)^+$, found: 359.0712. **UPC2**: IC column, isocratic CO_2/MeOH = 75:25, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +116.3, (c = 0.10, $CHCl_3$).

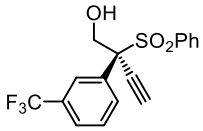


(*S*)-2-(Benzo[d][1,3]dioxol-5-yl)-2-(phenylsulfonyl)but-3-yn-1-ol (III.27k). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67-7.52 (m,

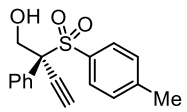
3H), 7.41 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 5.99-5.97 (m, 2H), 4.68 (dd, *J* = 11.8, 6.1 Hz, 1H), 4.29 (dd, *J* = 11.8, 8.4 Hz, 1H), 2.86 (s, 1H), 2.50 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.8, 147.9, 134.9, 134.4, 130.8, 128.3, 124.5, 123.5, 109.5, 108.1, 101.7, 80.7, 78.2, 72.5, 65.1. **IR** (ATR): *v* = 3516, 3257, 2919, 1504, 1303, 1250, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 353.0447 $(M + Na)^+$, found: 353.0454. **UPC2**: IC column, isocratic CO_2/MeOH = 75:25, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +109.1, (c = 0.14, $CHCl_3$).



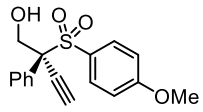
(*S*)-2-(Phenylsulfonyl)-2-(thiophen-3-yl)but-3-yn-1-ol (III.27l). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (t, *J* = 7.4 Hz, 1H), 7.56-7.51 (m, 2H), 7.39 (dd, *J* = 8.4, 7.4 Hz, 2H), 7.34 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.29 (dd, *J* = 5.1, 3.1 Hz, 1H), 7.22 (dd, *J* = 5.1, 1.4 Hz, 1H), 4.66 (dd, *J* = 11.8, 5.7 Hz, 1H), 4.30 (dd, *J* = 11.8, 7.7 Hz, 1H), 2.81 (s, 1H), 2.72 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.7, 134.3, 132.2, 130.5, 128.3, 127.5, 127.5, 126.2, 79.2, 78.1, 69.6. **IR** (ATR): *v* = 3489, 3267, 1299, 1142, 1058, 1033, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 315.0133 $(M + Na)^+$, found: 315.0120. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +65.2, (c = 0.10, $CHCl_3$).



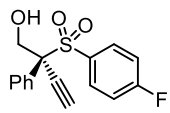
(*S*)-2-(Phenylsulfonyl)-2-(3-(trifluoromethyl)phenyl)but-3-yn-1-ol (III.27m). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 51%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87-7.77 (m, 1H), 7.67-7.58 (m, 3H), 7.53-7.45 (m, 3H), 7.43-7.35 (m, 2H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 2.93 (s, 1H), 2.63 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -62.48. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.7, 134.3, 132.5, 133.3, 132.3, 130.7, 129.2 (q, $^{2}J_{CF}$ = 33 Hz), 129.0, 128.5, 126.4 (q, $^{3}J_{CF}$ = 4 Hz), 122.3 (q, $^{1}J_{CF}$ = 271 Hz), 81.3, 77.4, 72.4, 64.7. **IR** (ATR): *v* = 3494, 3296, 1447, 1327, 1123, 1076, 721 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 377.0431 $(M + Na)^+$, found: 377.0430. **UPC2**: IC column, isocratic CO_2/MeOH = 90:10, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +46.7, (c = 0.10, $CHCl_3$).



(*S*)-2-Phenyl-2-tosylbut-3-yn-1-ol (III.27q). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56-7.49 (m, 2H), 7.40-7.34 (m, 3H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 2.86 (s, 1H), 2.61 (m, 1H), 2.40 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.5, 131.9, 131.3, 130.8, 129.6, 129.1, 128.9, 128.4, 80.5, 78.1, 72.6, 65.0, 21.8. **IR** (ATR): *v* = 3482, 3224, 2922, 2852, 1291, 1143, 1057, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 323.0717 $(M + Na)^+$, found: 323.0710. **UPC2**: IC column, isocratic CO_2/EtOH = 80:20, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +72.3 (*c* = 0.10, $CHCl_3$).

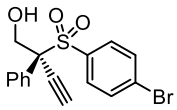


(S)-2-((4-Methoxyphenyl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27r). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 95%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.54-7.48 (m, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 3.84 (s, 3H), 2.86 (s, 1H), 2.63 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.3, 133.0, 131.4, 129.5, 129.1, 128.4, 126.2, 113.5, 80.4, 78.2, 72.7, 64.9, 55.7. **IR** (ATR): *v* = 3488, 3274, 1592, 1495, 1296, 1261, 1138, 660 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 339.0665 $(M + Na)^+$, found: 339.0662. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +22.9 (*c* = 0.10, $CHCl_3$).

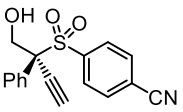


(*S*)-2-((4-Fluorophenyl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27s). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 83%. 97:3 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57-7.43 (m, 4H), 7.40-7.35 (m, 1H), 7.34-7.28 (m, 2H), 7.03 (dd, *J* = 9.0, 8.2 Hz, 2H), 4.80 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 2.90 (s, 1H), 2.53 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -102.33. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3 (d, $^{1}J_{CF}$ = 247 Hz), 133.6 (d, $^{3}J_{CF}$ = 9 Hz), 131.0, 130.9 (d, $^{4}J_{CF}$ = 3 Hz), 129.8, 129.0, 128.6, 115.6 (d, $^{2}J_{CF}$ = 21 Hz), 80.9, 77.9, 73.0, 64.9. **HRMS** (ESI+, MeOH): m/z calcd. 327.0460 $(M + Na)^+$, found: 327.0462. **IR** (ATR): *v* = 3277, 2962, 1589, 1491, 1289, 1079, 694

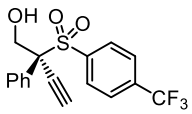
cm^{-1}. **UPC2**: IF column, isocratic CO_2/MeOH = 85:15, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +15.7 (*c* = 0.11, $CHCl_3$).



(*S*)-2-((4-Bromophenyl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27t). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58-7.46 (m, 4H), 7.41-7.29 (m, 5H), 4.80 (d, J = 11.7 Hz, 1H), 4.34 (d, J = 11.7 Hz, 1H), 2.90 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 133.9, 132.2, 131.6, 130.8, 130.0, 129.9, 129.1, 128.6, 81.1, 77.8, 73.0, 64.9. **IR** (ATR): *v* = 3286, 1572, 1388, 1312, 1066, 695 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 386.9664 $(M + Na)^+$, found: 386.9672. **UPC2**: IA column, isocratic CO_2/EtOH = 80:20, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +64.7 (*c* = 0.09, $CHCl_3$).

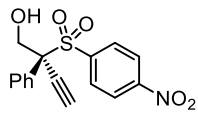


(*S*)-4-((1-Hydroxy-2-phenylbut-3-yn-2-yl)sulfonyl)benzonitrile (III.27u). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 63%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68-7.60 (m, 4H), 7.56-7.50 (m, 2H), 7.44-7.37 (m, 1H), 7.37-7.30 (m, 2H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 2.94 (s, 1H), 2.42 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.4, 131.9, 131.3, 130.3, 130.1, 129.0, 128.8, 117.9, 117.1, 81.6, 77.4, 73.4, 65.0. **IR** (ATR): *v* = 3494, 3275, 1317, 1288, 1144, 1063, 730 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 334.0511 $(M + Na)^+$, found: 334.0519. **UPC2**: IB column, isocratic CO_2/MeOH = 90:10, 3 mL/min, 1500 psi, *er* = 93:7, $[\alpha]_D^{25}$ = +89.4 (*c* = 0.10, $CHCl_3$).

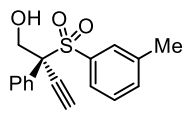


(*S*)-2-Phenyl-2-((4-(trifluoromethyl)phenyl)sulfonyl)but-3-yn-1-ol (III.27v). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 74%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.53 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.43-7.37 (m, 1H), 7.36-7.26 (m, 2H), 4.82 (dd, *J* = 11.7, 4.8 Hz, 1H), 4.36 (dd, J = 11.7, 7.1 Hz, 1H), 2.93 (s, 1H), 2.50 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -63.27. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 136.8 (q, $^2J_{CF}$ = 33 Hz), 131.3, 130.5, 130.0, 129.1, 128.7, 125.3 (q, $^3J_{CF}$ = 4 Hz), 125.8 (q, $^1J_{CF}$ = 271 Hz), 81.4, 77.6, 73.2, 64.9. **IR** (ATR): *v* = 3516, 3237, 1404, 1317,

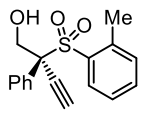
1127, 1016 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 377.0430 $(M + Na)^+$, found: 377.0416. **UPC2**: IC column, isocratic CO_2/MeOH = 90:10, 3 mL/min, 1500 psi, *er* = 94:6, $[\alpha]_D^{25}$ = +70.5 (*c* = 0.12, $CHCl_3$).



(*S*)-2-((4-Nitrophenyl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27w). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 47%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.55 (m, 2H), 7.44-7.40 (m, 1H), 7.37-7.33 (m, 2H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 2.96 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.0, 140.9, 132.2, 130.3, 130.2, 129.1, 128.9, 126.7, 123.2, 81.8, 77.4, 73.5, 65.0. **IR** (ATR): *v* = 2923, 2853, 1528, 1304, 1146, 1079 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 354.0397 $(M + Na)^+$, found: 354.0407. **UPC2**: IG column, isocratic CO_2/IPA = 70:30, 3 mL/min, 1500 psi, *er* = 93:7, $[\alpha]_D^{25}$ = +63.2 (*c* = 0.10, $CHCl_3$).

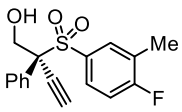


(*S*)-2-Phenyl-2-(m-tolylsulfonyl)but-3-yn-1-ol (III.27x). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54-7.46 (m, 2H), 7.32-7.27 (m, 5H), 7.25-7.20 (m, 2H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 2.87 (s, 1H), 2.58 (m, 1H), 2.27 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.4, 135.0, 134.5, 131.2, 131.2, 129.6, 129.1, 128.4, 1281, 127.9, 80.5, 78.0, 72.7, 64.8, 21.1. **IR** (ATR): *v* = 3423, 3283, 1450, 1296, 1141, 685 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 323.0717 $(M + Na)^+$, found: 323.0710. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +55.3 (*c* = 0.10, $CHCl_3$).

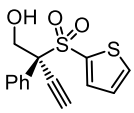


(*S*)-2-Phenyl-2-(*o*-tolylsulfonyl)but-3-yn-1-olol (III.27y). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.51-7.42 (m, 3H), 7.40-7.35 (m, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 4.87 (dd, *J* = 11.8, 5.2 Hz, 1H), 4.33 (dd, *J* = 11.8, 9.3 Hz, 1H), 2.85 (s, 1H), 2.73 (m, 1H), 2.10 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.6, 134.4, 133.9, 132.9, 132.5, 131.4, 129.7, 129.3, 128.5, 125.7, 80.5, 78.2, 73.4, 64.8,

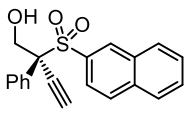
20.5. **IR** (ATR): ν = 3490, 3235, 1494, 1301, 1146, 1059, 692, 683 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 323.0703 $(M + Na)^+$, found: 323.0712. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 95.5:4.5, $[\alpha]_D^{25}$ = +58.5 (*c* = 0.11, $CHCl_3$).



(*S*)-2-((4-Fluoro-3-methylphenyl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27z). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 83%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.48 (m, 2H), 7.42-7.36 (m, 1H), 7.36-7.29 (m, 3H), 7.26-7.22 (m, 1H), 6.98 (t, *J* = 8.8 Hz, 1H), 4.80 (dd, *J* = 11.8, 5.9 Hz, 1H), 4.35 (dd, *J* = 11.8, 8.6 Hz, 1H), 2.88 (s, 1H), 2.52 (m, 1H), 2.18 (d, *J* = 2.0 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -106.60. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.9 (d, $^1J_{CF}$ = 247 Hz), 134.6 (d, $^3J_{CF}$ = 9 Hz), 131.2, 130.9 (d, $^4J_{CF}$ = 9 Hz), 130.2 (d, $^4J_{CF}$ = 3 Hz), 129.8, 129.2, 128.5, 125.8 (d, $^2J_{CF}$ = 21 Hz), 115.3 (d, $^2J_{CF}$ = 21 Hz), 80.8, 78.0, 72.9, 64.9, 14.4 (d, $^4J_{CF}$ = 3 Hz). **IR** (ATR): ν = 3275, 2925, 2118, 1809, 1581, 1489, 1300, 1242, 1061, 664 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 341.0619 $(M + Na)^+$, found: 341.0618. **UPC2**: IC column, isocratic CO_2/EtOH = 85:15, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +49.3 (*c* = 0.10, $CHCl_3$).

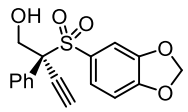


(*S*)-2-Phenyl-2-(thiophen-2-ylsulfonyl)but-3-yn-1-ol (III.27aa). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Orange solid, yield: 58%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.63-7.56 (m, 2H), 7.40-7.36 (m, 1H), 7.36-7.31 (m, 3H), 7.02 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.77 (dd, *J* = 11.8, 6.0 Hz, 1H), 4.39 (dd, *J* = 11.8, 8.3 Hz, 1H), 2.95 (s, 1H), 2.48 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.2, 135.8, 135.1, 131.1, 129.8, 129.0, 128.6, 127.3, 81.0, 77.8, 73.7, 65.0. **IR** (ATR): ν = 3497, 3271, 1396, 1306, 1140, 1056, 1014, 696 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 315.0119 $(M + Na)^+$, found: 315.0120. The *er* value was determined from the corresponding acetate. **UPC2**: IE column, isocratic CO_2/MeOH = 85:15, 3 mL/min, 1500 psi, *er* = 94:6, $[\alpha]_D^{25}$ = +23.8 (*c* = 0.09, $CHCl_3$).

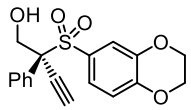


(*S*)-2-(Naphthalen-2-ylsulfonyl)-2-phenylbut-3-yn-1-ol (III.27ab). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 69%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 1.0 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.1 Hz,

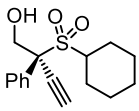
1H), 7.85-7.81 (m, 1H), 7.81-7.75 (m, 1H), 7.66 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.55-7.49 (m, 2H), 7.43 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.40-7.33 (m, 1H), 7.32-7.26 (m, 2H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 2.87 (s, 1H), 2.60 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.6, 133.2, 131.8, 131.6, 131.2, 129.7, 129.7, 129.2, 128.5, 128.1, 127.9, 127.6, 125.1, 80.8, 78.0, 73.0, 65.0. **IR** (ATR): *v* = 3245, 2924, 1301, 1127, 1068, 745, 693 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 359.0715 $(M + Na)^+$, found: 359.0710. **UPC2**: IA column, isocratic CO_2/EtOH = 75:25, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +60.6 (*c* = 0.10, $CHCl_3$).



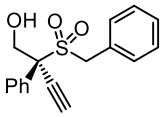
(*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-2-phenylbut-3-yn-1-ol (III.27ac). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 73%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59-7.51 (m, 2H), 7.41-7.28 (m, 3H), 7.01 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.07-6.03 (m, 2H), 4.76 (dd, *J* = 11.9, 3.8 Hz, 1H), 4.38-4.27 (m, 1H), 2.89 (s, 1H), 2.57 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.8, 147.6, 131.2, 129.6, 129.1, 128.5, 127.9, 127.2, 110.7, 107.7, 102.5, 80.6, 78.1, 72.8, 64.9. **IR** (ATR): *v* = 3502, 3222, 2925, 2853, 2115, 1723, 1601, 1241, 1033, 618 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 353.0454 $(M + Na)^+$, found: 353.0454. **UPC2**: IC column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +47.6 (*c* = 0.10, $CHCl_3$).



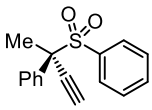
(*S*)-2-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2-phenylbut-3-yn-1-ol (III.27ad). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Brown solid, yield: 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60-7.51 (m, 2H), 7.42-7.35 (m, 1H), 7.34-7.28 (m, 2H), 7.07 (d, *J* = 2.2 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 4.75 (dd, *J* = 11.9, 4.4 Hz, 1H), 4.39-4.27 (m, 3H), 4.27-4.20 (m, 2H), 2.88 (s, 1H), 2.69-2.57 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.9, 143.0, 131.3, 129.6, 129.1, 128.4, 127.0, 124.7, 120.5, 117.0, 80.5, 78.2, 72.7, 65.0, 64.7, 64.1. **IR** (ATR): *v* = 3497, 3274, 2925, 1490, 1286, 1056, 876, 632 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 367.0612 $(M + Na)^+$, found: 367.0611. The *er* value was determined from the corresponding acetate. **UPC2**: IE column, isocratic CO_2/EtOH = 70:30, 3 mL/min, 1500 psi, *er* = 89:11, $[\alpha]_D^{25}$ = +4.65 (*c* = 0.11, $CHCl_3$).



(*S*)-2-(Cyclohexylsulfonyl)-2-phenylbut-3-yn-1-ol (III.27ae). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.46-7.40 (m, 3H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 3.20 (ddd, *J* = 12.0, 8.4, 3.6 Hz, 1H), 3.04 (s, 1H), 2.66 (m, 1H), 2.35-2.16 (m, 1H), 1.89-1.76 (m, 1H), 1.72-1.65 (m, 1H), 1.63-1.50 (m, 3H), 1.42-1.29 (m, 1H), 1.20-1.01 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 131.5, 129.7, 128.9, 128.5, 81.3, 71.3, 66.5, 61.1, 26.5, 26.1, 25.4, 25.2, 25.0. **IR** (ATR): *v* = 3469, 3277, 2928, 2855, 1449, 1293, 1126, 696 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 315.1022 $(M + Na)^+$, found: 315.1012. **UPC2**: IA column, isocratic CO_2/EtOH = 85:15, 3 mL/min, 1500 psi, *er* = 91.5:8.5, $[\alpha]_D^{25}$ = +22.9 (*c* = 0.09, $CHCl_3$).



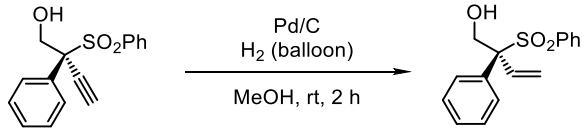
(*S*)-2-(Benzylsulfonyl)-2-phenylbut-3-yn-1-ol (III.27af). The title compound was prepared following the general procedure for the preparation of propargylic sulfones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid, yield: 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90-7.75 (m, 2H), 7.54-7.39 (m, 3H), 7.37-7.27 (m, 5H), 4.72 (dd, *J* = 11.8, 7.0 Hz, 1H), 4.55 (d, *J* = 13.1 Hz, 1H), 4.25 (d, *J* = 13.1 Hz, 1H), 4.16 (dd, *J* = 11.8, 7.0 Hz, 1H), 3.06 (s, 1H), 2.75 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 131.6, 130.6, 129.9, 129.0, 128.9, 128.9, 128.7, 125.9, 81.6, 77.6, 72.0, 65.8, 56.1. **IR** (ATR): *v* = 3479, 3294, 1304, 1124, 1078 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 323.0713 $(M + Na)^+$, found: 323.0710. **UPC2**: IA column, isocratic CO_2/EtOH = 80:20, 3 mL/min, 1500 psi, *er* = 92.5:7.5, $[\alpha]_D^{25}$ = +22.9 (*c* = 0.09, $CHCl_3$).



((*S*)-((2-Phenylbut-3-yn-2-yl)sulfonyl)benzene (III.36a). The title compound was prepared following the general procedure for the preparation of propargylic sulfones using electrophile **III.32**, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 4/1). Yellow solid. (Hexane/EtOAc = 4/1). Yellow solid, yield: 90%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60-7.55 (m, 1H), 7.52 (m, 4H), 7.39-7.31 (m, 3H), 7.31-7.26 (m, 2H), 2.77 (s, 1H), 2.14 (s, 3H).**^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.5, 133.9, 133.8, 131.0, 129.2, 128.9, 128.1, 128.1, 81.1, 78.1, 67.1, 22.0. **IR** (ATR): *v* = 3238, 1446, 1303, 1143, 686 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd.

293.0596 (M + Na)$^+$, found: 293.0607. **UPC2**: IC column, isocratic CO_2/MeOH = 90:10, 3 mL/min, 1500 psi, *er* = 75:25, $[\alpha]_D^{25}$ = +67.2 (*c* = 0.10, $CHCl_3$).

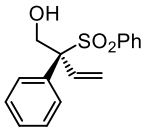
III.4.5 Synthetic transformations of tertiary propargylic sulfones



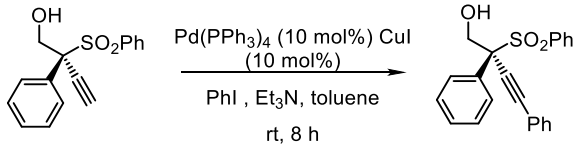
III.27a **III.40**

Scheme III-20. Procedure for allylic sulfone formation.

A Schlenk tube was charged with propargylic sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv) and Pd/C (5 mg, 10 wt % palladium on carbon). The Schlenk tube was evacuated/filled with H_2 (balloon) for three times. After that, MeOH (1 mL) was added and the reaction mixture was stirred under an H_2 atmosphere (balloon) for 2 h at room temperature and monitored by ^{1}H NMR. The reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (Hexane/EtOAc= 3:1) to afford the pure allylic sulfone **III.40** (51.3 mg, 89%, 96.5:3.5 *er*) as a yellow solid.



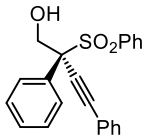
(*S*)-2-Phenyl-2-(phenylsulfonyl)but-3-en-1-ol (III.40). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61-7.54 (m, 1H), 7.42-7.28 (m, 9H), 6.49 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.72 (dd, *J* = 11.2, 0.6 Hz, 1H), 5.52 (dd, *J* = 17.6, 0.6 Hz, 1H), 4.48 (d, *J* = 12.2 Hz, 1H), 4.34 (d, *J* = 12.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.6, 134.0, 132.9, 132.1, 130.3, 130.0, 129.1, 128.5, 128.4, 123.0, 75.9, 63.3. **IR** (ATR): *v* = 3485, 2923, 1446, 1291, 1139, 1080, 686 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 311.0724 (M + Na)$^+$, found: 311.0712. **UPC2**: IC column, isocratic CO_2/ACN = 80:20, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +2.5 (*c* = 0.05, $CHCl_3$).



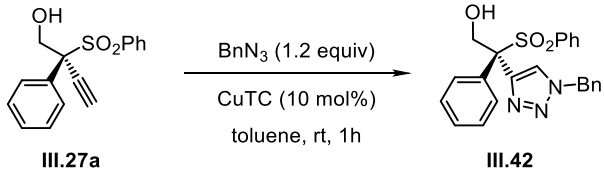
III.27a **III.41**

Scheme III-21. Procedure for the Sonogashira coupling using **III.27a**.

Sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv), iodobenzene (26.8 μL, 0.24 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol, 0.1 equiv) and CuI (3.8 mg, 0.02 mmol, 0.1 equiv) were added to a Schlenk tube charged with a stirring bar. The Schlenk tube was closed with a PTFE-lined cap and then it was three times evacuated and refilled with N_2. Et_3N (0.5 mL) and toluene (0.5 mL) were added by a syringe at room temperature and the resulting solution was then stirred for 12 h and monitored by TLC. Then, the crude mixture was passed through a short pad of silica gel, washed with EtOAc (10 mL) and concentrated. The residue was purified by silica gel chromatography (Hexane/EtOAc= 3:1) to afford the desired product **III. 41** (57.3 mg, 79%, 97:3 *er*) as a brown solid.

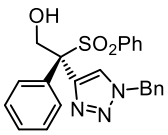


(*R*)-2,4-Diphenyl-2-(phenylsulfonyl)but-3-yn-1-ol (III.41). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.55 (m, 5H), 7.47 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.44-7.31 (m, 9H), 4.85 (dd, *J* = 11.7, 5.9 Hz, 1H), 4.42 (dd, *J* = 11.7, 8.4 Hz, 1H), 2.60 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.3, 134.2, 132.0, 131.8, 130.8, 129.6, 129.4, 129.3, 128.6, 128.5, 128.2, 121.6, 92.4, 83.1, 73.6, 65.1. **IR** (ATR): *v* = 3487, 1733, 1446, 1306, 1144, 1081, 688 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 385.0877 $(M + Na)^+$, found: 385.0869. **UPC2**: IE column, isocratic CO_2/EtOH = 70:30, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = -20.5 (*c* = 0.10, $CHCl_3$).

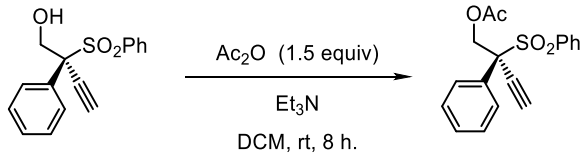


Scheme III-22. Procedure for the click-reaction performed between **III.27a** and benzyl azide.

A mixture of sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv) and copper(I) thiophene-2-carboxylate (CuTC) (3.8 mg, 0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was cooled by an ice-water bath. Subsequently, benzyl azide (30.0 μL, 0.24 mmol, 1.2 equiv) was added slowly, and the reaction mixture was allowed to warm to room temperature, stirred for 1 h and monitored by TLC. The reaction was quenched by saturated NH_4Cl aqueous solution, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/EtOAc= 3:1) to afford the desired triazole **III.42**(74.6 mg, 89%, 96.5:3.5 *er*) as a yellow solid.



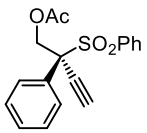
(*R*)-2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-phenyl-2-(phenylsulfonyl)ethan-1-ol (III.42). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (ddd, *J* = 5.3, 4.4, 2.4 Hz, 3H), 7.41-7.37 (m, 2H), 7.37-7.27 (m, 7H), 7.26-7.20 (m, 2H), 5.65 (d, *J* = 14.7 Hz, 1H), 5.56 (d, *J* = 14.7 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 3.95 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.1, 134.4, 134.0, 132.5, 130.5, 130.0, 129.4, 129.2, 129.0, 128.4, 128.4, 128.3, 125.7, 74.1, 65.2, 54.7. **IR** (ATR): *v* = 3471, 3136, 2922, 2853, 1445, 1287, 1137, 691 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 442.1204 $(M + Na)^+$, found: 442.1196. **UPC2**: IB column, isocratic CO_2/EtOH = 80:20, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = -35.2 (*c* = 0.10, $CHCl_3$).



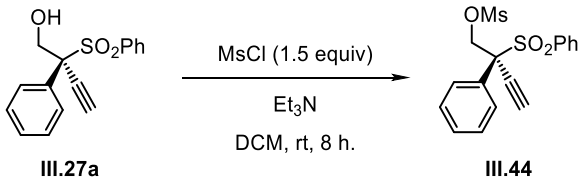
III.27a **III.43**

Scheme III-23. Procedure for *O*-protection of **III.27a**.

To a solution of sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv) in DCM (0.5 mL), Et_3N (41.8 μL, 0.30 mmol, 1.5 equiv) and acetic anhydride (28.4 μL, 0.30 mmol, 1.5 equiv) were added slowly, and the reaction mixture allowed to stirred for 8 h at room temperature (monitored by TLC). The reaction was quenched by saturated NH_4Cl aqueous solution, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/EtOAc= 3:1) to afford the desired acetate **III.43** (63.7 mg, 97%, 96.5:3.5 *er*) as a yellow solid.



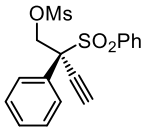
(*S*)-2-Phenyl-2-(phenylsulfonyl)but-3-yn-1-yl acetate (III.43). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68-7.51 (m, 4H), 7.46-7.26 (m, 6H), 5.14-4.92 (m, 2H), 2.83 (s, 1H), 1.95 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 135.3, 134.3, 131.4, 130.4, 129.7, 129.2, 128.4, 128.3, 80.1, 77.8, 70.9, 64.2, 20.7. **IR** (ATR): *v* = 3279, 1746, 1448, 1309, 1218, 1145, 1047, 757 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 351.0667 $(M + Na)^+$, found: 351.0662. **UPC2**: IG column, isocratic CO_2/MeOH = 75:25, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +12.5 (*c* = 0.09, $CHCl_3$).



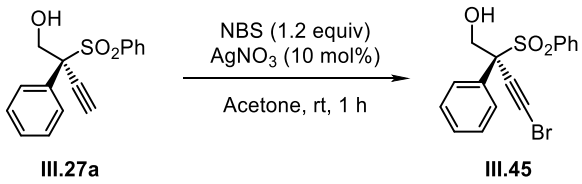
III.27a **III.44**

Scheme III-24. Procedure for *O*-mesylation of **III.27a**.

To a solution of sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv) in DCM (0.5 mL), Et_3N (41.8 μL, 0.30 mmol, 1.5 equiv) and trifluoromethanesulfonyl chloride (31.9 μL, 0.30 mmol, 1.5 equiv) were added slowly, and the reaction mixture was stirred for 8 h at room temperature while monitored by TLC. The reaction was quenched by saturated NH_4Cl aqueous solution, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/EtOAc= 3:1) to afford the desired mesylate **III.44** (63.7 mg, 97%, 96.5:3.5 *er*) as a yellow solid.



(*S*)-2-Phenyl-2-(phenylsulfonyl)but-3-yn-1-yl methanesulfonate (III.44). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64-7.57 (m, 1H), 7.55 (dd, *J* = 7.1, 1.5 Hz, 4H), 7.43-7.36 (m, 3H), 7.35-7.29 (m, 2H), 5.10 (d, *J* = 1.2 Hz, 2H), 2.95 (s, 3H), 2.91 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.6, 131.0, 130.0, 129.6, 129.1, 128.6, 128.4, 81.0, 77.3, 77.0, 70.7, 68.8, 38.1. **IR** (ATR): *v* = 3274, 1361, 1311, 1177, 1151, 1006 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 387.0346 $(M + Na)^+$, found: 387.0331. **UPC2**: IC column, isocratic CO_2/EtOH = 85:15, 3 mL/min, 1500 psi, *er* = 96.5:3.5, $[\alpha]_D^{25}$ = +58.0 (*c* = 0.10, $CHCl_3$).

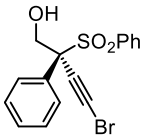


III.27a **III.45**

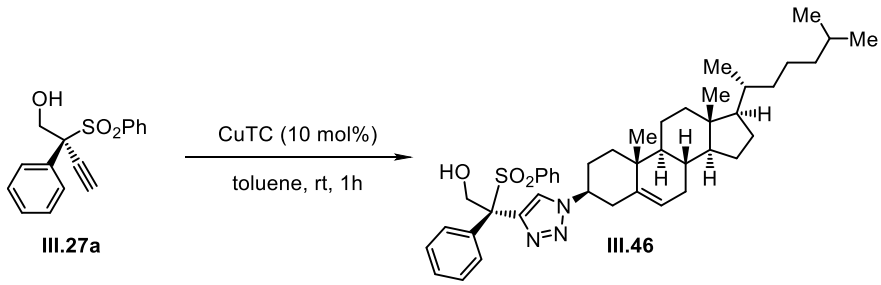
Scheme III-25. Procedure for terminal alkyne bromination in **III-27a**.

A mixture of sulfone **III.27a** ((57.2 mg, 0.20 mmol, 1.0 equiv) and N-bromo-succinimide (42.7 mg, 0.24 mmol, 1.2 equiv) in acetone (1 mL) was cooled by an ice-water bath. Subsequently, silver nitrate (3.4 mg, 0.02 mmol, 0.1 equiv) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 1 h while monitored by TLC. Then, the crude

mixture was passed through a short pad of silica gel, washed with ethyl acetate (10 mL) and concentrated. The residue was purified by silica gel chromatography (Hexane/EtOAc= 3:1) to afford the desired product **III.45** ((50.4 mg, 69%, 97:3 *er*) as a yellow solid.

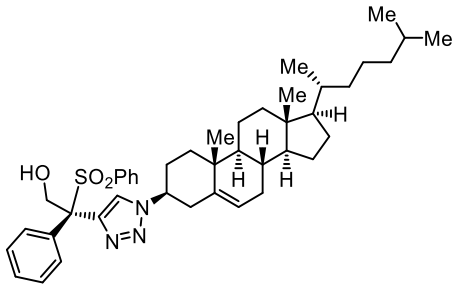


(*R*)-4-bromo-2-phenyl-2-(phenylsulfonyl)but-3-yn-1-ol (III.45). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64-7.57 (m, 1H), 7.48 (ddd, *J* = 12.9, 8.5, 1.4 Hz, 4H), 7.43-7.35 (m, 3H), 7.34-7.27 (m, 2H), 4.76 (dd, *J* = 11.8, 5.4 Hz, 1H), 4.33 (dd, *J* = 11.8, 8.2 Hz, 1H), 2.53 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.9, 134.4, 131.2, 130.6, 129.7, 129.1, 128.5, 128.4, 74.5, 73.8, 64.9, 52.9. **IR** (ATR): ν = 3491, 1447, 1305, 1143, 1080, 711, 686 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 386.9664 $(M + Na)^+$, found: 386.9661. **UPC2**: IA column, isocratic CO_2/MeOH = 80:20, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +9.1 (*c* = 0.11, $CHCl_3$).



Scheme III-26. Procedure for the click-reaction between **III.27a** and cholesterol azide.

A mixture of sulfone **III.27a** (57.2 mg, 0.20 mmol, 1.0 equiv) and copper (I) thiophene-2-carboxylate (CuTC) (3.8 mg, 0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was cooled by an ice-water bath. Subsequently, cholesterol azide (98.8 mg, 0.24 mmol, 1.2 equiv) was added slowly, and the reaction mixture allowed to warm to room temperature and stirred for 1 h while monitored by TLC. The reaction was quenched by saturated NH_4Cl aqueous solution, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/EtOAc= 3:1) to afford the desired triazole **III.46** (107.5 mg, 77%, 96.5:3.5 *dr*) as a white solid.



(*R*)-2-(1-((3*S*,8S,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)-1*H*-1,2,3-triazol-4-yl)-2-phenyl-2-(phenylsulfonyl)ethan-1-ol (III.46). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.55 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.45-7.30 (m, 9H), 5.51 (d, *J* = 5.1 Hz, 1H), 4.79 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.56 (dd, *J* = 12.0, 9.5 Hz, 1H), 4.47 (dq, *J* = 11.9, 7.2, 6.0 Hz, 1H), 4.08 (ddd, *J* = 9.5, 5.2, 1.0 Hz, 1H), 2.85 (t, *J* = 12.6 Hz, 1H), 2.62 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.19 (d, *J* = 2.9 Hz, 2H), 2.07 (d, *J* = 3.4 Hz, 3H), 1.85 (d, *J* = 2.1 Hz, 1H), 1.56-1.48 (m, 7H), 1.40-1.23 (m, 6H), 1.16-1.03 (m, 10H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.71 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.7, 139.0, 136.1, 134.1, 130.6, 130.0, 129.0, 128.5, 128.4, 123.8, 123.5, 77.3, 74.1, 65.2, 61.6, 56.8, 56.3, 50.2, 42.5, 39.8, 39.7, 39.6, 37.9, 36.9, 36.3, 35.9, 32.0, 31.9, 29.5, 28.3, 28.1, 24.4, 24.0, 22.9, 22.7, 21.1, 19.5, 18.8, 12.0. **IR** (ATR): *v* = 2943, 2866, 1299, 1148 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 698.4350 $(M + Na)^+$, found: 698.4350. **UPC2**: OJ column, isocratic CO_2/EtOH = 88:12, 3 mL/min, 1500 psi, *dr* = 96:4, $[\alpha]_D^{25}$ = -10.4 (*c* = 0.08, $CHCl_3$).

III.4.6 Crystallographic data

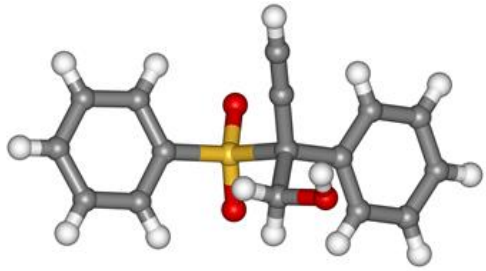


Table III-8. Crystal data and structure refinement for **III.27a** (CCDC-1574299).

Empirical formula	$C_{16}H_{14}O_3S$
Formula weight	286.33
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	a = 6.1183(4)Å α = 90°
	b = 12.2449(8)Å β = 90°
	c = 17.7727(11)Å γ = 90°
Volume	1331.49(15) $Å^3$
Z	4
Density (calculated)	1.428 Mg/m^3
Absorption coefficient	0.247 mm^{-1}
F(000)	600
Crystal size	0.15 × 0.05 × 0.02 mm^3
Theta range for data collection	2.020 to 28.348°.
Index ranges	-8<=h<=8,-16<=k<=15,-15<=l<=23
Reflections collected	15450
Independent reflections	3295[*R*(int) = 0.0401]
Completeness to theta =28.348°	99.9%
Absorption correction	Multi-scan
Max. and min. transmission	0.995 and 0.935
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3295/ 0/ 182
Goodness-of-fit on F^2	1.055
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0362, *wR*2 = 0.0811
R indices (all data)	*R*1 = 0.0455, *wR*2 = 0.0845
Flack parameter	*x* = 0.01(3)
Largest diff. peak and hole	0.498 and -0.353 e·$Å^{-3}$

Chapter IV

Copper-Catalyzed Synthesis of γ-Amino Acids Featuring Quaternary Stereocenters

The results described in this chapter have been published in:

Gómez, J. E.; Guo, W.; Gaspa, S.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2017**, *56*, 15035-15038

UNIVERSITAT ROVIRA I VIRGILI
STEREOSELECTIVE SYNTHESIS OF SULFONES AND AMINO ACIDS FROM FUNCTIONALIZED HETEROCYCLES
José Enrique Gómez Pulido

IV.1. Introduction

IV.1.1 γ-Amino acids

Amino acids (AAs) are among the most important molecules in nature since they play central roles as intermediates in metabolic processes as well as representing building blocks of proteins. The chemical properties of the active site of proteins are dictated by the presence of specific amino acid sequences that regulate protein activity, stability, bioavailability and binding specificity.[1] Biomedical research is constantly oriented towards the development of new drugs and biomedical devices based on peptides and proteins by introducing both structural and functional specific modifications while maintaining the features responsible for biological activity.[2] As part of this research area, unnatural amino acids (UAAs) are of particular interest.[3] Medicinal chemistry has taken advantage of the use of unnatural amino acid homologues to introduce elements of diversity for the generation of new drug candidates. Unlike proteinogenic amino acids, for which the preferred isolation/production method is extraction from natural sources, UAAs must be synthesized.[4]

In this context, the synthesis of enantiopure γ-amino acid derivatives is increasingly in demand by the pharmaceutical industry as they are potentially relevant for peptidomimetic and other single-enantiomer drugs (Figure IV-1).[5] For instance, the simplest γ-amino acid, γ-aminobutyric acid (GABA) **IV.1** is the major inhibitory neurotransmitter in the central nervous system (CNS) of mammals. GABA deficiency is associated with several neurological disorders such as Huntington and Parkinson disease, epilepsy as well as psychiatric disorders such as

1 Hardy, P. M. *Chemistry and biochemistry of the amino acids*. Chapman and Hall, New York, **1985**.

2 (a) Fosgerau, K.; Hoffmann, T. *Drug Discovery Today* **2015**, *20*, 122-128. (b) Craik, D. J.; Fairlie, D. P.; Liras, S.; Price, D. *Chem. Biol. Drug Des.* **2013**, *81*, 136-147.

3 (a) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5349-5356. (b) Blaskovich, M. A. T. *J. Med. Chem.* **2016**, *59*, 10807-10836.

4 (a) Saghyan, A. S., Langer, P. *Asymmetric Synthesis of Nonproteinogenic Amino Acids*. Wiley-VCH, Weinheim, **2016**. (b) Blaskovich, M. A. *Handbook on syntheses of amino acids: General routes for the syntheses of amino acids*. Oxford University Press, Oxford, New York, **2010**.

5 For the syntheses and applications of γ-amino acids please refer to: (a) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetr.* **2007**, *18*, 3-99. (b) Vasudev, P. G.; Chatterjee, S.; Shamala, N.; Balaram, P. *Chem. Rev.* **2011**, *111*, 657-687. (c) Conti, P.; Tamborini, L.; Pinto, A.; Blondel, A.; Minoprio, P.; Mozzarelli, A. De Micheli, C. *Chem. Rev.* **2011**, *111*, 6919-6946. (d) Isidro-Llobet, A.; Álvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455-2504. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013-3028. (f) Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, *9*, 1127-1153. (g) Ordóñez, M.; Cativiela, C.; Romero-Estudillo, I. *Tetrahedron: Asymmetr.* **2016**, *27*, 999-1055.

anxiety and pain.[6] Thus, the synthesis of structurally diverse enantioenriched GABA analogs has attracted a great deal of interest in drug development programs, especially with the aim to improve their physicochemical properties.[5] In particular, a number of GABA analogs bearing a tertiary chiral carbon on the carbon chain have been developed as anticonvulsant, anti-seizure, and anti-epilepsy drugs. As an example, baclofen **IV.2**, pregabalin **IV.3**, vigabatrin **IV.4** and gabapentin **IV.5** have been commercialized over the past years to treat a range of CNS-disorders (Figure IV-1a).[5, 7] Additionally, γ-amino acids have great potential as building blocks for the synthesis of biologically active short γ-peptides such as pepstatine **IV.6**, hapalosin **IV.7** and dolastatins **IV.8** (Figure IV-1b).[5, 8] Last but not least, oligomers constructed from γ-amino acid synthons have demonstrated great potential in materials science.[5, 9] These protein-like foldamers display interesting functional properties. Specifically, stereodefined γ-amino acid monomers are highly essential to control the folding patterns.

6 Purdy, R. H.; Morrow, A. L.; Moore, P. H.; Paul, S. M. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 4553-4557.

7 (a) Fromm, G. H.; Terrence, C. F.; Chattha, A. S.; Glass, J. D. *Arch. Neurol.* **1980**, *37*, 768-771. (b) Sachais, B. A.; Logue, J. N.; Carey, M. S. *Arch. Neurol.* **1977**, *34*, 422-428. (c) Silverman, R. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3500-3504. (d) Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823-826. (e) Lapin, I. *CNS Drug Rev.* **2001**, *7*, 471-481.

8 (a) H. Rich, D. *J. Med. Chem.* **1985**, *28*, 263-273. (b) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259-262. (c) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1994**, *59*, 7219-7226. (d) Pettit, G. R.; Kamano, Y.C.; Herald, L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H. Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883-6885.

9 For the formation of γ-peptide foldamers from γ-amino acids, see: (a) Fisher, B. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2016**, *138*, 10766-10769. (b) Awada, H.; Grison, C. M.; Charnay-Pouget, F.; Baltaze, J.-P.; Brisset, F.; Guillot, R.; Robin, S.; Hachem, A.; Jaber, N.; Naoufal, D.; Yazbeck, O.; Aitken, D. J. *J. Org. Chem.* **2017**, *82*, 4819-4828. (c) Mathieu, L.; Legrand, B.; Deng, C.; Vezenkov, L.; Wenger, E.; Didierjean, C.; Amblard, M.; Averlant-Petit, M.-C.; Masurier, N.; Lisowski, V.; Martinez, J.; Maillard, L. T. *Angew. Chem. Int. Ed.* **2013**, *52*, 6006-6010. (d) Grison, C. M.; Miles, J. A.; Robin, S.; Wilson, A. J.; Aitken, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11096-11100. (e) Fisher, B. F.; Guo, L.; Dolinar, B. S.; Guzei, I. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2015**, *137*, 6484-6487.

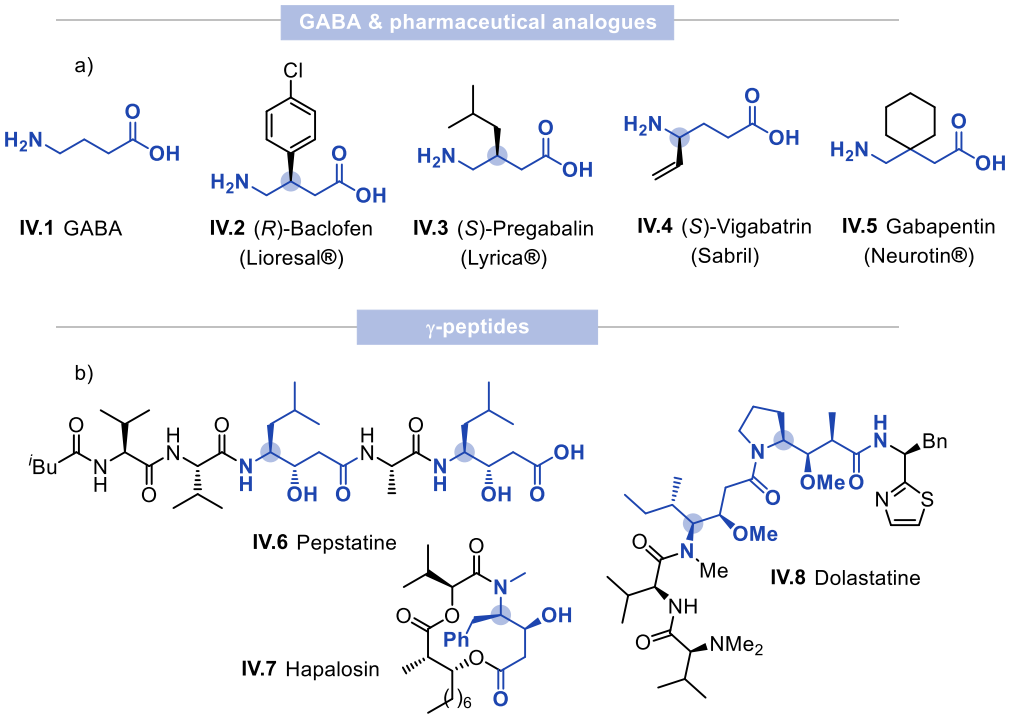


Figure IV-1. (a) Structure of GABA and pharmaceutical analogues. (b) Biologically active short γ-peptides.

Importantly, for the majority of the abovementioned examples the biological activity of γ-amino acids is largely determined by the absolute configuration of a stereogenic carbon atom. Therefore, organic chemists have been encouraged to design and develop novel approaches that enable their stereoselective synthesis.[5] While a variety of synthetic procedures have been developed over the years allowing for the synthesis of structurally diverse enantiopure γ-amino acids,[5] to date only rare examples exist for the preparation of enantioenriched γ-amino acids featuring tetrasubstituted stereocenters (Figure IV-2).

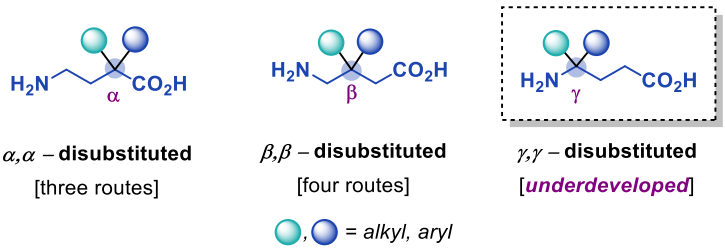
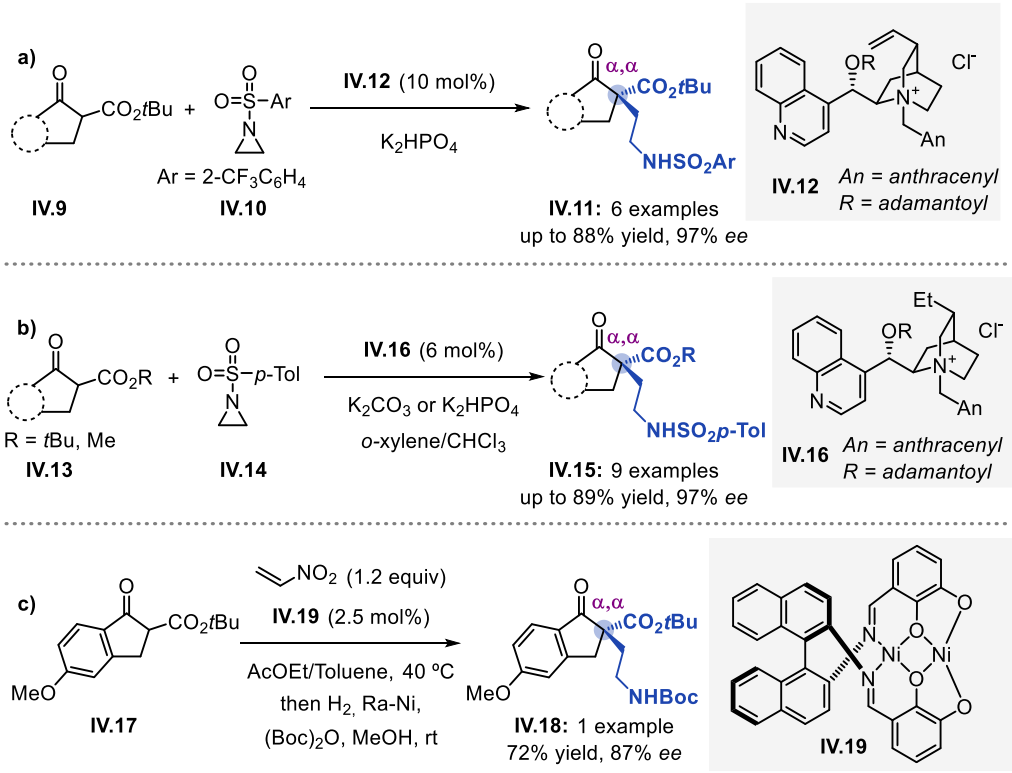


Figure IV-2. Examples of chiral quaternary γ-amino acids.

The groups of Dixon[10] and Jørgensen[11] have independently described a catalytic alkylation reaction of enolates derived from β-ketoesters (**IV.9** and **IV.13**) and aziridines (**IV.10** and **IV.14**), to prepare α,α-disubstituted γ-amino acid derivatives (**IV.11** and **IV.15**) by phase-transfer catalysis (PTC) (Scheme IV-1a and Scheme IV-1b). Additionally, catalytic asymmetric 1,4-addition of β-ketoester **IV.17** to nitroethylene catalyzed by a dinuclear Ni_2/Schiff base complex **IV.19**, followed by nitro-reduction, was also successfully employed for their synthesis (Scheme IV-1c).[12]

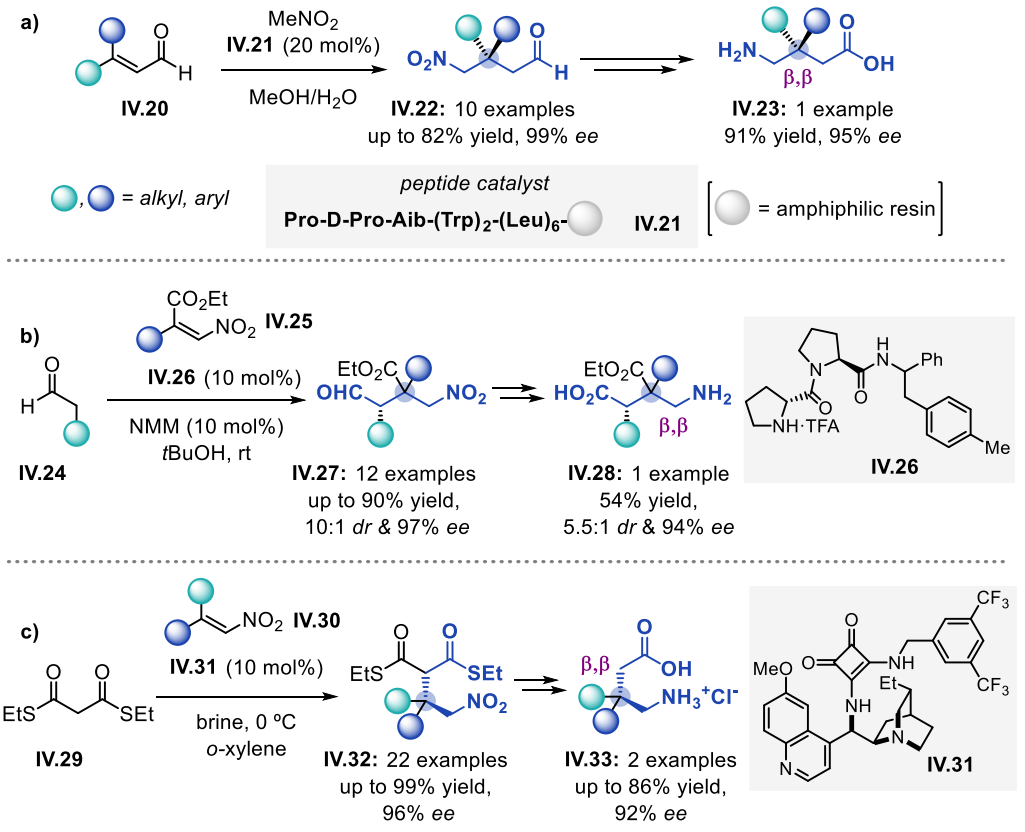


Scheme IV-1. Synthesis of α,α-disubstituted γ-amino acids.

On the other hand, β,β-disubstituted γ-amino acid analogs can be attained by conjugate addition of nitromethane to α,β-unsaturated aldehydes. For example, Kudo and co-workers developed a chiral peptide catalyzed Michael addition of nitroalkanes to enals (**IV.20**) as a key

10 Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076-10077.
11 Paixão, M. W.; Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2008**, *6*, 3467-3470.
12 Mitsunuma, H.; Matsunaga, S. *Chem. Commun.* **2011**, *47*, 469-471.

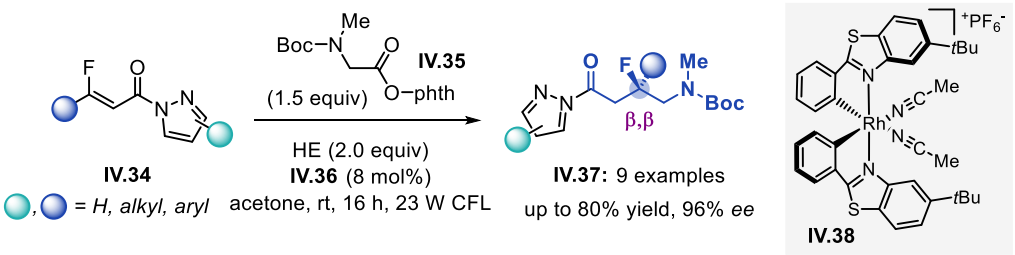
step for the preparation of β,β-disubstituted γ-amino acids **IV.23** (Scheme IV-2a).[13] Related approaches based on Michael additions of carbonyl compounds (**IV.24** and **IV.29**) to nitroolefins (**IV.25** and **IV.30**) were also realized by the groups of Wennemers[14] and Song[15] (Scheme IV-2b and Scheme IV-2c).



Scheme IV-2. Synthesis of β,β-disubstituted γ-amino acids. (NMM stands for N-methyl morpholine).

Recently the Meggers group developed an efficient photoredox-based catalytic asymmetric radical conjugate addition to prepare a variety of previously inaccessible GABA analogues possessing β-fluorinated quaternary stereocenters (**IV.37**) using simple glycine derivatives **IV.35** as the precursors for nucleophilic α-aminoalkyl radical reactions (Scheme IV-3).[16]

13 Akagawa, K.; Kudo, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12786-12789.
14 Kastl, R.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7228-7232.
15 Sim, J. H.; Song, C. E. *Angew. Chem. Int. Ed.* **2017**, *56*, 1835-1839.
16 Ma, J.; Lin, J.; Zhao, L.; Harms, K.; Marsch, M.; Xie, X.; Meggers, E. *Angew. Chem. Int. Ed*. **2018**, *57*, 11193-11197.



Scheme IV-3. Synthesis β,β-disubstituted γ-amino acids through enantioselective photoredox catalysis.

Despite this progress in the catalytic asymmetric synthesis of quaternary γ-amino acids,[5] unfortunately, the synthesis of γ,γ-disubstituted γ-amino acids is still a challenging task[17] and thus far there are no general methods available for their preparation (Figure IV-2).[18] Hence, designing new synthetic methods to access chiral γ,γ-disubstituted γ-amino acids with various substitution patterns will be of high interest to reinforce their implementation as synthons in drug discovery.

IV.1.2 Transition-metal catalyzed ring-opening of five-membered lactones

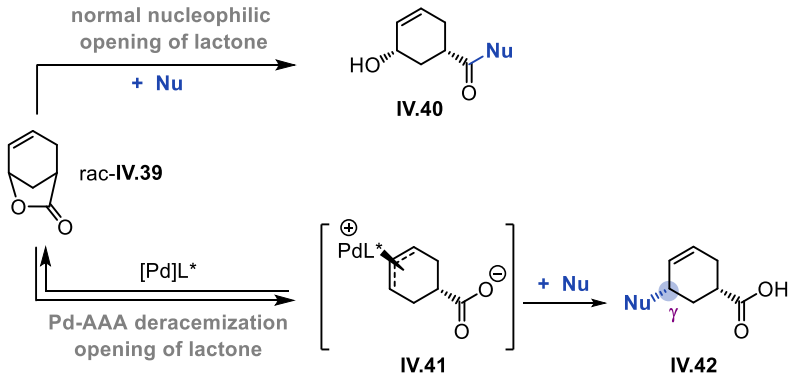
An attractive methodology for the synthesis of enantioenriched γ-amino acids could be accomplished by the asymmetric catalytic ring-opening reaction at the γ-position of racemic five-membered lactones by nitrogen-centered nucleophiles. However, considerable challenges exist in developing such a protocol (Scheme IV-4).

Ring opening of lactones (**IV.39**) generally occurs via nucleophilic acyl substitution, as the carbonyl carbon is the inherent more electrophilic site. Consequently, instead of a nucleophilic attack at the desired γ-position of the heterocycle, a direct attack at the carbonyl carbon of the lactone might occur, resulting in the formation of an alternative ring-opened product **IV.40**

17 The construction of quaternary stereocenters represents a challenging task: (a) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev*. **2016**, *116*, 7330-7396. (b) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037-2066.

18 After reporting the results included in this chapter, Enders and co-workers reported an asymmetric synthesis using *N*-heterocyclic carbene (NHC) catalysis: Chen, X.-Y.; Xiong, J.-W.; Liu, Q.; Li, S.; Sheng, H.; von Essen, C.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 300-304. Later, Deng and Hu found a new catalytic system combining cinchona phase-transfer catalysts and phenol additives to realize the synthesis of trifluoromethylated γ,γ-disubstituted γ-amino esters: Hu, B.; Deng, L. *J. Org. Chem*. **2019**, *84*, 994-1005.

(Scheme IV-4).[19] Moreover, five-membered lactones are thermodynamically highly stable and virtually no ring strain is released after ring opening of these heterocycles.[20] This low reactivity poses a big challenge as the formation of the ring-opened product at the γ-position **IV.41** is in equilibrium with the starting lactone. Thus, intramolecular reaction with the resulting carboxylate will compete with the desired intermolecular nucleophilic attack (Scheme IV-4). With non-strained lactones, this equilibrium is very much on the side of the lactone and therefore the position of this equilibrium must be shifted in order to achieve ring-opened products. In spite of these challenges, the palladium catalyzed nucleophilic ring opening of vinyl lactones toward (amino) acid formation **IV.42** has been developed (Scheme IV-4).[21] In this case, the regioselective attack at the γ-position is preferred over the innate acyl substitution.



Scheme IV-4. Different product outcomes between a typical nucleophilic ring-opening of a lactone and a Pd-AAA deracemizing ring-opening of the lactone.

On the other hand, asymmetric propargylic substitution reactions have been extensively studied since enantioselective bond-forming reactions at the propargylic position provide a highly useful synthetic means to construct a chiral carbon center with a synthetically versatile

19 We recently reported on amide synthesis from nonstrained lactones: Guo, W.; Gómez, J. E.; Martínez-Rodríguez, L.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *ChemSusChem* **2017**, *10*, 1969-1975.

20 (a) Myers, D.; Cyriac, A.; Williams, C. K. *Nature Chem.* **2016**, *8*, 3-4. (b) Hong, M.; Chen, E. Y.-X. *Nature Chem*. **2016**, *8*, 42-49.

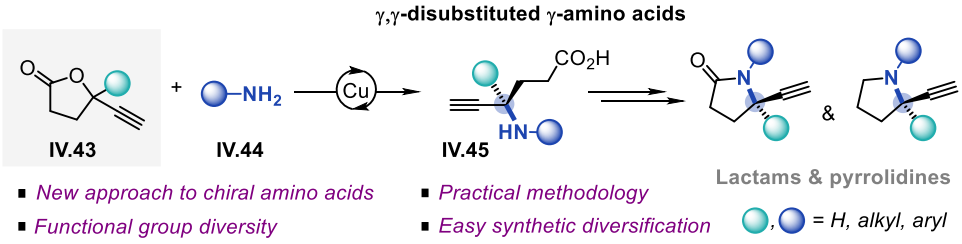
21 (a) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756-6758. (b) Nallasivam, J. L.; Fernandes, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 13238-13245. For the conversion of bicyclic 5- and 6-membered lactones, please refer to: (c) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem*. **1996**, *61*, 1192-1193. (d) Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 3759-3761. (e) Trost, B. M.; Zhang, T. *Chem. Eur. J.* **2011**, *17*, 3630-3643.

alkyne functionality.[22] In particular, copper-catalyzed propargylic amination reactions have been reported to give the corresponding propargylic amines in good yields and enantiomeric excess. It is noteworthy that these reactions are considered to proceed via copper-allenylidene complexes acting as key intermediates (see Chapter III, Scheme III-5).

Therefore, inspired by the palladium-catalyzed carboxylic amino acid formation from vinyl-lactones (Scheme IV-4)[21] and also our own work on challenging amine synthesis (see Chapter I, Scheme I-15 and Scheme I-16),[23] we envisaged that non-strained five-membered alkyne-substituted lactones **IV.43** could be used as precursors to generate copper-allenylidene complexes[22] leading, after amination, to chiral γ,γ-disubstituted γ-amino acids.

IV.1.3 Aim of the project

The aim of the work described in this chapter was therefore *the development of a general asymmetric synthesis of γ,γ-disubstituted γ-amino acids based on a copper-allenylidene-mediated ring opening of non-strained five-membered lactones with amines.* With this methodology our goal was to provide a practical entry to an ample scope of highly functionalized enantioenriched γ-amino acids featuring quaternary stereocenters from readily available, cheap and modular starting materials (Scheme IV-5). Furthermore, an additional goal was the subsequent application of these enantioenriched amino acids as molecular synthons to provide access to other enantioenriched, cyclic scaffolds.



Scheme IV-5. Copper-catalyzed synthesis of γ,γ-disubstituted γ-amino acids.

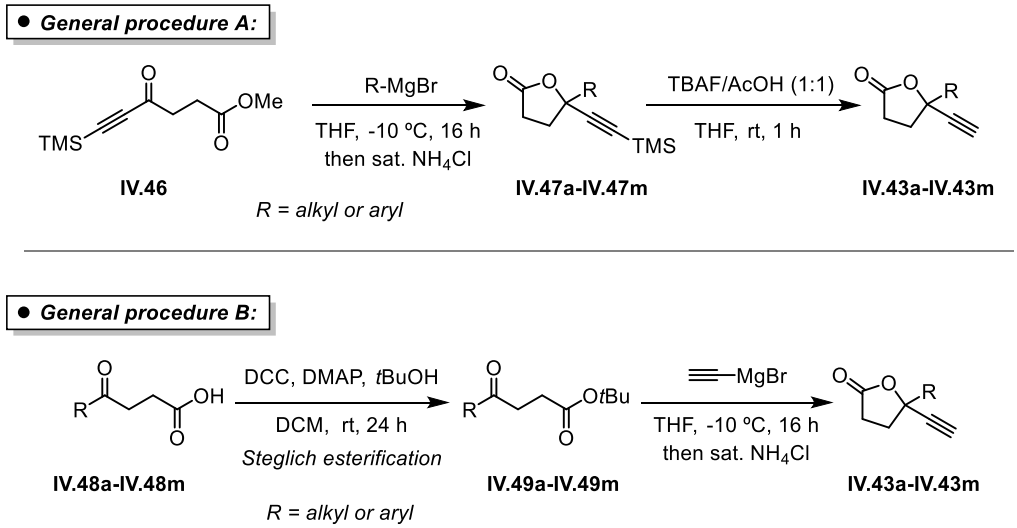
22 For reviews: (a) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. **2009**, 6263-6276. (b) Zhang, D.-Y.; Hu, X.-P. *Tetrahedron Lett*. **2015**, *56*, 283-295. (c) Nishibayashi, Y. *Synthesis* **2012**, 489-503. For additional related references, please see Chapter III of this thesis.

23 (a) Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc*. **2016**, *138*, 11970-11978. (b) Cai, A. Guo, W. Martínez-Rodríguez, L. Kleij, A. W. *J. Am. Chem. Soc.* **2016**, *138*, 14194-14197. (c) Guo, W. Cai, A. Xie, J. Kleij, A. W. *Angew. Chem. Int. Ed.* **2017**, *56*, 11797-11801.

IV.2. Results and discussion

IV.2.1 Substrate synthesis

To test our working hypothesis, initially two synthetic routes were designed to access the requisite alkyne-substituted five-membered lactones as shown in Scheme IV-6. On one hand, these substrates can be easily obtained from methyl 4-oxo-6-(trimethylsilyl)hex-5-ynoate **IV.46** via a sequential Grignard reaction-intramolecular cyclization, and subsequent fluoride-based deprotection of the trimethylsilyl protecting group (General procedure **A**, section IV.4.2). On the other hand, the alkyne precursors can be generated from commercially available γ-oxobutanoic acids **IV.48a-IV.48m** via esterification and subsequent addition of ethynyl magnesium bromide followed by a spontaneous cyclization to deliver the desired lactones (General procedure **B**, section IV.4.2).



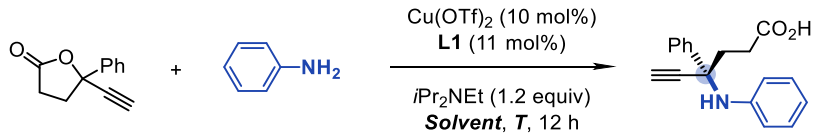
Scheme IV-6. Two different approaches for the synthesis of alkyne-substituted five-membered lactones.

IV.2.2 Screening studies

With the desired starting materials in hand, we commenced our optimization studies by firstly investigating the reaction between lactone **IV.43a** and aniline as a model reaction in the presence of *i*Pr_2NEt and 10 mol% of $Cu(OTf)_2$. The Trost-type ligand **L1** using THF as solvent at rt was probed first and promisingly, the desired amino acid was isolated in 47% yield with

60:40 *er* (Table IV-1, entry 1). Decreasing the reaction temperature resulted in higher enantioselectivity though low conversion (<15%, Table IV-1, entries 2–3). Encouraged by these results, we evaluated the solvent effect on the enantioselective reaction, and it turned out that by changing the solvent to MeOH at 0 ºC led to quantitative product formation albeit with a lower *er* value (Table IV-1, entries 3-7, entries 3 *vs* 6). Therefore, mixtures of solvents were re-evaluated and we found that a mixed solvent MeOH/THF (1:3) afforded the desired amino acid in 40% yield and 87:13 *er* (Table IV-1, entry 9).

Table IV-1. Effect of solvent and temperature on the formation of γ-amino acid **IV.45a**.[a]



IV.43a **IV.44a** **IV.45a**

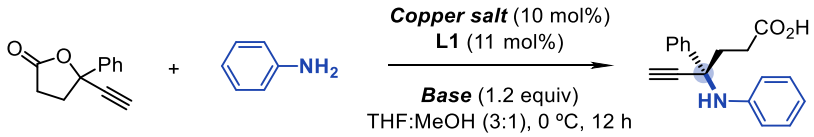
Entry	Ligand	T [ºC]	Solvent (v/v)	Yield [%][b]	*er*[c]
1	**L1**	25	THF	47	60:40
2	**L1**	10	THF	15	73:27
3	**L1**	0	THF	10	77.5:22.5
4	**L1**	0	Acetone	46	69:31
5	**L1**	0	Et_2O	20	62.5:37.5
6	**L1**	0	MeOH	96	60.5:39.5
7	**L1**	0	*i*PrOH	50	68:32
8	**L1**	0	MeOH/THF (1:1)	96	77:23
9	**L1**	**0**	**MeOH/THF (1:3)**	**54**	**80:20**

[*a*] Reaction conditions unless otherwise stated: lactone **IV.43a** (0.20 mmol), aniline **IV.44a** (0.30 mmol, 1.5 equiv), iPr_2NEt (0.24 mmol, 1.2 equiv), $Cu(OTf)_2$ (10 mol%), **L1** (11 mol%), **solvent** (0.20 mL), 12 h. [*b*] Isolated yield. [*c*] Determined by UPC2.

The effect of the copper-catalyst precursor and type of base were also investigated as shown in Table IV-2, and both parameters showed a significant effect towards the reaction outcome. The addition of a base proved to be crucial for this reaction, and although a variety of bases were tested (Table IV-2, entries 1-4) none of them improved the results obtained with iPr_2NEt. In contrast, other copper sources, including $(CuOTf)_2 \cdot Tol$, $(CuOTf)_2 \cdot Ph$, $Cu(ACN)_4PF_6$, $CuCl_2$, and

$Cu(OAc)_2$ were also tested (Table IV-2, entries 5–10), and the results demonstrated that $Cu(ACN)_4(OTf)$ was most effective.

Table IV-2. Effect of the copper salt and base on the formation of γ-amino acid **IV.45a**.[a]



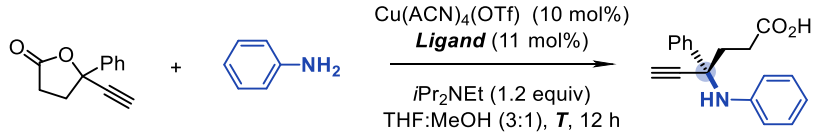
IV.43a **IV.44a** **IV.45a**

Entry	Ligand	Copper salt	Base	Yield [%][b]	*er*[c]
1	**L1**	$Cu(OTf)_2$	Cs_2CO_3	55	50:50
2	**L1**	$Cu(OTf)_2$	Et_3N	40	77:23
3	**L1**	$Cu(OTf)_2$	DABCO	38	60:40
4	**L1**	$Cu(OTf)_2$	*i*Pr_2NEt	54	80:20
5	**L1**	$(CuOTf)_2$·Tol	*i*Pr_2NEt	36	85:15
6	**L1**	$(CuOTf)_2$·Ph	*i*Pr_2NEt	40	70:30
7	**L1**	**$Cu(ACN)_4(OTf)$**	***i*Pr_2NEt**	**40**	**87:13**
8	**L1**	$Cu(ACN)_4PF_6$	*i*Pr_2NEt	30	84:16
9	**L1**	$CuCl_2$	*i*Pr_2NEt	20	50:50
10	**L1**	$Cu(OAc)_2$	*i*Pr_2NEt	15	74:26

[*a*] Reaction conditions unless otherwise stated: lactone **IV.43a** (0.20 mmol), aniline **IV.44a** (0.30 mmol, 1.5 equiv), **base** (0.24 mmol, 1.2 equiv), **copper salt** (10 mol%), **L1** (11 mol%), THF:MeOH (3:1) (0.20 mL), 12 h. [*b*] Isolated yield. [*c*] Determined by UPC2.

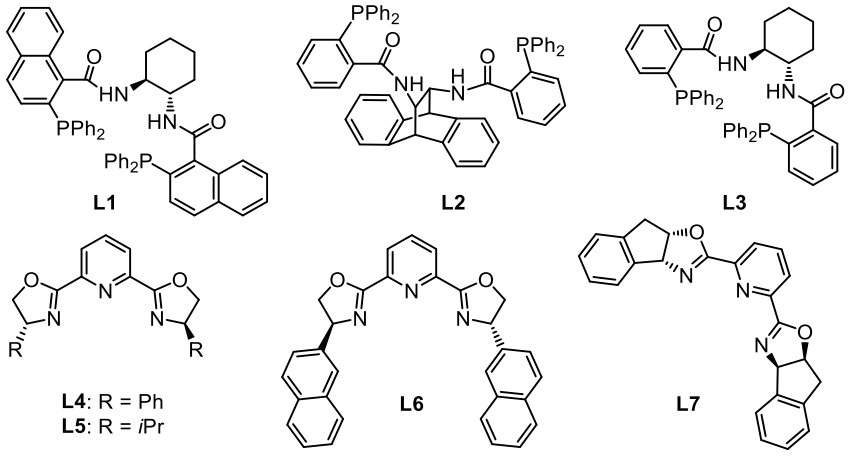
After evaluating different solvents, copper salts and bases, we then turned our attention to examine the role of the ligand in the copper-catalyzed amination reaction. We focused our attention on the evaluation of other structurally related Trost-type ligands as well as on chiral ligands widely used in related Cu-catalyzed asymmetric propargylic substitution (APS) reactions (Table IV-3, entries 1-7). We were pleased to find that the use of Pybox ligand **L6** resulted in quantitative yield of product **IV.45a** and excellent enantioselectivity (Table IV-3, entry 6: 98% yield and 90:10 *er*). To further improve this result, we then lowered the reaction temperature, concentration, and amount of aniline **IV.44a** employed (Table IV-3, entries 8-10). Gratifyingly, the resulting γ-amino acid was obtained in 98% yield and 95:5 *er*.

Table IV-3. Effect of ligand, temperature and concentration on the formation of γ-amino acid **IV.45a**.[a]



IV.43a **IV.44a** **IV.45a**

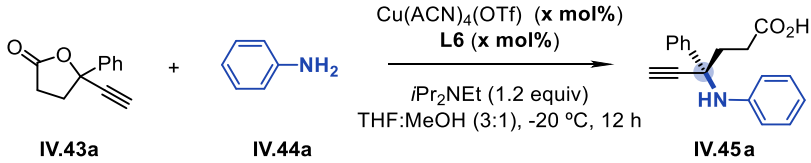
Entry	Ligand	Copper salt	T [ºC]	Yield [%][b]	*er*[c]
1	**L1**	Cu(ACN)$_4$(OTf)	0	40	87:13
2	**L2**	Cu(ACN)$_4$(OTf)	0	38	60:40
3	**L3**	Cu(ACN)$_4$(OTf)	0	88	74:26
4	**L4**	Cu(ACN)$_4$(OTf)	0	98	73:27
5	**L5**	Cu(ACN)$_4$(OTf)	0	98	56:44
6	**L6**	Cu(ACN)$_4$(OTf)	0	98	90:10
7	**L7**	Cu(ACN)$_4$(OTf)	0	98	62:38
8[d]	**L6**	Cu(ACN)$_4$(OTf)	-5	98	92:8
9[d]	**L6**	Cu(ACN)$_4$(OTf)	-10	98	93:7
10[d,e]	**L6**	Cu(ACN)$_4$(OTf)	-20	98	94:6
11[d,f]	**L6**	**Cu(ACN)$_4$(OTf)**	**-20**	**98**	**95:5**



[*a*] Reaction conditions unless otherwise stated: lactone **IV.43a** (0.20 mmol), aniline **IV.44a** (0.30 mmol, 1.5 equiv), *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv), Cu(ACN)$_4$(OTf) (10 mol%), **Ligand** (11 mol%), THF:MeOH (3:1) (0.20 mL), 12 h. [*b*] Isolated yield. [*c*] Determined by UPC2. [*d*] Aniline **IV.44a** (0.22 mmol). [*e*] Solvent (400 μL). [*f*] Solvent (600 μL).

Lastly, we examined the impact of the catalyst loading on the general outcome of the reaction. Notably, the reaction could be performed open to air without any special precautions, requiring only 3 mol% of Cu (Table IV, entry 3: 94% yield and 97:3 *er*) which is a significant advantage compared to other Cu-catalyzed reactions generally requiring 10 mol% of metal loading.

Table IV-4. Effect of the catalyst loading on the formation of γ-amino acid **IV.45a**.[a]



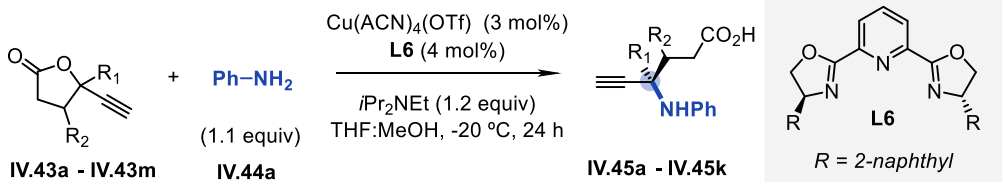
IV.43a **IV.44a** **IV.45a**

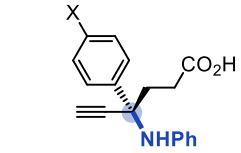
Entry	$Cu(ACN)_4(OTf)$ [mol%]	**L6** [mol%]	Yield [%][b]	*er*[c]
1	10	11	98	95:5
2	5	6	97	96:4
3[d]	**3**	**4**	**94**	**97:3**

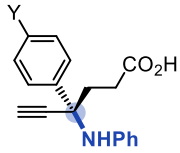
[*a*] Reaction conditions unless otherwise stated: lactone **IV.43a** (0.20 mmol), aniline **IV.44a** (0.22 mmol, 1.1 equiv), *i*Pr2NEt (0.24 mmol, 1.2 equiv), amount of $Cu(ACN)_4(OTf)$ and **L6** indicated, THF:MeOH (3:1) (600 μL), -20 ºC, 12 h. [*b*] Isolated yield. [*c*] Determined by UPC2. [*d*] 24 h.

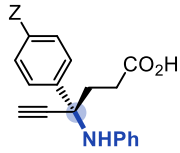
IV.2.3 Substrate scope of lactones

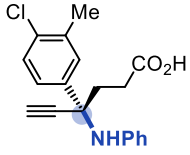
With the optimized reaction conditions in hand for the synthesis of **IV.45a** (Table IV-4, entry 3: 94% yield, 97:3 *er*), the enantioselective ring-opening reactions of other alkyne-substituted lactones (**IV.43a-IV.43k**) using aniline was first investigated (Scheme IV-7).

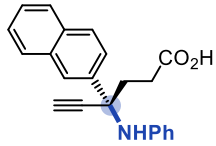


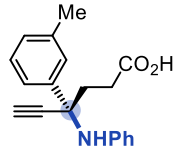

IV.45a: X = H, 94%, 97:3 *er*
IV.45b: X = Br, 76%, 96:4 *er* [a]

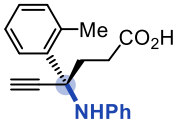

IV.45c: Y = F, 97%, 96:4 *er*
IV.45d: Y = Me, 88%, 95.5:4.5 *er*

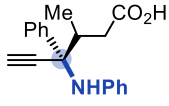

IV.45e: Z = CF_3, 67%, 95.5:4.5 *er*
IV.45f: Z = Ph, 83%, 97:3 *er*


IV.45g: 74%
95:5 *er*

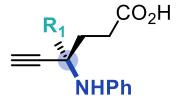

IV.45h: 97%
96:4 *er*


IV.45i: 85%
96:4 *er*


IV.45j: 42% [b,c]
80.5:19.5 *er*


IV.45k: 71%, 84:16 *dr* [b,d]
54:46 *er*

Unsuccessful substrates


IV.45l: R_1 = Cy, 0%
IV.45m: R_1 = Me, 0%

Scheme IV-7. Scope in alkyne-substituted lactone substrates (0.20 mmol scale) with the reactions performed under the optimized conditions. The *er* values were determined by UPC2. [*a*] $Cu(ACN)_4(OTf)$ (5 mol%), **L6** (6 mol%). [*b*] $Cu(ACN)_4(OTf)$ (10 mol%), **L6** (11 mol%), solvent (200 μL). [*c*] 0 ºC. [*d*] Performed at rt; the desired product was obtained as the corresponding γ-lactam.

A variety of alkyne-substituted lactones participated smoothly in this reaction manifold (**IV.43a-IV.43k**). For example, the catalytic system proved to be efficient in the conversion of lactones with electron-withdrawing (*e.g.* **IV.45b**, **IV.45c** and **IV.45e**) and electron-donating

groups (*e.g.* **IV.45d**, **IV.45g**, **IV.45i** and **IV.45j**) present in the aryl-substituents and gave rise to the amino acid products generally with *er* values higher than 95:5. Likewise, the presence of *meta*-substituted aryl substituents in the lactones (*e.g.* **IV.45g** and **IV.45i**) allowed the formation of γ-amino acids with high enantioselectivity and isolated yield, while the *ortho*-Me-aryl substituted lactone showed lower reactivity and enantioselectivity (**IV.45j**). This later result may be explained considering that π–π interactions from ligand to substrate play a role in achieving high enantioinduction in copper-catalyzed propargylic aminations.[24] The edge-to-face interaction between the two aromatic groups may help to position the ligand in close proximity to the cationic center.[25] Thus, the presence of a C-H moiety at the *ortho*-position in the γ-aromatic ring of the lactone substrate is necessary to achieve high enantioselectivity. On the other hand, the presence of a bulky naphthyl group did not reduce the efficiency of the catalysis (**IV.45h**). Moreover, substitution at the β-position of the lactone is possible (though with virtually no enantioinduction) as exemplified by the successful isolation of compound **IV.45k** as its corresponding lactam.

Unfortunately, the lactones bearing a γ-cyclohexyl or -methyl group proved to be unproductive and did not even result in product formation at higher reaction temperatures of up to 50 ºC and higher catalyst loading of up to 10 mol% (**IV.45l** and **IV.45m**). This suggests that a significant electronic effect is operative within this catalytic process. The lactones bearing aromatic rings as side chain may stabilize better the electrophilic copper-allenylidene intermediate[26] than lactones bearing alkyl-side chains explaining the lower reactivity of the latter.

IV.2.4 Substrate scope of amines

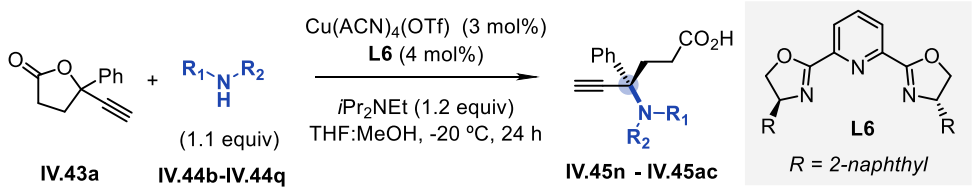
Next, we investigated the scope and limitations of the amine substrates in the catalytic ring-opening amination reaction (Scheme IV-8). In addition to aniline, the use of aryl amines bearing electron-donating groups also afforded the γ-amino acids in both high yield and enantioselectivity (**IV.45n-IV.45q** and **IV.45z**). In contrast, aryl amines equipped with strongly electron-withdrawing substituents such as nitro, ester and trifluoromethyl groups gave rise to

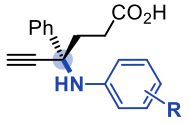
24 Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc*. **2010**, *132*, 10592-10608.

25 For the edge-to-face aromatic interaction, see: (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995-8001. (c) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210-1250. (d) Nishio, M. *Tetrahedron* **2005**, *61*, 6923-6950.

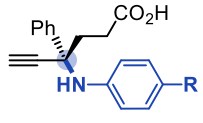
26 Please refer to the mechanistic section of this chapter.

only trace amount of product under the optimized conditions. Performing these reactions at higher reaction temperature (products **IV.45v–IV.45x**) significantly improved the reaction outcome.

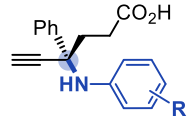




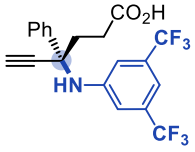
IV.45n: R = *p*-OMe, 98%, 94:6 *er*
IV.45o: R = *m*-OMe, 90%, 96:4 *er*
IV.45p: R = *o*-OMe, 95%, 98:2 *er*



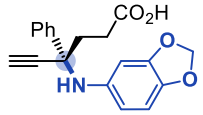
IV.45q: R = Me, 94%, 95:5 *er*
IV.45r: R = Bpin, 71%, 95:5 *er* [a]
IV.45s: R = F, 93%, 96:4 *er*
IV.45t: R = Br, 77%, 95:5 *er* [b]



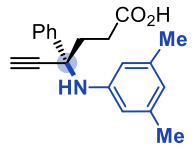
IV.45u: R = *p*-Ph, 93%, 95:5 *er*
IV.45v: R = *p*-CO_2Me, 55%, 93:7 *er* [b,c]
IV.45w: R = *m*-NO_2, 58%, 92:8 *er* [b,c,d]



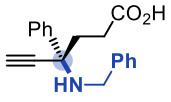
IV.45x: 62% [b,c,d]
89:11 *er*



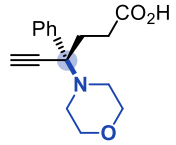
IV.45y: 72% [e]
94:6 *er*



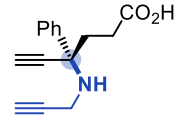
IV.45z: 98%
96:4 *er*



IV.45aa: 41%
52:48 *er*



IV.45ab: 92% [b,c,f]
86:14 *er*



IV.45ac: 51% [b,c]
50:50 *er*

Scheme IV-8. Scope in amine substrates (0.20 mmol scale). The reactions were performed under the optimized conditions. The *er* values were determined by UPC2. [*a*] $Cu(ACN)_4(OTf)$ (5 mol%), **L6** (6 mol%). [*b*] $Cu(ACN)_4(OTf)$ (10 mol%), **L6** (11 mol%), solvent (200 µL). [*c*] 0 ºC. [*d*] Solvent (200 µL) [*e*] The desired product was obtained as the corresponding γ-lactam. [*f*] The *er* value was determined by using a chiral shift reagent (please see experimental section of this chapter for more details).

The incorporation of a heterocycle in the final product also proved to be feasible (**IV.45y**), which is potentially interesting for pharmaceutical development,[27] whereas the installation of a boron- and halogen-functionality (**IV.45r** and **IV.45t**) is potentially useful for the application of these γ-amino acid products in Suzuki-coupling reactions. It is also noteworthy that the presence of *meta*- or *ortho*-substituents in the aryl amine (**IV.45o**, **IV.45p**, **IV.45w**, **IV.45x** and **IV.45z**) is tolerated and allows for efficient amino acid formation.

Finally, the reactions with cyclic amines such as morpholine at -20 ºC for 24 h displayed low conversions (<5%), while moderate reactivity was observed at 0 ºC though with lower degrees of enantioinduction (**IV.45ab**). Additionally, primary alkyl amines such as benzyl or propargyl amine are also productive substrates albeit without any observable asymmetric induction (**IV.45aa** and **IV.45ac**).

IV.2.5 Synthetic transformations of γ-amino acids

With a range of γ,γ–disubstituted GABA analogues in hand, we next evaluated the synthetic application of these compounds (Scheme IV-9). Notably, γ-amino acid **IV.45a** could be easily converted into various enantioenriched products with complete retention of the enantiomeric ratio. The γ-lactam **IV.50**, which was additionally analyzed by X-ray diffraction analysis, served to deduce the absolute configuration (*R*) of the amino acid product **IV.45a** (see inset in Scheme IV-9). Furthermore, allylic γ-lactam **IV.51** was obtained smoothly under mild conditions by semi-reduction of the corresponding alkyne group. Notably, chiral γ-lactams are very important building blocks in pharmaceutical development.[28]

Treating γ-lactam **IV.50** with $LiAlH_4$ in THF provided the corresponding *N*-phenyl pyrrolidine **IV.52** in 96% yield. The pendant alkyne functional group in these amino acid scaffolds creates potential for *in vivo* biorthogonal reactions through click chemistry.[29] As such,

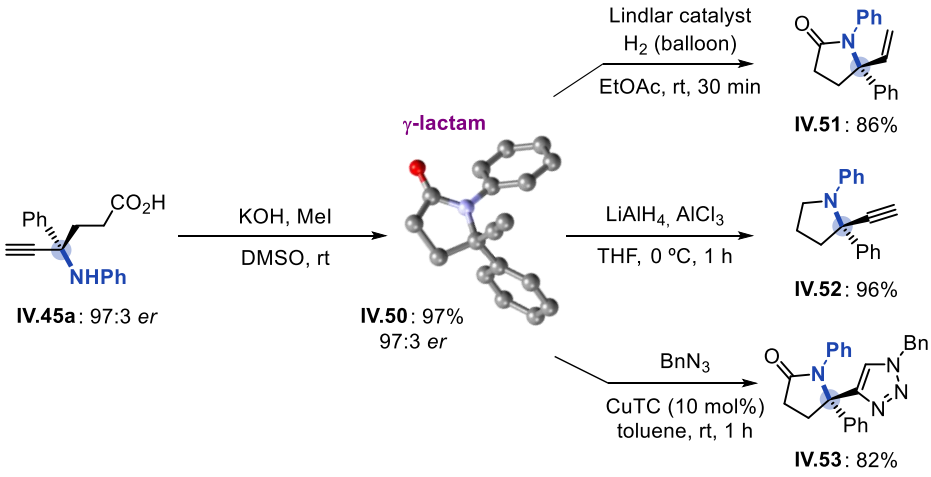
27 The 1,3-benzodioxole motif is frequently encountered in pharmaceuticals, see for example: Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem*. **1992**, *35*, 3081-3084.

28 Chiral lactams are frequently encountered in drugs: (a) Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem*. **2014**, *12*, 1833-1845. (b) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res*. **2014**, *47*, 3439-3447. (c) Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem*. **2016**, *14*, 10134-10156. For their asymmetric synthesis see: (d) Tan, D. Q.; Martin, K. S.; Fettinger, J. C.; Shaw, J. T. *Proc. Natl. Acad. Sci*. **2011**, *108*, 6781-6786.

29 For click reactions in bio-orthogonal applications: (a) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 4900-4908. (b) Yang, M.; Li, J.; Chen, P. R. *Chem. Soc. Rev.* **2014**, *43*, 6511-6526. (c) Lim, R. K. V.; Lin, Q. *Chem. Commun.* **2010**, *46*, 1589-1600.

triazole **IV.53** was prepared by Cu-catalyzed azide-alkyne cycloaddition between **IV.50** and benzyl azide in good yield.

Overall, the herein outlined synthetic applications clearly demonstrate that the functional character of the γ,γ-substituted γ-amino acids permits the synthesis of structurally diverse enantioenriched scaffolds.



Scheme IV-9. Synthetic conversions of chiral amino acid **IV.45a**.

IV.2.6 Mechanistic considerations

The way how pyridine–bisoxazoline (pybox) ligands induce high levels of enantioselectivity in copper-catalyzed APS reactions has been a topic of interest for some time.[30] Previous studies in related transformations suggested that a dicopper–allenylidene species, such as **IV.55**, is a key intermediate in these reactions. Consistent with this notion, we observed a (positive) nonlinear relationship between the enantiomeric purity of **L6** and that of product **IV.45a** (Figure IV-3), suggesting the potential involvement of a dinuclear copper complex as an active catalytic species that promotes this transformation.

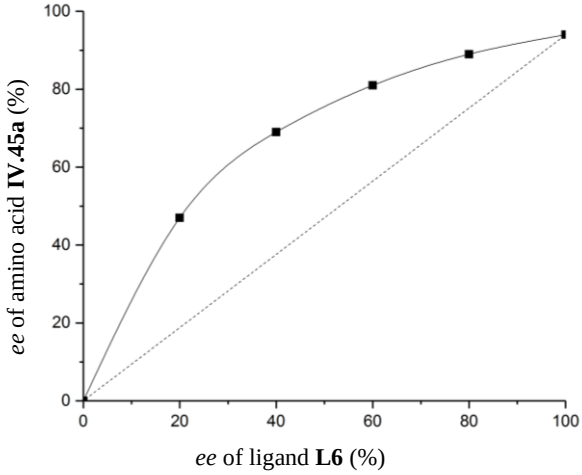


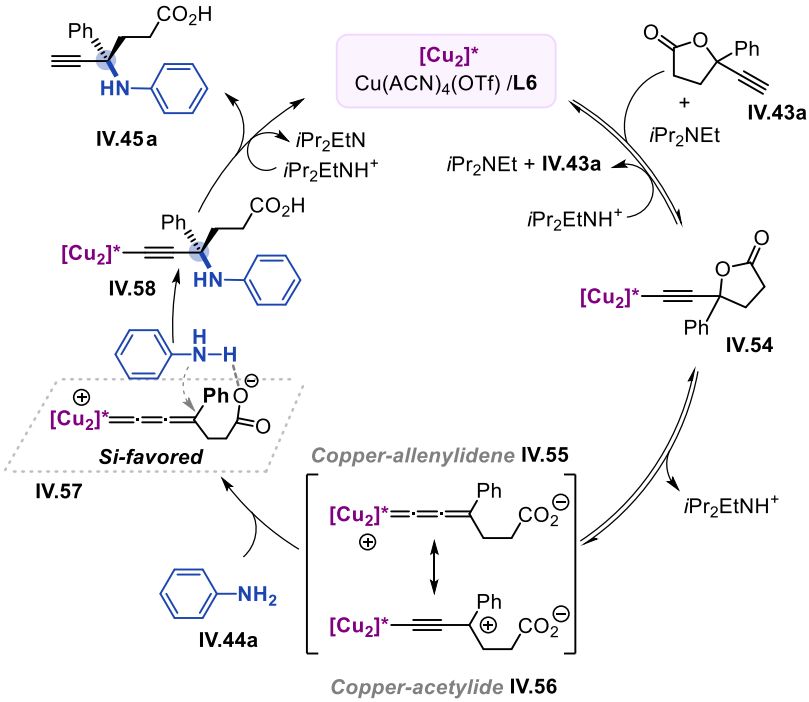
Figure IV-3. Mathematical expression of a (positive) nonlinear relationship.

Therefore, based on previous mechanistic investigations on related chemistry[22, 24, 30] and our experimental observations, a plausible mechanism is proposed in Scheme IV-10. First, the Cu-complex activates the alkyne group of lactone **IV.43a** through a π-complex (not shown), which in the presence of *i*Pr$_2$NEt generates a Cu-acetylide species **IV.54**. Then, ring opening of **IV.54** leads to a zwitterionic species **IV.55**, which is in resonance with **IV.56**. Considering the thermodynamically stable nature of five-membered lactones,[20] the back conversion of

30 Research articles, please refer to: (a) Nakajima, K.; Shibata, M.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2015**, *137*, 2472-2475. (b) Wang, Q.; Li, T.-R.; Lu, L.-Q.; Li, M.-M.; Zhang, K.; Xiao, W.-J. *J. Am. Chem. Soc.* **2016**, *138*, 8360-8363. (c) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1758-1762. (d) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed*. **2008**, *47*, 3777-3780. (e) Zhang, K.; Lu, L.-Q.; Yao, S.; Chen, J.-R.; Shi, D.-Q.; Xiao, W.-J. *J. Am. Chem. Soc*. **2017**, *139*, 12847-12854.

intermediate **IV.55** into starting material **IV.43a** through intermediate **IV.54** is likely dominant over the nucleophilic attack of the amine;[21c-e] thus, a hydrogen bond assisted amine attack is proposed to be involved (**IV.55** to **IV.58**) enabling the formation of a Cu-bound product **IV.58**.[31] Hereafter, the amino acid product is obtained through a proteolysis with regeneration of the catalyst and the base.

The absolute configuration of the amino acid **IV.45a** was deduced to be (*R*) on the basis of the X-ray molecular structure determined for γ-lactam **IV.50** (inset in Scheme IV-9). Thus, the asymmetric induction in the present Cu-catalyzed reaction may be rationalized by a well-established bimetallic model[22, 24, 30, 32] in which the amine attack on the *Si*-face of the Cu-allenylidene intermediate is favored, thus resulting in the (*R*)-amino acid as major product. Regardless, more detailed studies are warranted to further validate this mechanistic hypothesis.



Scheme IV-10. Plausible mechanism for the formation of the γ–amino acid **IV.45a** from lactone **IV.43a**.

31 For hydrogen bond assisted processes, see: (a) Trost, B. M.; Jiang, C.; Hammer, K. *Synthesis* **2005**, 3335-3345. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976; also see refs. 23a and 23c in this chapter.

32 (a) Díez, J.; Gamasa, M. P.; Panera, M. *Inorg. Chem.* **2006**, *45*, 10043-1045. (b) Panera, M.; Díez, J.; Merino, I.; Rubio, E.; Gamasa, M. P. *Inorg. Chem.* **2009**, *48*, 11147-11160.

IV.3. Conclusions

In conclusion, in this chapter we have described the first general approach toward the asymmetric synthesis of γ,γ-disubstituted γ-amino acids through Cu-catalyzed ring opening of non-strained lactones with amine nucleophiles. The reaction is considered to proceed via a key copper-allenylidene intermediate. Interestingly, the newly developed protocol features ample product scope, wide functional group diversity and high asymmetric induction with typical *er* values being >95:5. Moreover, this procedure is user-friendly (no special precautions required) and thus marks a great step forward in the challenging synthesis of chiral γ-amino acids featuring quaternary stereocenters.

Complementary, the versatility of the amino acid products obtained through our methodology was showcased by the synthesis of other interesting enantioenriched cyclic products containing quaternary stereocenters such as γ-lactams and pyrrolidines. Despite quaternary γ-lactams are important structural motifs found in natural products as well as in medicinal lead compounds, these scaffolds are challenging to synthesize via conventional means. Thus, this protocol opens up a synthetic alternative to γ-lactams containing quaternary stereocenters, which can be readily prepared in good yields and with excellent enantioselectivities in a two-step sequence.

IV.4. Experimental section

IV.4.1 General information and instrumentation

Commercially available amines and solvents were purchased from Aldrich or TCI, and used without further purification. Copper salts were purchased from Aldrich. Trost type ligands **L1**, **L2** and **L3** and Pybox ligands **L4**, **L5** and **L7** were purchased from Aldrich or TCI; **L6** was prepared according to a reported procedure as reported below. Alkyne-substituted lactones **IV.43a-IV.43m** were prepared according to the procedures described below. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Bruker AV-500 spectrometer and referenced to the residual deuterated solvent signals. All reported NMR data are given in parts per million (ppm). FT-IR measurements were carried out using a Bruker Optics FTIR Alpha spectrometer. Optical rotations were measured with a Jasco P-1030 Polarimeter. Mass spectrometric analyses, UPC2 analyses, and X-ray diffraction analysis were performed by the Research Support Area (RSA) at ICIQ.

IV.4.2 General procedures for the synthesis of lactones

General Procedure A:

Methyl 4-oxo-6-(trimethylsilyl)hex-5-ynoate **IV.46** (10.0 mmol, 1.0 equiv) was prepared following a previous reported protocol with slight modifications.[33]

Compound **IV.46** was charged into a flame-dried round-bottom flask equipped with a stirring bar under N_2 atmosphere and anhydrous THF (20 mL) was introduced with a syringe. The desired Grignard reagent (1.0 M in THF, 15.0 mmol, 1.5 equiv) was added dropwise to the resultant reaction solution at -10 ºC (ice/salt bath). The reaction mixture was allowed to warm up to room temperature, stirred for 16 h and then quenched with saturated NH_4Cl (aq, 20 mL). The organic components were extracted with Et_2O (3 × 20 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the product **IV.47a-IV.47m** which could be used directly in the next step without further purification. [**NOTE**: The amount of the Grignard reagent is crucial to achieve the reported yield. In those cases where the Grignard reagent was not commercially available, the Grignard reagent (1.0 M in THF) was prepared following the procedure described as below. Magnesium turnings (15.0

33 Trost, B. M.; Hung, C.-I. *J. Am. Chem. Soc*. **2015**, *137*, 15940-15946.

mmol, 1.5 equiv) and I_2 (0.025 equiv) were introduced into a well-dried Schlenk flask equipped with a stirring bar; the mixture was subjected to three cycles of vacuum/filling with N_2. After that, under protection of N_2, the flask was gently heated with a heat gun until the iodine melted completely. The resultant mixture was stirred for 30 min at room temperature. Then dry THF (15 mL) was added affording a brown solution, to which commercially available aryl or alkyl bromide (15.0 mmol, 1.5 equiv) was added in one portion. Upon stirring for 30 min at room temperature until all the magnesium turnings were consumed, the required Grignard reagent was obtained].

A mixture of TBAF (1.0 M in THF, 15.0 mmol, 1.5 equiv) and glacial acetic acid (15.0 mmol, 1.5 equiv) was added dropwise to a solution of the compound **IV.47a-IV.47b** in THF (20 mL). The reaction mixture was stirred for 1 h at room temperature and was then concentrated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding lactone **IV.43a-IV.43m**.

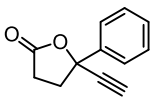
General Procedure B:

Ester intermediates **IV.49a-IV.49m** were prepared from the corresponding γ-oxobutanoic acids[34] using conventional Steglich esterification: To a solution of γ-oxobutanoic acid **IV.48a-IV.48m** (10.0 mmol, 1.0 equiv) and *tert*-butyl alcohol (20.0 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL), DMAP (3.0 mmol, 0.3 equiv) was added. The resultant solution was allowed to cool down to 0 ºC and *N,N'*-dicyclohexylcarbodiimide (DCC) (12.0 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The formed urea byproduct was filtered off and the organic layer was concentrated under vacuum. The crude residue was purified by flash chromatography to give the corresponding ester products **IV.49a-IV.49m**.

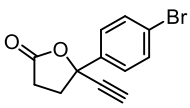
The esters **IV.49a-IV.49m** were charged into a flame-dried round-bottom flask equipped with a stirring bar. Under the protection of N_2, anhydrous THF (20 mL) was introduced with a syringe, and then ethynyl magnesium bromide (0.5 M in THF, 15.0 mmol, 1.5 equiv) was added dropwise to the reaction mixture at -10 ºC (ice/salt bath). After the mixture had been stirred at room temperature for 16 h, saturated NH_4Cl (aq) (20 mL) was added to quench the reaction. The organic components were extracted with Et_2O (3 × 20 mL), washed with brine, dried over

34 Sakai, N.; Horikawa, S.; Ogiwara, Y. *RSC Adv*. **2016**, *6*, 81763-81766.

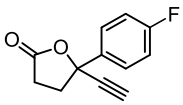
anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding lactones **IV.43a-IV.43m**.



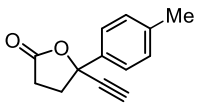
5-Ethynyl-5-phenyl-dihydrofuran-2(3*H*)-one (IV.43a). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 79% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.45-7.35 (m, 3H), 2.95-2.88 (m, 1H), 2.83-2.78 (m, 1H), 2.79 (s, 1H), 2.68-2.62 (m, 1H), 2.53-2.47 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.6, 140.0, 128.9, 128.8, 124.9, 82.4, 81.5, 76.1, 39.3, 29.1. **IR** (ATR): ν = 3281, 3063, 2115, 1776, 1450, 1156, 697 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 209.0576 $(M + Na)^+$, found: 209.0573.



5-(4-Bromophenyl)-5-ethynyl-dihydrofuran-2(3*H*)-one (IV.43b). The title compound was prepared following the general procedure **B** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc= 20/1). Light yellow oil, yield: 82% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 2.95-2.88 (m, 1H), 2.82-2.77 (m, 1H), 2.81 (s, 1H), 2.68-2.62 (m, 1H), 2.46-2.40 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.2, 139.1, 132.0, 126.7, 123.1, 81.9, 80.9, 76.5, 39.2, 29.0. **IR** (ATR): ν = 3287, 1777, 1458, 1189, 1155 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 286.9679 $(M + Na)^+$, found: 286.9678.

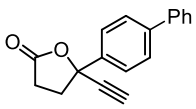


5-Ethynyl-5-(4-fluorophenyl)-dihydrofuran-2(3*H*)-one (IV.43c). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 71% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.10-7.07 (m, 2H), 2.95-2.88 (m, 1H), 2.81 (s, 1H), 2.81-2.76 (m, 1H), 2.68-2.62 (m, 1H), 2.49-2.43 (m, 1H). **^{19}F NMR** (376 MHz, CDCl3) δ -113.05. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 162.9 (d, $^1J_{CF}$ = 247 Hz), 135.8 (d, $^4J_{CF}$ = 3 Hz), 126.9 (d, $^3J_{CF}$ = 9 Hz), 115.7 (d, $^2J_{CF}$ = 21 Hz), 82.1, 81.0, 76.4, 39.3, 29.1. **IR** (ATR): ν = 3281, 3063, 2115, 1776, 1450, 1156, 697 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 227.0476 $(M + Na)^+$, found: 227.0479.



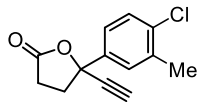
5-Ethynyl-5-(*p*-tolyl)-dihydrofuran-2(3*H*)-one (IV.43d). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 78% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 2.95-2.86 (m, 1H), 2.81-2.75 (m, 1H), 2.77 (s, 1H), 2.68-2.60 (m, 1H), 2.53-2.45 (m, 1H), 2.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7, 138.8, 137.1, 129.5, 124.9, 82.5, 81.5, 76.0, 39.2, 29.1, 21.2. **IR** (ATR): ν = 3276, 2921, 2652, 1777, 1453, 1156, 897 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 223.0729 $(M + Na)^+$, found: 223.0730.

5-Ethynyl-5-(4-(trifluoromethyl)-phenyl)dihydrofuran-2(3*H*)-one (IV.43e). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 62% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (s, 4H), 2.98-2.91 (m, 1H), 2.87-2.82 (m, 1H), 2.83 (s, 1H), 2.70-2.64 (m, 1H), 2.48-2.42 (m, 1H). **^{19}F NMR** (376 MHz, CD_3OD) δ -62.86. **^{13}C NMR** (126 MHz, CD_3OD) δ 175.0, 144.0, 131.2 (q, $^2J_{CF}$ = 33 Hz), 125.9 (q, $^3J_{CF}$ = 4 Hz), 125.3, 123.9 (q, $^1J_{CF}$ = 271 Hz), 81.7, 80.7, 76.7, 39.3, 28.9. **IR** (ATR): *v* = 3294, 2118, 1782, 1620, 1413, 1325, 842 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 277.0448 $(M + Na)^+$, found: 277.0447.

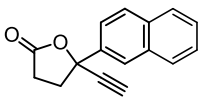


5-([1,1'-Biphenyl]-4-yl)-5-ethynyl-dihydrofuran-2(3*H*)-one (IV.43f). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Brown solid, yield: 79% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (s, 4H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 2.98-2.91 (m, 1H), 2.87-2.82 (m, 1H), 2.83 (s, 1H), 2.71-2.66 (m, 1H), 2.58-2.52 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.6, 141.9, 140.3, 138.9, 129.0, 127.8, 127.5, 127.2, 125.4, 82.4, 81.4, 76.2, 39.2, 29.1. **IR** (ATR): *v* = 3237, 3033, 2958, 2117, 1766, 1486, 1184, 837 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 285.0881 $(M + Na)^+$, found: 285.0886.

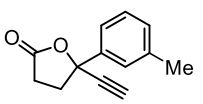
5-(4-Chloro-3-methylphenyl)-5-ethynyl-dihydrofuran-2(3*H*)-one (IV.43g). The title



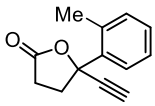
compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 76% over two steps **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.5 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.30-7.29 (m, 1H), 2.96-2.87 (m, 1H), 2.82-2.76 (m, 1H), 2.80 (s, 1H), 2.68-2.61 (m, 1H), 2.49-2.41 (m, 1H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4, 138.7, 136.8, 135.1, 129.5, 127.5, 123.8, 82.2, 81.0, 76.4, 39.3, 29.1, 20.4. **IR** (ATR): *v* = 3289, 2927, 2117, 1760, 1479, 1179, 907 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 257.0339 $(M + Na)^+$, found: 257.0340.



5-Ethynyl-5-(naphthalen-2-yl)-dihydrofuran-2(3*H*)-one (IV.43h). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Brown solid, yield: 82% over two steps**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 1.4 Hz, 1H), 7.91-7.85 (m, 3H), 7.60 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.55-7.51 (m, 2H), 2.99-2.92 (m, 1H), 2.91-2.85 (m, 1H), 2.85 (s, 1H), 2.72-2.66 (m, 1H), 2.63-2.56 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.6, 137.2, 133.3, 132.9, 129.0, 128.5, 127.8, 126.9, 126.8, 123.9, 122.6, 82.4, 81.6, 76.3, 39.1, 29.1. **IR** (ATR): *v* = 3242, 3058, 2958, 2116, 1761, 1419, 1187, 749 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 259.0730 $(M + Na)^+$, found: 259.0730.

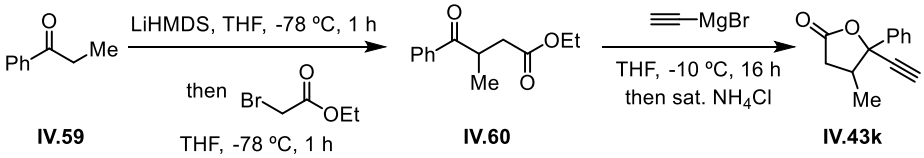


5-Ethynyl-5-(*m*-tolyl)-dihydrofuran-2(3*H*)-one (IV.43i). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 66% over two steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 10.9 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 2.94-2.87 (m, 1H), 2.82-2.77 (m, 1H), 2.79 (s, 1H), 2.67-2.61 (m, 1H), 2.52-2.46 (m, 1H), 2.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 140.0, 138.7, 129.6, 128.7, 125.4, 121.9, 82.5, 81.5, 76.0, 39.2, 29.1, 21.6. **IR** (ATR): *v* = 3280, 2957, 2116, 1776, 1454, 1179, 903 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 223.0733 $(M + Na)^+$, found: 223.0730.



5-Ethynyl-5-(*o*-tolyl)-dihydrofuran-2(3*H*)-one (IV.43j). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 58% over two steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.32-7.18 (m, 3H), 2.99-2.86 (m, 2H), 2.75 (s, 1H), 2.66-2.55 (m, 2H), 2.59 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3, 137.6, 135.3, 132.4, 128.8, 126.2, 124.4, 82.1, 80.9, 75.5, 36.7, 28.5, 21.0. **IR** (ATR): *ν* = 3277, 2930, 2113, 1776, 1456, 1189, 907 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 201.0904 $(M + H)^+$, found: 201.0910.

5-Ethynyl-4-methyl-5-phenyl-dihydrofuran-2(3*H*)-one (IV.43k). The title compound was prepared following the following general procedure:



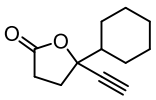
Scheme IV-11. General procedure **A** for the preparation of propargylic lactone **IV.43k**.

A solution of lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF, 12.0 mmol, 1.2 equiv) in THF (10 mL) was cooled down to -78 ºC. A solution of ketone **IV.59** (10 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the resultant solution was stirred at –78 ºC for 1 h. Hereafter, a solution of methyl bromoacetate (12.0 mmol, 1.2 equiv) in THF (10 mL) was added dropwise and the reaction mixture was stirred at -78 ºC for 1 h, quenched with hydrochloric acid (1 N) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was then purified by flash chromatography affording product **IV.60**.

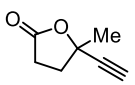
The ester **IV.60** was charged into a separate flame-dried round-bottom flask equipped with a stirring bar. Under N_2 atmosphere, anhydrous THF (20 mL) was introduced with a syringe and then ethynyl magnesium bromide (0.5 M in THF, 15.0 mmol, 1.5 equiv) was added dropwise to the reaction mixture at -10 ºC (ice/salt bath). After the mixture had been stirred at room temperature for 16 h, it was quenched with saturated NH_4Cl (aq) (20 mL). The reaction mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was

purified by flash chromatography (Hexane/DCM = 1/1), to afford the corresponding lactone **IV.43k** as a yellow oil in 68% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.32 (m, 5H), 3.10-3.01 (m, 1H), 3.00-2.94 (m, 1H), 2.75 (s, 1H), 2.31 (dd, *J* =16.9, 4.1 Hz, 1H), 0.67 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4, 136.7, 128.6, 128.5, 125.4, 84.3, 83.5, 75.1, 43.2, 36.9, 16.0. **IR** (ATR): *v* = 3283, 2931, 2115, 1782, 1450, 1162, 698 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 223.0738$(M + Na)^+$, found: 223.0729.



5-Cyclohexyl-5-ethynyl-dihydrofuran-2(3*H*)-one (IV.43l). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 82% over two steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.84-2.74 (m, 1H), 2.58 (s, 1H), 2.56-2.49 (m, 1H), 2.41-2.35 (m, 1H), 2.22-2.14 (m, 1H), 2.02-1.8 (m, 1H), 1.81-1.61 (m, 5H), 1.28-1.16 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.0, 84.8, 81.5, 75.5, 47.3, 34.1, 28.9, 27.7, 26.9, 26.1, 25.9, 25.6. **IR** (ATR): *v* = 3258, 2928, 2855, 1777, 1450, 1174, 911 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 193.1225 $(M + H)^+$, found: 193.1223.

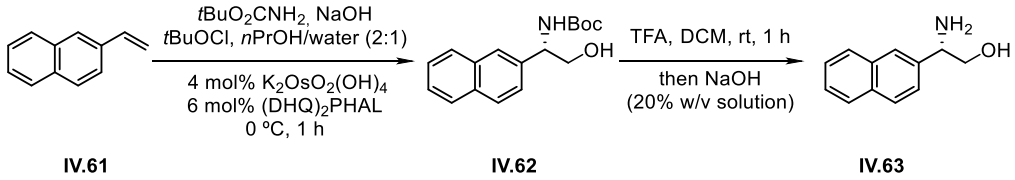


5-Cyclohexyl-5-ethynyl-dihydrofuran-2(3*H*)-one (IV.43m). The title compound was prepared following the general procedure **A** for the preparation of propargylic lactones, and the desired product was obtained after purification by silica gel column chromatography (Hexane/DCM = 1/1). Yellow oil, yield: 69% over two steps. The NMR spectroscopic data correspond to those previously reported in the literature.[35] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.84-2.75 (m, 1H), 2.62-2.54 (m, 1H), 2.59 (s, 1H), 2.53-2.45 (m, 1H), 2.22-2.14 (m, 1H), 1.71 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7, 83.3, 78.0, 73.8, 36.7, 29.1, 27.9.

35 Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem*. **1990**, *55*, 891-895.

IV.4.3 Synthesis of ligands

Amino alcohol **IV.63** was prepared according to a reported procedure with slight modifications.[36]



Scheme IV-12. General procedure for the preparation of amino alcohol **IV.63**.

A freshly prepared solution of sodium hydroxide (0.40 g, 9.70 mmol, 3.0 equiv) in water (24 mL) and *tert*-butyl hypochlorite (1.06 g, 9.70 mmol, 3.0 equiv) was added in this order to a solution of *tert*-butyl carbamate (1.15 g, 9.70 mmol, 3.0 equiv) in *n*PrOH (12 mL). The resultant solution was stirred for 5 min at room temperature and then allowed to cool down to 0 ºC (ice bath). Hereafter, a solution of $(DHQ)_2PHAL$ (0.16 g, 0.20 mmol, 0.06 equiv) in *n*PrOH (12 mL) and a solution of 2-vinylnaphthalene **IV.61** (0.50 g, 3.20 mmol, 1.0 equiv) in *n*PrOH (24 mL) and $K_2OsO_2(OH)_4$ (0.05 g, 0.13 mmol, 0.04 equiv) were added successively. Upon stirring for 1 h at 0 ºC, the reaction mixture became pale yellow and the starting material **IV.61** had been consumed completely as checked by TLC. Saturated aqueous Na_2SO_3 (15 mL) was added and the mixture stirred for 15 min at room temperature. Then, the organic layer was extracted with EtOAc (3 × 15 mL), washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The yellow solid residue was purified by flash chromatography (Hexane/EtOAc= 3:1) to afford the pure *N*-Boc protected amino alcohol **IV.62** (0.80 g, 86%) as a white solid.

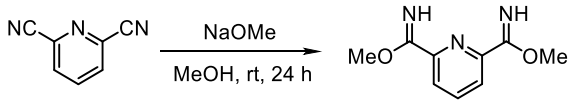
Preparation of *tert*-butyl hypochlorite (*t*BuOCl): A mixture of *tert*-butyl alcohol (11.1 mL, 0.12 mol, 1.0 equiv) and glacial acetic acid (7.3 mL, 0.12 mol, 1.0 equiv) was added in one portion to a commercial household bleach solution (150.0 mL; 5.25% NaOCl) at 0 ºC in a 1 L round bottom flask. The resultant solution was stirred vigorously for 5 min and then the two layers were separated. The yellow organic layer was washed with 10% of Na_2CO_3 aqueous solution (50 mL) and then with water (50 mL), dried over anhydrous Na_2SO_4 and filtered. The *tert*-butyl hypochlorite was obtained as a yellow liquid and was used without further purification.

36 O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans*. **1998**, *1*, 2519-2526.

Note: The *tert*-butyl hypochlorite can be stored in a foil-covered vial in the freezer for up to 3 weeks without any change in performance.

Trifluoroacetic acid (TFA, 1.1 mL, 14.0 mmol, 5.0 equiv) was added dropwise to a stirred solution of the *N*-Boc protected amino alcohol **IV.62** in CH_2Cl_2 (20 mL) at room temperature. The resultant reaction mixture was stirred for 1 h at room temperature and was then carefully evaporated under reduced pressure. The residue was dissolved into 20% aqueous NaOH solution (20 mL) and stirred for 30 min, and then extracted with CH_2Cl_2 (6 × 10 mL). The combined organic layers were washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (DCM/EtOH= 10:1) to afford the pure amino alcohol **IV.63** (0.3 g, 57%) as a white solid.

Compound **IV.65** was prepared according to a reported procedure with slight modifications.[37]



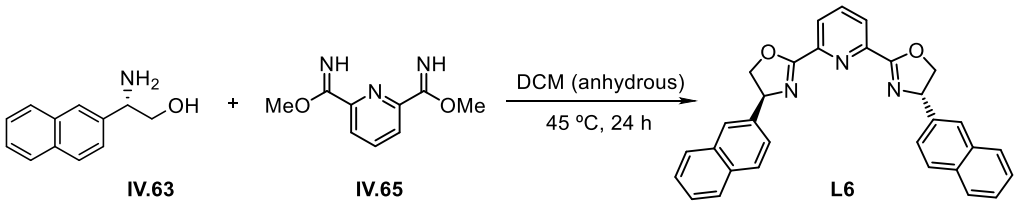
IV.64 **IV.65**

Scheme IV-13. General procedure for the preparation of **IV.65**.

To a 50 mL round bottom flask equipped with magnetic stirring bar was added sodium methoxide (220 µL, 0.97 mmol, 0.1 equiv, 25 wt% in MeOH) and methanol (20 mL). The resultant solution was cooled to 0 ºC and added pyridine-2,6-dicarbonitrile **IV.64** (1.2 g, 9.67 mmol, 1.0 equiv). The reaction mixture was allowed to warm up to room temperature and stirred overnight. It was quenched by the addition of acetic acid (120 µL) at 0 ºC. Upon the removal of the solvent, compound **IV.65** with a small amount of impurities was obtained as a white solid (1.4 g, 72% yield) which was used without further purification.

37 Eno, M. S.; A. Lu.; Morken, J. P. *J. Am. Chem. Soc*. **2016**, *138*, 7824-7827.

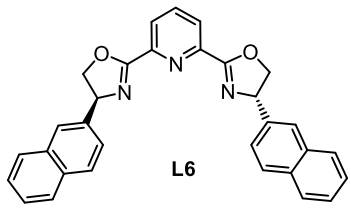
Ligand **L6** was prepared according to a reported procedure with slight modifications.[38]



IV.63 **IV.65** **L6**

Scheme IV-14. General procedure for the preparation of ligand **L6**.

A suspension of dimethyl pyridine-2,6-bis(carbimidate) **IV.65** (0.16 g, 0.80 mmol, 1.0 equiv) and amino alcohol **IV.63** (0.30 g, 1.6 mmol, 2.0 equiv) in anhydrous dichloromethane (10 mL) was heated under reflux for 24 h. The solvent was removed under vacuum and the residue was solidified by addition of methanol. The yellow solid that formed was filtered off and washed with water and methanol. The ligand **L6** was obtained as a white solid upon recrystallization from hot methanol (0.26 g, 70%). [Note: anhydrous conditions are very important to achieve the reported isolated yield].

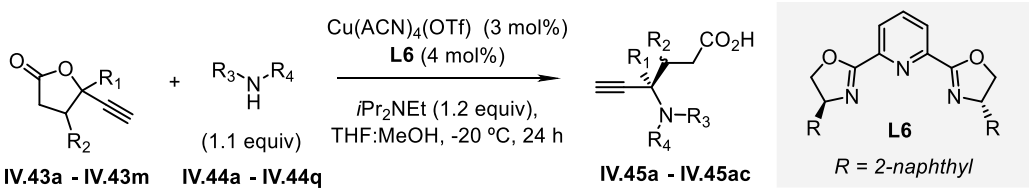


L6

2,6-Bis-((*R*)-4-(naphthalen-2-yl)-4,5-dihydrooxazol-2-yl)pyridine (L6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.9 Hz, 2H), 7.95 (t, *J* = 7.9 Hz, 1H), 7.87-7.81 (m, 8H), 7.49-7.42 (m, 6H), 5.65 (dd, *J* = 10.3, 8.5 Hz, 2H), 5.01 (dd, *J* = 10.4, 8.7 Hz, 2H), 4.52 (t, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 146.9, 139.0, 137.6, 133.5, 133.0, 128.9, 128.0, 127.8, 126.5, 126.4, 126.1, 125.8, 124.7, 75.5, 70.6.

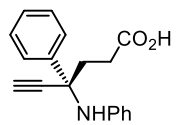
38 Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron: Asymmetr.* **2002**, *13*, 1651-1654.

IV.4.4 Typical procedure for the formation of γ-amino acids

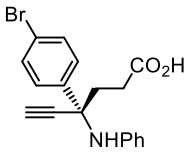


Scheme IV-15. General procedure for the preparation of γ-amino acids.

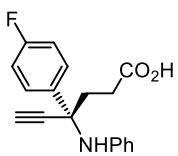
In a screw-capped vial, $Cu(CH_3CN)_4(OTf)$ (2.3 mg, 3 mol%, stored in a glove-box) and **L6** (3.8 mg, 4 mol%) were combined with MeOH/THF (MeOH/THF = 1:3, 0.6 mL). The resultant solution was stirred for 30 min at room temperature. Then *i*Pr_2NEt (42.0 μL, 0.24 mmol, 1.2 equiv), amine (0.22 mmol, 1.1 equiv) and the corresponding lactone (0.20 mmol, 1.0 equiv) were added successively. The reaction mixture was stirred at -20 ºC for 24 h (monitored by NMR), and then quenched by saturated NH_4Cl aqueous solution (5 mL). The organic components were extracted with CH_2Cl_2 (3 × 5 mL), dried over anhydrous Na_2SO_4, following filtration and concentration under vacuum. The resultant crude product was purified by flash chromatography to afford the pure γ-amino acid. All purified products were fully characterized by ^{1}H, ^{13}C NMR, IR spectra and HRMS analysis, and ^{19}F NMR experiments where necessary.



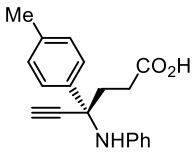
(*R*)-4-Phenyl-4-(phenylamino)hex-5-ynoic acid (IV.45a). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 94%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.93-6.90 (m, 2H), 6.56-6.52 (m, 3H), 2.95 (s, 1H), 2.63-2.56 (m, 1H), 2.36-2.31 (m, 1H), 2.29-2.22 (m, 1H), 2.20-2.12 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 177.0, 147.0, 143.8, 129.3, 129.0, 128.4, 127.4, 118.4, 116.7, 85.7, 75.4, 59.6, 42.4, 30.7. **IR** (ATR): *ν* = 3381, 3284, 3055, 2926, 1705, 1600, 1498, 1446, 1293, 1027, 749 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 278.1183 $(M - H)^-$, found: 278.1187. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +130.0 (*c* = 0.09, $CHCl_3$).



(*R*)-4-(4-Bromophenyl)-4-(phenylamino)hex-5-ynoic acid (IV.45b). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 76%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.58-6.53 (m, 3H), 3.00 (s, 1H), 2.66-2.57 (m, 1H), 2.37-2.25 (m, 2H), 2.20-2.11 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.8, 146.7, 143.4, 132.4, 129.6, 129.1, 122.2, 118.7, 116.7, 85.1, 75.8, 59.3, 42.1, 30.6. **IR** (ATR): *v* = 3376, 3292, 2923, 2852, 2073, 1705, 1484, 1264, 1008, 783 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 356.0290 $(M - H)^-$, found: 356.0292. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +47.2 (*c* = 0.09, $CHCl_3$).

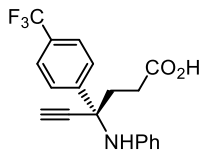


(*R*)-4-(4-Fluorophenyl)-4-(phenylamino)hex-5-ynoic acid (IV.45c). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 97%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.66-7.63 (m, 2H), 7.07-7.02 (m, 2H), 6.96-6.92 (m, 2H), 6.58-6.53 (m, 3H), 2.99 (s, 1H), 2.63-2.56 (m, 1H), 2.37-2.24 (m, 2H), 2.20-2.14 (m, 1H). **^{19}F NMR** (376 MHz, CD_3OD) δ -117.92. **^{13}C NMR** (126 MHz, CD_3OD) δ 176.8, 163.5 (d, $^{1}J_{CF}$ = 247 Hz), 146.8, 139.8, 129.4 (d, $^{3}J_{CF}$ = 9 Hz), 129.1, 118.6, 116.7, 115.9 (d, $^{2}J_{CF}$ = 21 Hz), 85.5, 75.6, 59.2, 42.4, 30.7. **IR** (ATR): *v* = 3369, 3290, 2927, 2514, 1707, 1601, 1225, 839 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 296.1081 $(M - H)^-$, found: 296.1092. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +133.1 (*c* = 0.10, $CHCl_3$).

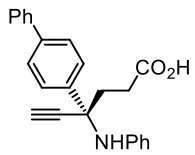


(*R*)-4-(Phenylamino)-4-(*p*-tolyl)hex-5-ynoic acid (IV.45d). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow solid, yield: 88%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.92 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.62-6.47 (m, 3H), 2.93 (s, 1H), 2.61-2.54 (m, 1H), 2.35-2.26 (m, 1H), 2.31 (s, 3H), 2.24-2.12 (m, 2H). **^{13}C NMR** (126 MHz, CD_3OD) δ 177.0, 147.0, 140.7, 138.2, 130.0, 129.0, 127.4, 118.4, 116.7, 85.9, 75.2, 59.4, 42.4, 30.7, 21.0. **IR**

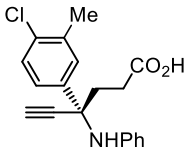
(ATR): ν = 3284, 3028, 2924, 2513, 2071, 1704, 1498, 1104, 750 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 292.1340 $(M - H)^-$, found: 292.1343. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 95.5:4.5, $[\alpha]_D^{25}$ = +139.9 (*c* = 0.11, $CHCl_3$).



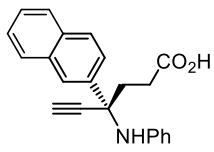
(*R*)-4-(Phenylamino)-4-(4-(trifluoromethyl)phenyl)hex-5-ynoic acid (IV.45e). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown oil, yield: 67%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 6.95 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.59-6.52 (m, 3H), 3.05 (s, 1H), 2.66-2.60 (m, 1H), 2.40-2.28 (m, 2H), 2.23-2.15 (m, 1H). **^{19}F NMR** (376 MHz, CD_3OD) δ -63.89. **^{13}C NMR** (126 MHz, CD_3OD) δ 176.6, 148.7, 146.5, 130.7 (q, $^2J_{CF}$ = 33 Hz), 129.2, 128.2, 126.3 (q, $^3J_{CF}$ = 4 Hz), 125.6 (q, $^1J_{CF}$ = 271 Hz), 118.7, 116.6, 84.9, 76.2, 59.5, 42.1, 30.6. **IR** (ATR): ν = 3294, 2931, 2072, 1706, 1324, 1068, 693 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 346.1052 $(M - H)^-$, found: 346.1060. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 95.5:4.5, $[\alpha]_D^{25}$ = +94.2 (*c* = 0.10, $CHCl_3$).



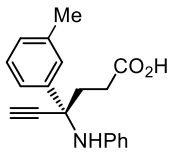
(*R*)-4-([1,1'-Biphenyl]-4-yl)-4-(phenylamino)hex-5-ynoic acid (IV.45f). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 83%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.60-7.56 (m, 4H), 7.39 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.94 (dd, *J* = 8.7, 7.2 Hz, 2H), 6.61-6.60 (m, 2H), 6.55 (t, *J* = 7.3 Hz, 1H), 2.97 (s, 1H), 2.67-2.61 (m, 1H), 2.41-2.28 (m, 2H), 2.25-2.20 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.9, 146.9, 142.9, 141.9, 141.6, 129.7, 129.1, 128.3, 128.0, 127.9, 127.9, 118.5, 116.7, 85.7, 75.5, 59.5, 42.3, 30.7. **IR** (ATR): ν = 3285, 3029, 2928, 2070, 1703, 1497, 1076, 694 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 354.1498 $(M - H)^-$, found: 354.1500. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 85:15:0.1, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = +81.3 (*c* = 0.10, $CHCl_3$).



(*R*)-4-(4-Chloro-3-methylphenyl)-4-(phenylamino)hex-5-ynoic acid (IV.45g). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown oil, yield: 74%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.45-7.42 (m, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.58-6.53 (m, 3H), 2.98 (s, 1H), 2.-2.56 (m, 1H), 2.40-2.24 (m, 2H), 2.34 (s, 3H), 2.19-2.13 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.9, 146.8, 142.8, 137.0, 134.2, 130.1, 129.9, 129.1, 126.6, 118.6, 116.6, 85.3, 75.7, 59.2, 42.2, 30.7, 20.2. **IR** (ATR): *v* = 3250, 2925, 2507, 2229, 2072, 1710, 1601, 1047, 692 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 326.0945 $(M - H)^-$, found: 326.0953. **UPC2**: IC column, isocratic CO_2/IPA/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +96.8 (*c* = 0.11, $CHCl_3$).

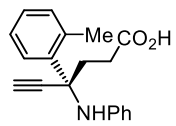


(*R*)-4-(Naphthalen-2-yl)-4-(phenylamino)hex-5-ynoic acid (IV.45h). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 97%. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.82-7.80 (m, 3H), 7.72 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.47-7.45 (m, 2H), 6.90 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.61-6.58 (m, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 3.05 (s, 1H), 2.69-2.59 (m, 1H), 2.47-2.39 (m, 1H), 2.32-2.24 (m, 2H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.9, 147.0, 141.3, 134.5, 134.3, 129.3, 129.1, 128.5, 127.2, 127.0, 126.8, 125.0, 118.5, 116.7, 85.7, 75.7, 59.9, 42.0, 30.7. **IR** (ATR): *v* = 3285, 3058, 2927, 2701, 1702, 1600, 1310, 692 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 328.1340 $(M - H)^-$, found: 328.1343. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +155.8 (*c* = 0.12, $CHCl_3$).

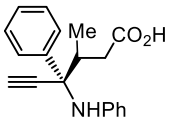


(*R*)-4-(Phenylamino)-4-(*m*-tolyl)hex-5-ynoic acid (IV.45i). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 85%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.47 (s, 1H), 7.43 (d, *J* = 7.8, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.08-7.06 (m, 1H), 6.94-6.91 (m, 2H), 6.57-6.53 (m, 3H), 2.92 (s, 1H), 2.62-2.56 (m, 1H), 2.37-2.30 (m, 1H), 2.31 (s, 3H), 2.28-2.22 (m, 1H), 2.19-2.13 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD)

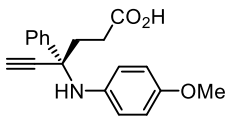
δ 176.9, 147.0, 143.7, 139.1, 129.2, 129.1, 129.0, 127.9, 124.6, 118.4, 116.7, 85.8, 75.3, 59.6, 42.3, 30.7, 21.6. **IR** (ATR): *v* = 3273, 2915, 2501, 2106, 1704, 1301, 749, 688 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 292.1344 $(M - H)^-$, found: 292.1343. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +110.8 (*c* = 0.10, $CHCl_3$).



(*R*)-4-(Phenylamino)-4-(*o*-tolyl)hex-5-ynoic acid (IV.45j). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 42%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.88 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.19-7.13 (m, 2H), 7.07-7.06 (m, 1H), 6.93-6.90 (m, 2H), 6.55-6.51 (m, 3H), 2.94 (s, 1H), 2.67-2.61 (m, 1H), 2.50 (s, 3H), 2.42-2.39 (m, 2H), 2.30-2.24 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 177.1, 146.9, 140.0, 136.8, 133.9, 130.1, 129.0, 128.5, 126.7, 118.1, 115.9, 75.2, 60.9, 38.2, 30.9, 21.8. **IR** (ATR): *v* = 3268, 3062, 2914, 2505, 2248, 2100, 1704, 1057, 665 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 292.1343 $(M - H)^-$, found: 292.1343. **UPC2**: IC column, isocratic CO_2/MeOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +70.4 (*c* = 0.11, $CHCl_3$).

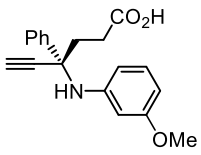


(3*R*,4*R*)-3-Methyl-4-phenyl-4-(phenylamino)hex-5-ynoic acid (IV.45k). The title compound was prepared following the general procedure for the preparation of γ-amino acids. The desired product was obtained as the corresponding γ-lactam, after purification by silica gel column chromatography (Hexane/EtOAc = 5/1). Yellow oil, yield: 71%; *dr* = 84:16. Only the signals for the major isomer are listed. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52-7.27 (m, 6H), 7.25-7.03 (m, 4H), 2.92 (s, 1H), 2.79-2.70 (m, 1H), 2.61-2.55 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 138.5, 137.1, 128.4, 128.4, 128.2, 127.0, 125.8, 125.1, 80.6, 79.0, 71.2, 44.8, 38.7, 13.9. **IR** (ATR): *v* = 3298, 2922, 2855, 1701, 1497, 1325, 1142, 694 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 298.1199 $(M + Na)^+$, found: 298.1202. **UPC2**: OJ column, isocratic CO_2/EtOH = 95:5, 3 mL/min, 1500 psi, *er* = 54:46, $[\alpha]_D^{25}$ = +7.8 (*c* = 0.10, $CHCl_3$).

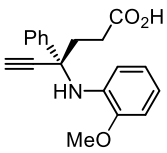


(*R*)-4-((4-Methoxyphenyl)amino)-4-phenylhex-5-ynoic acid (IV.45n). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 98%. **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ 7.70-7.68 (d, *J* = 7.5 Hz, 2H), 7.38-

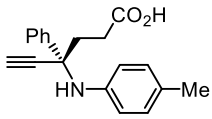
7.34 (t, *J* = 7.5 Hz, 2H), 7.30-7.26 (t, *J* = 7.5 Hz, 1H), 6.59-6.54 (m, 4H), 3.61 (s, 3H), 3.09 (s, 1H), 2.63-2.57 (m, 1H), 2.38-2.25 (m, 2H), 2.23-2.14 (m, 1H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ 153.1, 143.7, 140.5, 129.1, 128.1, 127.1, 117.7, 114.5, 114.0, 85.7, 75.5, 59.7, 55.5, 42.2, 29.2. **IR** (ATR): *v* = 3276, 2833, 2494, 1706, 1509, 1236, 822 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 308.1307 (M - H)$^-$, found: 308.1292. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 85:15:0.1, 3 mL/min, 1500 psi, *er* = 94:6, $[\alpha]_D^{25}$ = +76.2 (*c* = 0.11, $CHCl_3$).



(*R*)-4-((3-Methoxyphenyl)amino)-4-phenylhex-5-ynoic acid (IV.45o). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 90%. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.65-7.63 (d, *J* = 7.5 Hz, 2H), 7.35-7.31 (t, *J* = 7.5 Hz, 2H), 7.27-7.23 (t, *J* = 7.5 Hz, 1H), 6.85-6.81 (t, *J* = 8.5 Hz, 1H), 6.21-6.18 (d, *J* = 8.5 Hz, 1H), 6.15-6.12 (m, 2H), 3.54 (s, 3H), 2.98 (s, 1H), 2.64-2.59 (m, 1H), 2.57-2.11 (m, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.9, 161.2, 148.3, 143.9, 129.7, 129.4, 128.4, 127.4, 109.7, 104.1, 102.5, 85.7, 75.5, 59.7, 55.2, 42.3, 30.7. **IR** (ATR): *v* = 3282, 2933, 3835, 2069, 1706, 1492, 1161, 700 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 308.1281 (M - H)$^-$, found: 308.1292. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +101.7 (*c* = 0.10, $CHCl_3$).

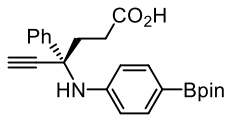


(*R*)-4-((2-Methoxyphenyl)amino)-4-phenylhex-5-ynoic acid (IV.45p). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown oil, yield: 95%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.64-7.62 (d, *J* = 8.5 Hz, 2H), 7.35-7.31 (t, *J* = 7.4 Hz, 2H), 7.28-7.23 (t, *J* = 7.4 Hz, 1H), 6.81-6.90 (d, *J* = 7.6 Hz, 1H), 6.59-6.55 (t, *J* = 7.6 Hz, 1H), 6.49-6.44 (t, *J* = 7.6 Hz, 1H), 6.34-6.32 (d, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 2.95 (s, 1H), 2.64-2.55 (m, 1H), 2.40-2.33 (m, 1H), 2.32-2.19 (m, 2H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.7, 149.0, 143.7, 136.0, 129.4, 128.5, 121.0, 118.6, 115.8, 110.6, 85.5, 75.5, 59.7, 56.1, 42.5, 30.7. **IR** (ATR): *v* = 3396, 2933, 1705, 1508, 1221, 1128, 736 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 308.1288 (M - H)$^-$, found: 308.1292. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 98:2, $[\alpha]_D^{25}$ = +147.1 (*c* = 0.10, $CHCl_3$).

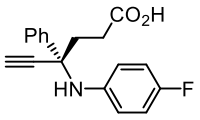


(*R*)-4-Phenyl-4-(*p*-tolylamino)hex-5-ynoic acid (IV.45q). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow solid, yield: 94%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.64-7.62 (d, *J* = 7.5 Hz, 2H), 7.33-7.30 (t, *J* = 7.5 Hz 2H), 7.25-7.23 (t, *J* = 7.5 Hz, 1H), 6.75-6.73 (d, *J* = 8.2 Hz, 2H), 6.47-6.45 (d, *J* = 8.2 Hz, 2H), 2.93 (s, 1H), 2.60-2.55 (m, 1H), 2.33-2.28 (m, 1H), 2.27-2.14 (m, 2H), 2.11 (s, 3H). **^{13}C NMR** (126 MHz, CD_3OD) δ 177.0, 144.6, 143.9, 129.5, 129.3, 128.3, 127.7, 127.5, 117.1, 85.9, 75.4, 59.9, 42.4, 30.7, 20.4. **IR** (ATR): *ν* = 3284, 2920, 2219, 1705, 1514, 1298, 809 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 292.1339 $(M - H)^-$, found: 292.1343. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +108.0 (*c* = 0.10, $CHCl_3$).

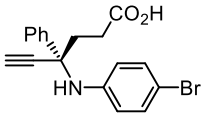
(*R*)-4-Phenyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)hex-5-



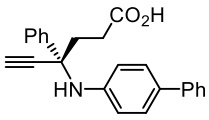
ynoic acid (IV.45r). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 71%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.62 (d, *J* = 7.1 Hz, 2H), 7.34-7.31 (m, 4H), 7.27-7.24 (m, 1H), 6.53 (d, *J* = 8.6 Hz, 2H), 3.00 (s, 1H), 2.64-2.58 (m, 1H), 2.36-2.25 (m, 2H), 2.20-2.15 (m, 1H), 1.27 (s, 12H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.8, 149.9, 143.6, 136.1, 129.4, 128.5, 127.3, 115.6, 85.3, 84.4, 75.6, 59.4, 42.3, 30.6, 25.1. **^{11}B NMR** (160 MHz, CD_3OD) δ 30.6. **IR** (ATR): *ν* = 3286, 2978, 2520, 2071, 1706, 1604, 1358, 1141, 823 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 403.2088 $(M - H)^-$, found: 403.2075. **UPC2**: IB column, isocratic CO_2/MeOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +97.2 (*c* = 0.07, $CHCl_3$).



(*R*)-4-((4-Fluorophenyl)amino)-4-phenylhex-5-ynoic acid (IV.45s). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 93%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.64-7.63 (d, *J* = 7.5 Hz, 2H), 7.35-7.31 (t, *J* = 7.5 Hz, 2H), 7.27-7.24 (t, *J* = 7.5 Hz, 1H), 6.69-6.64 (t, *J* = 9.0 Hz, 2H), 6.54-6.51 (m, 2H), 2.97 (s, 1H), 2.62-2.55 (m, 1H), 2.38-2.30 (m, 1H), 2.28-2.11 (m, 2H). **^{19}F NMR** (376 MHz, CD_3OD) δ -130.07. **^{13}C NMR** (101 MHz, CD_3OD) δ 176.9, 157.28(d, $^{1}J_{CF}$ = 247 Hz), 143.5, 143.4, 143.4, 129.4, 128.5, 127.5, 117.8 (d, $^{3}J_{CF}$ = 9 Hz), 115.3 (d, $^{2}J_{CF}$ = 21 Hz), 85.6, 75.6, 60.0, 42.3, 30.7. **IR** (ATR): *v* = 3278, 2902, 2494, 2107, 1704, 1507, 1216, 822 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 296.1086 $(M - H)^-$, found: 296.1092. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 95:5:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +67.3 (*c* = 0.10, $CHCl_3$).



(*R*)-4-((4-Bromophenyl)amino)-4-phenylhex-5-ynoic acid (IV.45t). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 77%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.62-7.61 (d, *J* = 7.5 Hz, 2H), 7.35-7.32 (t, *J* = 7.5 Hz, 2H), 7.27-7.24 (t, *J* = 7.5 Hz, 1H), 7.03-7.01 (d, *J* = 8.5 Hz, 2H), 6.48-6.46 (d, *J* = 8.5 Hz, 2H), 2.99 (s, 1H), 2.62-2.56 (m, 1H), 2.36-2.23 (m, 2H), 2.19-2.14 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.8, 146.2, 143.3, 131.7, 129.5, 128.6, 127.4, 118.2, 110.0, 85.2, 75.7, 59.6, 42.2, 30.6. **IR** (ATR): *v* = 3279, 2928, 2520, 2071, 1702, 1590, 1489, 1304, 814 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 356.0276 $(M - H)^-$, found: 356.0292. **UPC2**: IA column, isocratic CO_2/MeOH/TFA = 80:20:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +66.4 (*c* = 0.09, $CHCl_3$).



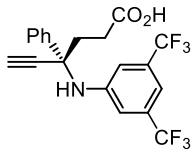
(*R*)-4-([1,1'-Biphenyl]-4-ylamino)-4-phenylhex-5-ynoic acid (IV.45u). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 93%. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.67-7.66 (d, *J* = 7.5 Hz, 2H), 7.44-7.42 (d, *J* = 7.5 Hz, 2H), 7.35-7.26 (m, 5H), 7.23-7.20 (d, *J* = 8.6 Hz, 2H), 7.18-7.14 (t, *J* = 7.6 Hz, 1H), 6.65-6.62 (d, *J* = 7.6 Hz, 2H), 2.98 (s, 1H), 2.65-2.58 (m, 1H), 2.40-2.14 (m, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.9, 146.5, 143.7, 142.6, 131.4, 129.5, 129.4, 128.5, 127.6, 127.4, 127.0, 126.8,

116.9, 85.6, 75.5, 59.7, 42.3, 30.7. **IR** (ATR): ν = 3286, 3028, 2926, 2231, 1703, 1611, 1485, 1265, 1071, 827 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 354.1506 $(M - H)^-$, found: 354.1500. **UPC2**: IC column, isocratic CO_2/EtOH/TFA = 85:15:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +118.8 (*c* = 0.10, $CHCl_3$).

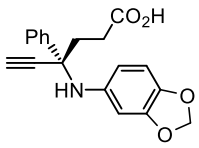
(*R*)-4-((4-(Methoxycarbonyl)phenyl)amino)-4-phenylhex-5-ynoic acid (IV.45v). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 55%. 93:7 *er*. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.62-7.60 (dd, *J* = 8.5 Hz, *J* = 7.5 Hz, 4H), 7.36-7.32 (t, *J* = 7.5 Hz, 2H), 7.29-7.25 (t, *J* = 7.5 Hz, 1H), 6.58-6.56 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 3.06 (s, 1H), 2.66-2.58 (m, 1H), 2.41-2.34 (m, 1H), 2.28-2.25 (m, 1H), 2.22-2.15 (m, 1H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.7, 169.2, 151.5, 143.2, 131.3, 129.6, 128.7, 127.2, 119.0, 115.3, 84.7, 76.0, 59.5, 51.9, 42.1, 30.6. **IR** (ATR): ν = 3285, 2950, 2515, 2227, 1688, 1603, 1278, 971, 771 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 336.1237 $(M - H)^-$, found: 336.1241. **UPC2**: IA column, isocratic CO_2/IPA/TFA = 80:20:0.1, 3 mL/min, 1500 psi, *er* = 93:7, $[\alpha]_D^{25}$ = +29.1 (*c* = 0.10, $CHCl_3$).

(*R*)-4-((3-Nitrophenyl)amino)-4-phenylhex-5-ynoic acid (IV.45w). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 58%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.66-7.64 (d, *J* = 7.5 Hz, 2H), 7.43-7.34 (m, 4H), 7.30-7.26 (t, *J* = 7.5 Hz, 1H), 7.16-7.11 (t, *J* = 8.0 Hz, 1H), 6.94-6.91 (dd, *J* = 8.0 Hz, *J* = 2.3 Hz, 1H), 3.09 (s, 1H), 2.67-2.59 (m, 1H), 2.42-2.36 (m, 1H), 2.31-2.15 (m, 2H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.7, 149.8, 148.1, 142.8, 129.8, 129.6, 128.8, 127.3, 122.2, 112.5, 110.2, 84.5, 76.3, 59.6, 42.0, 30.6. **IR** (ATR): ν = 3384, 3290, 2928, 1706, 1524, 1346, 1265, 734 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 323.1037 $(M - H)^-$, found: 323.1037. **UPC2**: IA column, isocratic CO_2/IPA/TFA = 80:20:0.1, 3 mL/min, 1500 psi. *er* = 92:8, $[\alpha]_D^{25}$ = +13.3 (*c* = 0.10, $CHCl_3$).

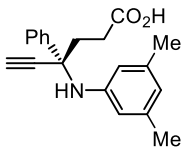
(*R*)-4-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-phenylhex-5-ynoic acid (IV.45x). The title



compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown oil, yield: 62%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.65-7.63 (d, *J* = 7.5 Hz, 2H), 7.40-7.36 (t, *J* = 7.5 Hz, 2H), 7.32-7.29 (t, *J* = 7.5 Hz, 1H), 7.03 (s, 2H), 7.01 (s, 1H), 3.14 (s, 1H), 2.67-2.59 (m, 1H), 2.45-2.38 (m, 1H), 2.32-2.19 (m, 2H). **^{19}F NMR** (376 MHz, CD_3OD) δ -64.92. **^{13}C NMR** (126 MHz, CD_3OD) δ 176.5, 148.3, 142.3, 132.4 (q, $^{2}J_{CF}$ = 33 Hz), 129.7, 129.0, 127.2, 123.6 (q, $^{1}J_{CF}$ = 271 Hz), 115.6, 110.3 (d, $^{3}J_{CF}$ = 4 Hz), 84.0, 76.5, 59.7, 41.8, 30.6. **IR** (ATR): *ν* = 3303, 2928, 2493, 2236, 2074, 1707, 1620, 1274, 1125, 806 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 414.0926 $(M - H)^-$, found: 414.0934. **UPC2**: IB column, isocratic CO_2/EtOH/TFA = 97:3:0.1, 3 mL/min, 1500 psi, *er* = 89:11, $[\alpha]_D^{25}$ = +30.4 (*c* = 0.10, $CHCl_3$).

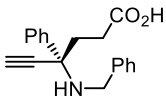


(*R*)-4-(Benzo[*d*][1,3]dioxol-5-ylamino)-4-phenylhex-5-ynoic acid (IV.45y). The title compound was prepared following the general procedure for the preparation of γ-amino acids. The desired product was obtained as the corresponding γ-lactam, after purification by silica gel column chromatography (Hexane/EtOAc = 3/1). Yellow solid, yield: 72%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 2H), 2.91-2.83 (m, 1H), 2.82 (s, 1H), 2.76-2.69 (m, 2H), 2.50-2.44 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8, 147.5, 146.2, 140.1, 130.6, 128.7, 128.4, 126.6, 120.1, 107.9, 107.9, 101.4, 83.5, 76.7, 66.8, 39.8, 30.6. **IR** (ATR): *ν* = 3429, 2918, 1699, 1488, 1237, 1033, 821, 698 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 306.1114 $(M + H)^+$, found: 306.1125. **UPC2**: IB column, isocratic CO_2/EtOH/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 94:6, $[\alpha]_D^{25}$ = +18.4 (*c* = 0.10, $CHCl_3$).

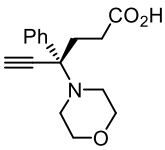


(*R*)-4-((3,5-Dimethylphenyl)amino)-4-phenylhex-5-ynoic acid (IV.45z). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Brown solid, yield: 98%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.63 (d, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.22-6.20 (m, 3H), 2.95 (s, 1H), 2.62-2.56 (m, 1H), 2.34-

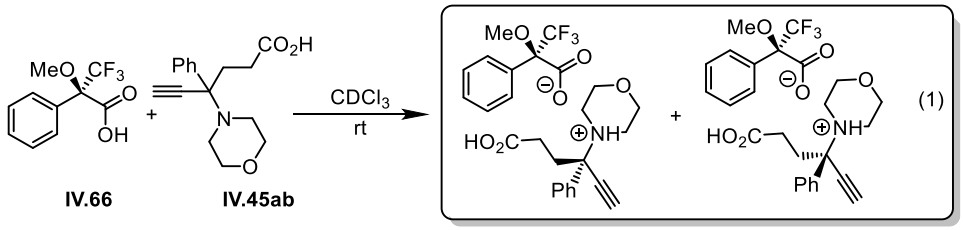
2.23 (m, 2H), 2.18-2.13 (m, 1H), 2.03 (s, 6H). **^{13}C NMR** (101 MHz, CD_3OD) δ 176.9, 146.9, 144.0, 138.4, 129.3, 128.3, 127.5, 120.4, 114.8, 85.8, 75.4, 59.7, 42.4, 30.7, 21.5. **IR** (ATR): *v* = 3282, 2919, 2072, 1705, 1600, 1447, 1018, 689 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 306.1500 $(M - H)^-$, found: 306.1500. **UPC2**: IC column, isocratic CO_2/IPA/TFA = 90:10:0.1, 3 mL/min, 1500 psi, *er* = 96:4, $[\alpha]_D^{25}$ = +77.6 (*c* = 0.10, $CHCl_3$).



(*R*)-4-(Benzylamino)-4-phenylhex-5-ynoic acid (IV.45aa). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 41%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.63 (d, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.30-7.24 (m, 3H), 7.23-7.20 (m, 3H), 4.30 (s, 2H), 3.07 (s, 1H), 2.48-2.42 (m, 1H), 2.38-2.32 (m, 1H), 2.25-2.15 (m, 2H). **^{13}C NMR** (126 MHz, CD_3OD) δ 175.4, 145.6, 139.9, 129.4, 129.0, 128.6, 128.4, 128.1, 126.6, 87.2, 75.3, 72.8, 44.0, 42.3, 32.7. **IR** (ATR): *v* = 3285, 3029, 2455, 1621, 1449, 1061, 698 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 292.1342 $(M - H)^-$, found: 292.1343. **UPC2**: IC column, isocratic CO_2/IPA/TFA = 65:35:0.1, 3 mL/min, 1500 psi, *er* = 52:48.



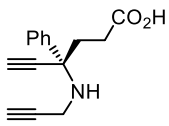
(*R*)-4-Morpholino-4-phenylhex-5-ynoic acid (IV.45ab). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 92%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 3.69-3.67 (m, 4H), 3.16 (s, 1H), 2.68 (s, 2H), 2.40-2.34 (m, 3H), 2.25-2.18 (m, 1H), 2.13-2.01 (m, 1H), 1.79-1.71 (m, 1H). **^{13}C NMR** (126 MHz, CD_3OD) δ 176.7, 141.9, 129.3, 128.9, 128.5, 81.5, 78.6, 68.3, 67.7, 49.1, 37.3, 30.8. **IR** (ATR): *v* = 3287, 2854, 2102, 1708, 1269, 1112, 998, 702, 609 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 272.1303 $(M - H)^-$, found: 272.1292.



IV.66 **IV.45ab**

molar ratio of **IV.66** : **IV.45ab** = 1:1

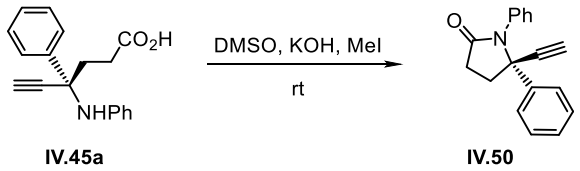
The *er* value was determined using a chiral shift reagent **IV.66** following a reported procedure.[39] The chiral shift reagent **IV.66** (0.01 mmol) and amino acid **IV.45ab** (0.01 mmol) were mixed in $CDCl_3$ (0.6 mL) at room temperature. The ^{1}H NMR spectrum of the resultant mixture was then measured at room temperature. The *er* value was calculated based on the integral of the proton of the alkyne group of both diastereoisomers (equation 1), *er* = 86:14, $[\alpha]_D^{25}$ = -0.7 (*c* = 0.12, $CHCl_3$).



(*R*)-4-Phenyl-4-(prop-2-yn-1-ylamino)hex-5-ynoic acid (IV.45ac). The title compound was prepared following the general procedure for the preparation of γ-amino acids, and the desired product was obtained after purification by silica gel column chromatography (Hexane/EtOAc = 1/1). Yellow oil, yield: 51%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29-7.27 (m, 1H), 3.88 (d, *J* = 2.6 Hz, 2H), 3.09 (s, 1H), 2.53 (t, *J* = 2.6 Hz, 1H), 2.43-2.24 (m, 2H), 2.22-2.12 (m, 2H). **^{13}C NMR** (126 MHz, CD_3OD) δ 175.1, 145.6, 129.1, 128.6, 126.6, 87.1, 80.5, 75.3, 72.8, 72.0, 42.1, 32.4, 29.4. **IR** (ATR): *v* = 3285, 2927, 2461, 1630, 1447, 1342, 1061, 921, 762 cm^{-1}. **HRMS** (ESI-, MeOH): *m/z* calcd. 240.1027 $(M - H)^-$, found: 240.1030. **UPC2**: IC column, isocratic CO_2/IPA/TFA = 75:25:0.1, 3 mL/min, 1500 psi, *er* = 50:50.

39 Nemes, A.; Csóka, T.; Béni, S.; Farkas, V.; Rábai, J.; Szabó. D. *J. Org. Chem*. **2015**, *80*, 6267-6274.

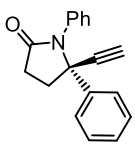
IV.4.5 Synthetic transformations of γ-amino acids



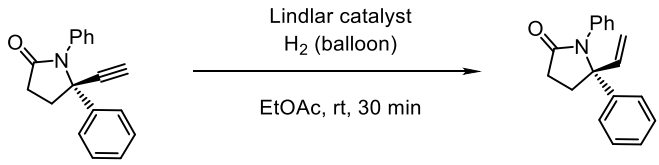
IV.45a **IV.50**

Scheme IV-16. Procedure for γ-lactam formation.

The γ-amino acid **IV.45a** (55.8 mg, 0.20 mmol, 1.0 equiv) and powdered KOH (15.7 mg, 0.28 mmol, 1.4 equiv) were dissolved in DMSO (1.0 mL), and the solution was stirred for 1 h at room temperature. Then, MeI (19.0 μL, 0.30 mmol, 1.5 equiv) was added and the resultant solution was stirred for 1 h at room temperature. After the reaction, water (5 mL) was added and the organic components were extracted with CH_2Cl_2 (3 × 5 mL). Upon removal of the organic solvent, the crude was purified by flash chromatography (Hexane/EtOAc= 3:1) to afford the pure γ-lactam **IV.50** (50.7 mg, 97%, 95:5 *er*) as a light yellow oil.



(*R*)-5-Ethynyl-1,5-diphenylpyrrolidin-2-one (IV.50). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.0 Hz, 2H), 7.35-7.30 (m, 5H), 7.21 (t, *J* = 7.5 Hz, 1H) 7.09 (t, *J* = 7.4 Hz, 1H), 2.93-2.83 (m, 1H), 2.80 (s, 1H), 2.77-2.69 (m, 2H), 2.48-2.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5, 140.3, 136.9, 128.7, 128.5, 128.3, 126.4, 126.2, 125.4, 83.5, 76.4, 66.4, 40.3, 30.8. **IR (ATR):** *v* = 3283, 3061, 2923, 2107, 1699, 1347, 752 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 284.1039 $(M + Na)^+$, found: 284.1046. **UPC2**: IB column, isocratic CO_2/IPA = 90:10, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = +56.5 (*c* = 0.06, $CHCl_3$).

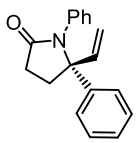


IV.50 **IV.51**

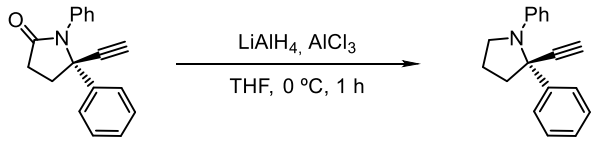
Scheme IV-17. Procedure for the formation of vinylic γ-lactam **IV.51**.

A Schlenk tube was charged with γ-lactam **IV.50** (52.4 mg, 0.20 mmol, 1.0 equiv) and Lindlar catalyst (5 mg, 5 wt% palladium on calcium carbonate), and then the reactor was evacuated/filled with H_2 (balloon) for three times. Hereafter, EtOAc (1 mL) was added and the

reaction mixture was stirred under a H_2 atmosphere (balloon) for 30 min at room temperature and monitored by NMR. The reaction mixture was filtered through Celite. The solvent in the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (Hexane/EtOAc= 3:1) to afford the pure vinylic γ-lactam **IV.51** (45.3 mg, 86%, 97:3 *er*) as a yellow solid.



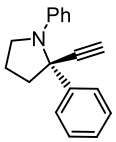
(*R*)-1,5-Diphenyl-5-vinylpyrrolidin-2-one (IV.51). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.1 Hz, 1H), 7.19-7.18 (m, 4H), 7.10-7.03 (m, 1H), 6.31 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.47-5.44 (dd, *J* = 17.0, 10.8 Hz, 2H), 2.63-2.59 (m, 2H), 2.51-2.44 (m, 1H), 2.34-2.27 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1, 142.0, 138.2, 137.1, 128.6, 128.3, 127.7, 126.9, 125.5, 125.4, 117.3, 72.6, 37.1, 30.2. **IR (ATR):** *v* = 3093, 2978, 2926, 1892, 1687, 1356, 758 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 286.1216 $(M + Na)^+$, found: 286.1202. **UPC2**: IA column, isocratic CO_2/ACN = 80:20, 3 mL/min, 1500 psi, *er* = 97:3, $[\alpha]_D^{25}$ = -1.9 (*c* = 0.10, $CHCl_3$).



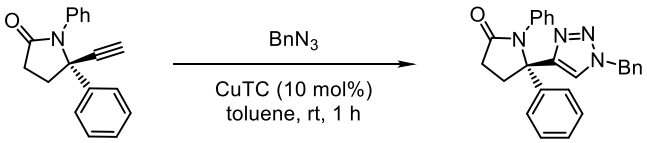
IV.50 **IV.52**

Scheme IV-18. Procedure for pyrrolidine **IV.52** formation.

An oven-dried round bottom flask was charged with γ-lactam **IV.50** (52.4 mg, 0.20 mmol, 1.0 equiv), anhydrous $AlCl_3$ (53.3 mg, 0.40 mmol, 2.0 equiv) and THF (1 mL). Then $LiAlH_4$ (37.9 mg, 1.00 mmol, 5.0 equiv) was added in one portion at 0 ºC and the mixture was allowed to warm up to rt and stirred for 1 h. After full consumption of lactam **IV.50**, the mixture was quenched with saturated NH_4Cl aqueous solution, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Pyrrolidine **IV.52** (47.9 mg, 97%, >99:1 *er*) was obtained as a yellow oil upon flash chromatographic purification (Hexane/EtOAc= 3:1).



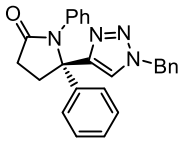
(*R*)-2-Ethynyl-1,2-diphenylpyrrolidine (IV.52). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.23 (m, 1H), 7.13-7.10 (m, 2H), 6.67 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 9.0 Hz, 2H), 3.87-3.83 (m, 1H), 3.68-3.64 (m, 1H), 2.67-2.62 (m, 1H), 2.53 (s, 1H), 2.27-2.18 (m, 2H), 2.11-2.04 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1, 143.5, 128.6, 128.4, 127.2, 125.7, 116.8, 114.9, 85.3, 73.0, 64.5, 50.5, 48.4, 23.1. **IR (ATR):** ν = 3281, 3025, 2926, 1597, 1503, 1338, 748 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd. 248.1435 $(M + H)^+$, found: 248.1434. **UPC2**: IB column, isocratic CO_2/MeOH = 99:1, 3 mL/min, 1500 psi, *er* >99:1, $[\alpha]_D^{25}$ = +189.8 (*c* = 0.10, $CHCl_3$).



IV.50 **IV.53**

Scheme IV-19. Procedure for triazole **IV.53** formation.

A mixture of γ-lactam **IV.50** (52.4 mg, 0.20 mmol, 1.0 equiv) and copper (I) thiophene-2-carboxylate (CuTC) (3.8 mg, 0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was cooled in an ice-water bath. Subsequently, benzyl azide (30.0 μL, 0.24 mmol, 1.2 equiv) was added slowly, and the reaction mixture allowed to warm to room temperature, stirred for 1 h and monitored by TLC. The reaction was quenched by saturated NH_4Cl aqueous solution, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/EtOAc= 3:1) to afford the desired product **IV.53** (62.4 mg, 82%, 95:5 *er*) as a yellow oil.



(*S*)-5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1,5-diphenylpyrrolidin-2-one (IV.53). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.44 (d, *J* = 7.2 Hz, 2H), 7.39-7.36 (m, 2H), 7.34-7.31 (m, 1H), 7.29-7.27 (m, 3H), 7.07-6.98 (m, 5H), 6.95 (s, 1H), 6.86 (d, *J* = 6.4 Hz, 2H), 5.49 (d, *J* = 15.2 Hz, 1H), 5.27 (d, *J* = 15.2 Hz, 1H), 3.65-3.58- (m, 1H), 2.64-2.61 (m, 2H), 2.43-2.39 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2, 148.9, 142.7, 137.0, 134.5, 129.0, 128.7, 128.5, 128.4, 127.9, 127.3, 126.8, 126.3, 126.1, 124.5, 70.5, 54.0, 37.7, 29.9. **IR (ATR):** ν = 3134, 3061, 2952, 2242, 1689, 1597, 1345, 694 cm^{-1}. **HRMS** (ESI+, MeOH): *m/z* calcd.

417.1677 $(M + Na)^+$, found: 417.1686. **UPC2**: IA column, isocratic CO_2/MeOH/DEA = 75:25:0.1, 3 mL/min, 1500 psi, *er* = 95:5, $[\alpha]_D^{25}$ = -64.5 (*c* = 0.10, $CHCl_3$).

IV.4.6 Crystallographic data

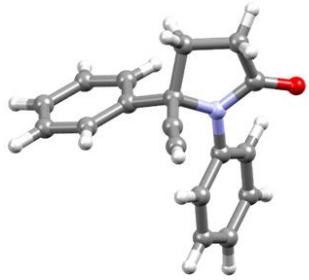


Table IV-5. Crystal data and structure refinement for **IV.50** (CCDC-1574299).

Empirical formula	$C_{18}H_{15}NO$	
Formula weight	261.31	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*P*2(1)2(1)2(1)	
Unit cell dimensions	*a* = 9.76561(5) Å	α = 90°
	b = 11.08490(6) Å	β = 90°
	c = 13.12357(7) Å	γ = 90°
Volume	1420.638(13) $Å^3$	
Z	4	
Density (calculated)	1.222 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	552	
Crystal size	0.10 x 0.10 x 0.06 mm^3	
Theta range for data collection	2.405 to 66.263°	
Index ranges	-23<=h<=25,-22<=k<=28,-28<=l<=31	
Reflections collected	135156	
Independent reflections	24051[*R*(int) = 0.0394]	
Completeness to theta = 66.263°	96.3%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.985 and 0.758	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	24051/ 0/ 241	
Goodness-of-fit on F^2	1.051	
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0277, *wR*2 = 0.0738	
R indices (all data)	*R*1 = 0.0321, *wR*2 = 0.0762	
Flack parameter	*x* =0.06(10)	
Largest diff. peak and hole	0.543 and -0.241 e·$Å^{-3}$	

Chapter V

General conclusions

UNIVERSITAT ROVIRA I VIRGILI
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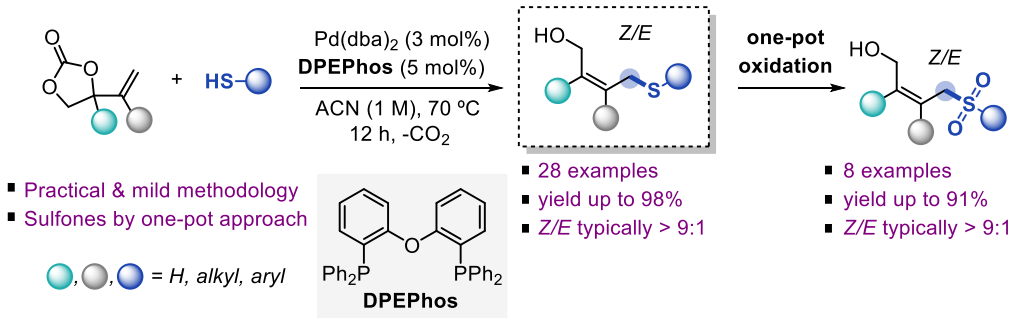
José Enrique Gómez Pulido

V.1. General conclusions

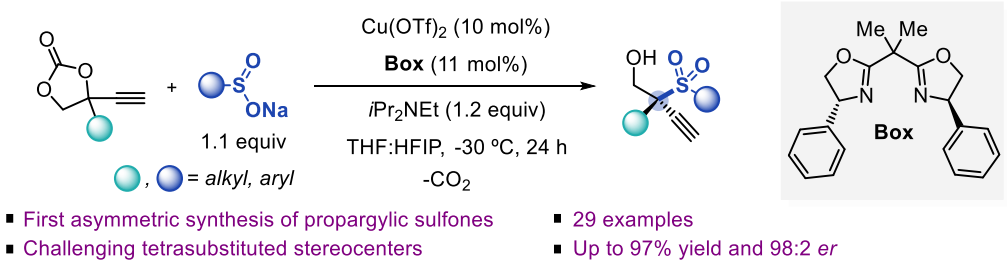
To conclude this doctoral dissertation, it is useful to reflect on the degree to which our initial objectives have been met. This PhD thesis aimed at developing new TM-catalyzed stereo- and enantioselective processes for the synthesis of previously inaccessible stereodefined and chiral building blocks useful in fine chemical and pharmaceutical synthesis. In this regard, the use of functionalized heterocycles such as cyclic organic carbonates and minimally strained lactones have been considered as modular substrates. In total, the results of three projects have been disclosed in this thesis.

As described in **Chapter II**, a new methodology aiming at stereoselective synthesis of highly functionalized (*Z*)-configured allylic thioethers and their corresponding (*Z*)-allylic sulfones has been developed. This protocol based on a Pd-catalyzed thiolation of vinyl cyclic carbonate substrates features good yields and high (*Z*)-selectivity. Although effective methodologies for the synthesis of allylic thioether/sulfones are well established, a general catalytic methodology for the stereoselective synthesis of (*Z*)-configured tri- and tetra-substituted allylic thioethers/sulfones remained previously elusive. Our newly developed procedure therefore offers complementary synthetic potential as clearly demonstrated by the synthesis of 28 thioethers and 8 sulfones. Key to the high (*Z*) selectivity found in these transformations was the *in situ* generation of a six-membered palladacycle previously revealed by DFT calculations. Importantly, the ligand employed (DPEPhos) turned out to be crucial to achieve such a high selectivity. Extension of the repertoire of nucleophiles (*i.e.*, S-centered ones) that can be used to deliver highly substituted and stereodefined linear allylic compounds marks a useful step forward in synthetic chemistry.



Scheme V-1. *Chapter II*: Pd-catalyzed synthesis of (*Z*)-configured allylic thioethers and sulfones.

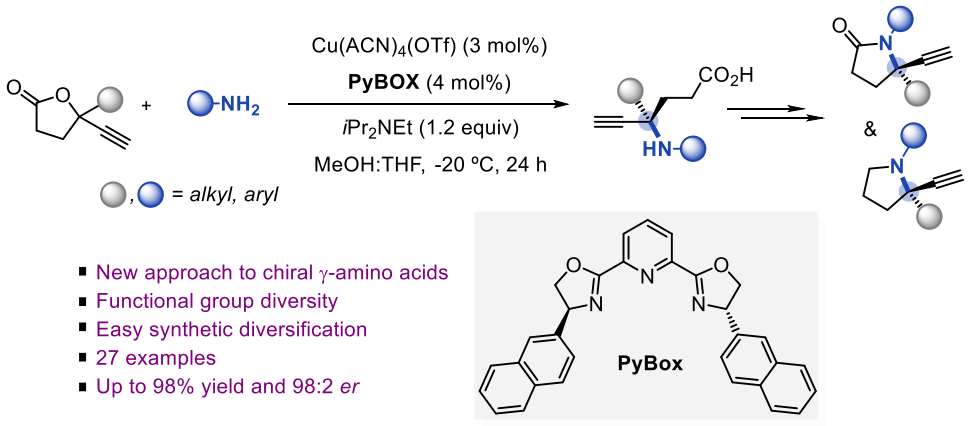
In **Chapter III** we describe the first asymmetric synthesis of tertiary propargylic sulfones. These building blocks are of significant importance in organic synthesis and medicinal chemistry. The recently introduced alkyne-functionalized cyclic organic carbonates inspired us to pursue a copper-catalyzed asymmetric propargylic sulfonylation reaction of these versatile precursors by using sulfinate salts. This practical method provided a new approach targeting the construction of sulfur-containing, tetrasubstituted carbon stereocenters featuring high enantioselectivity and wide functional group diversity. Moreover, this synthetic route can be scaled up as demonstrated by the preparation of gram quantities of a representative tertiary sulfone while maintaining high enantioselectivity. The applicability of the transformation was demonstrated by various functionalization reactions of the tertiary β-hydroxy sulfone building blocks. Finally, a catalytic cycle was proposed suggesting the key intermediacy of copper-allenylidenes, although further studies are ongoing in order to support our mechanistic hypothesis. Importantly, the developed protocol is one of the very few examples of alkyne-substituted cyclic organic carbonates used as modular substrates in asymmetric synthesis, and thus such building blocks show great prospective as versatile starting points in synthetic development.



Scheme V-2. *Chapter III*: Cu-catalyzed enantioselective construction of tertiary propargylic sulfones.

Lastly, in **Chapter IV** a new protocol that enables the efficient assembly of enantioenriched γ,γ-disubstituted γ-amino acids is reported. Notably, in this project we took advantage of the catalytic formation of copper-allenylidene intermediates that can be intercepted by a series of amine nucleophiles in an enantioselective fashion allowing the ring opening aminolysis of minimally strained, alkyne-substituted five-membered lactones. The reaction temperature and the choice of the employed tridentate ligand were key to control both the overall efficiency as well as the asymmetric induction in this reaction manifold. Fine-tuning of these parameters led to an ample scope of 27 amino acid products with wide functional group diversity and high

enantiomeric ratios. The versatility of the amino acid products was also showcased by the synthesis of cyclic enantioenriched products, such as γ-lactams and pyrrolidines.



Scheme V-3. *Chapter IV*: Cu-catalyzed enantioselective synthesis of γ-amino acids.

Overall, the methods described in this thesis support our initial hypothesis that cyclic organic carbonates and related heterocycles are valuable precursors and can be employed to design novel types of TM-mediated transformations in synthetic organic chemistry. A key common factor in the above-mentioned transformations is the presence of suitable functionalities in the heterocyclic substrates being of vital importance; the presence of either vinyl or alkynyl groups has permitted to develop new and challenging stereoselective/asymmetric allylic and propargylic substitution reactions that proved to be so far elusive. TM-catalysis plays a crucial role in this new sub-area, and serves as a principal strategy to enhance the overall reactivity and stereocontrol in several organic conversions. Functional heterocyclic precursors such as cyclic carbonates, lactones and alike therefore hold great promise to be applied in a variety of organic transformations including the ones developed in this thesis, new cross-coupling processes, macrocyclic ring formation through [*n* + *m*] cycloaddition reactions, and stereocontrolled isomerization reactions.

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Chapter VI

Annex

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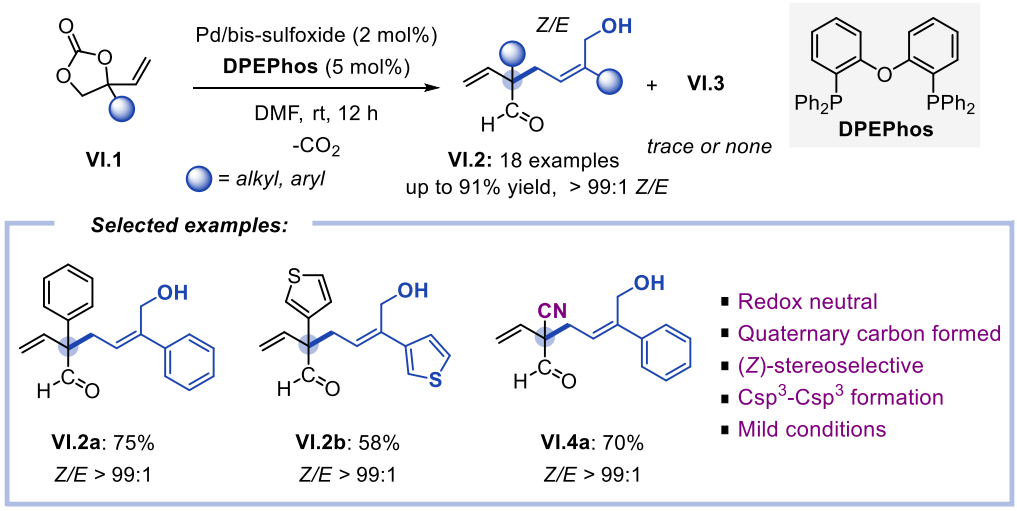
STEREOSELECTIVE SYNTHESIS OF SULFONES AND AMINO ACIDS FROM FUNCTIONALIZED HETEROCYCLES
José Enrique Gómez Pulido

During the development of these doctoral studies, the reactivity of cyclic carbonates and related heterocycles (lactones) has been also explored through different collaborative projects. This chapter is dedicated to briefly summarize those projects, although they will not be discussed in detail.

VI.1 A domino process toward functionally dense quaternary carbons through Pd-catalyzed decarboxylative C(sp^3)-C(sp^3) bond formation

Transition-metal catalyzed decarboxylative processes have emerged as attractive and powerful methodologies in synthetic chemistry and they are regarded as a versatile tool for total synthesis since these reactions occur in a single step under mild conditions and produce minimal waste. However, intermolecular coupling of reaction partners to generate highly functionalized quaternary carbons with new C(sp^3)-C(sp^3) bond formation via decarboxylative methodologies is usually elusive. Conventional methods to prepare such motifs usually require tedious steps and only limited, direct strategies have been developed. Consequently, it is essential to consider novel approaches that enable smooth access towards their synthesis.

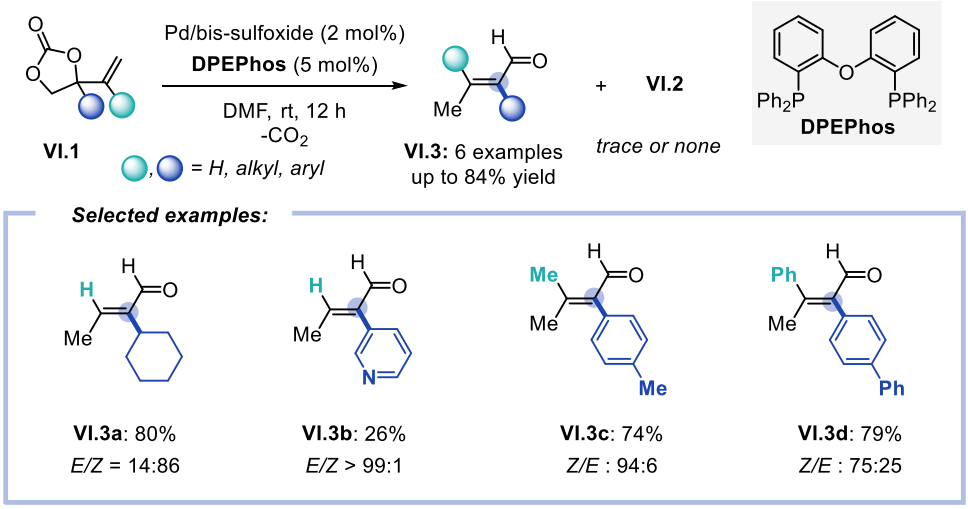


Scheme VI-1. Pd-catalyzed decarboxylative transformation of VCCs towards C(sp^3)-C(sp^3) bond formation. The (*Z*) configuration refers to the allylic fragment.

In this regard, in this project we developed an efficient protocol to forge functionally dense quaternary carbons via a Pd-catalyzed decarboxylative transformation of vinyl cyclic carbonates (VCCs) (Scheme VI-1).

Unlike previously unveiled Pd-catalyzed decarboxylation reactions of VCCs (Chapter I and II), under strict anhydrous conditions and in the absence of a suitable electrophile or nucleophile, the VCC itself can produce a nucleophilic species *in situ* through an umpolung event, and engage with a second decarboxylated VCC to form unusual cross-coupled products containing an all-carbon quaternary center **VI.2**. These products feature stereocenters substituted by a synthetically attractive aldehyde, a vinyl and a multisubstituted (*Z*)-configured allylic alcohol fragments that can be selectively modified to obtain other functional scaffolds (*e.g.*, **VI.4a**). Notably, these products were isolated in remarkably high yields (up to 91%)

Unexpectedly, the utilization of alkyl-substituted carbonates and carbonate substrates incorporating heterocyclic and/or disubstituted double bonds gave selectively rise to stereodefined crotonaldehydes **VI.3** (Scheme VI-2), where trace amounts of the former more complex aldehyde products **VI.2** were noted. To provide a rationale for this interesting finding, the mechanism of this domino reaction was studied using DFT calculations. These computational studies supported a complex scenario where subtle electronic effects exerted by the cyclic carbonate substituents are key to direct the formation either aldehyde product.



Scheme VI-2. Alternative products obtained in the carbonate cross-coupling protocol.

Despite the fact that this work was only focusing on the use of VCCs, we anticipate that these findings will shed light on the development of new catalytic domino reactions for challenging $C(sp^3)$-$C(sp^3)$ bond formations via decarboxylative methodologies. The development of an asymmetric version of this cross-coupling process should be highly attractive.

This work is mainly based on the research developed by Dr. Wusheng Guo, and was carried out in collaboration with Dr. Roshita Kuniyil and Prof. Feliu Maseras at ICIQ, who performed the computational studies leading to the elucidation of the mechanism.[1]

VI.2. Copper-mediated S_N2' allyl-alkyl and allyl-boryl couplings of vinyl cyclic carbonates

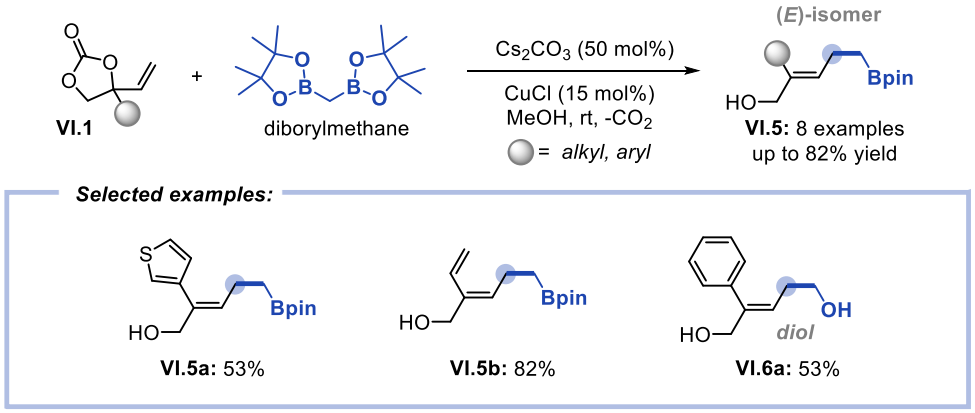
Organoboron compounds are indispensable synthetic intermediates in modern organic synthesis because the C–B bond can be readily and selectively transformed into various C–C and C–heteroatom bonds under appropriate conditions. Additionally, organoboron compounds themselves are found to show unique biological activity. Accordingly, the preparation of functionalized organoboron compounds is an important research objective in synthetic chemistry. In this context, *gem*-diborylalkanes have recently received significant attention since these reagents are useful to straightforwardly prepare homologated organoboron products.

In the area of allylic substitution reactions, the reaction of *gem*-diborylalkanes with various allylic electrophiles affords homoallylic borylation products, which are difficult to prepare by other methods. Usually, diborylmethane reacts with allylic electrophiles to promote selective substitution reactions via S_N2 pathways under Pd/Cu catalysis or metal-free conditions. However, the complementary nucleophilic borylmethylation through an S_N2' mechanism had been rarely studied at the time we started this project.

In order to be able to extend the nucleophilic borylmethylation reaction through an S_N2' mechanism and with the aim to complement previous studies we explored a copper(I)-catalyzed S_N2' allylic alkylation with diborylmethane using various VCCs as allylic surrogates (Scheme VI-3). Interestingly, this new borylmethylation proceed without the addition of a

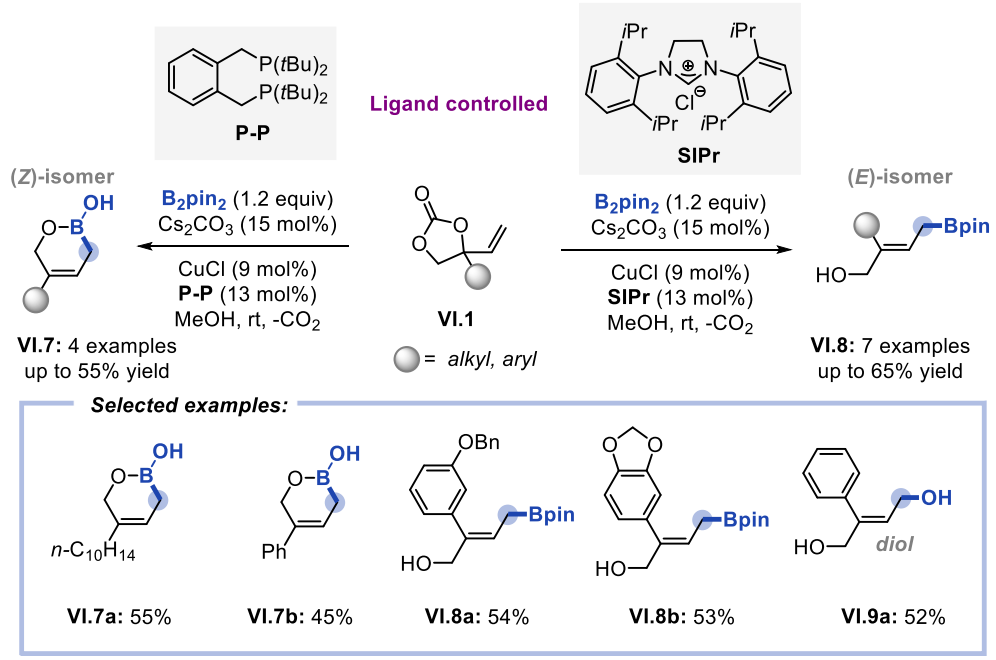
1 Guo, W.; Kuniyil, R.; Gómez, J. E.; Maseras, F.; Kleij, A. W. *J. Am. Chem. Soc*. **2018**, *140*, 3981-3987. Highlighted in *JACS* Spotlights (*J. Am. Chem. Soc.* **2018**, *140*, 3809) and as a Front Cover. The specific contribution of JEG to this work was in extension of the product scope, some of the post-modifications and mechanistic discussions.

ligand, and allowed additional functionality to be retained in the homoallylic borylated product since an alcohol group is generated (**VI.5**), that in combination with oxidation allows to prepare valuable 1,5-diols (*e.g.*, **VI.6a**).



Scheme VI-3. Allyl-alkyl couplings between diborylmethane and vinyl cyclic carbonates.

For the sake of comparison, the copper(I)-catalyzed S_N2' allylic borylation of the same VCCs with B_2pin_2 was also studied (Scheme VI-4).



Scheme VI-4. Stereocontrolled Cu-catalyzed conversion of VCCs into borylated allylic scaffolds.

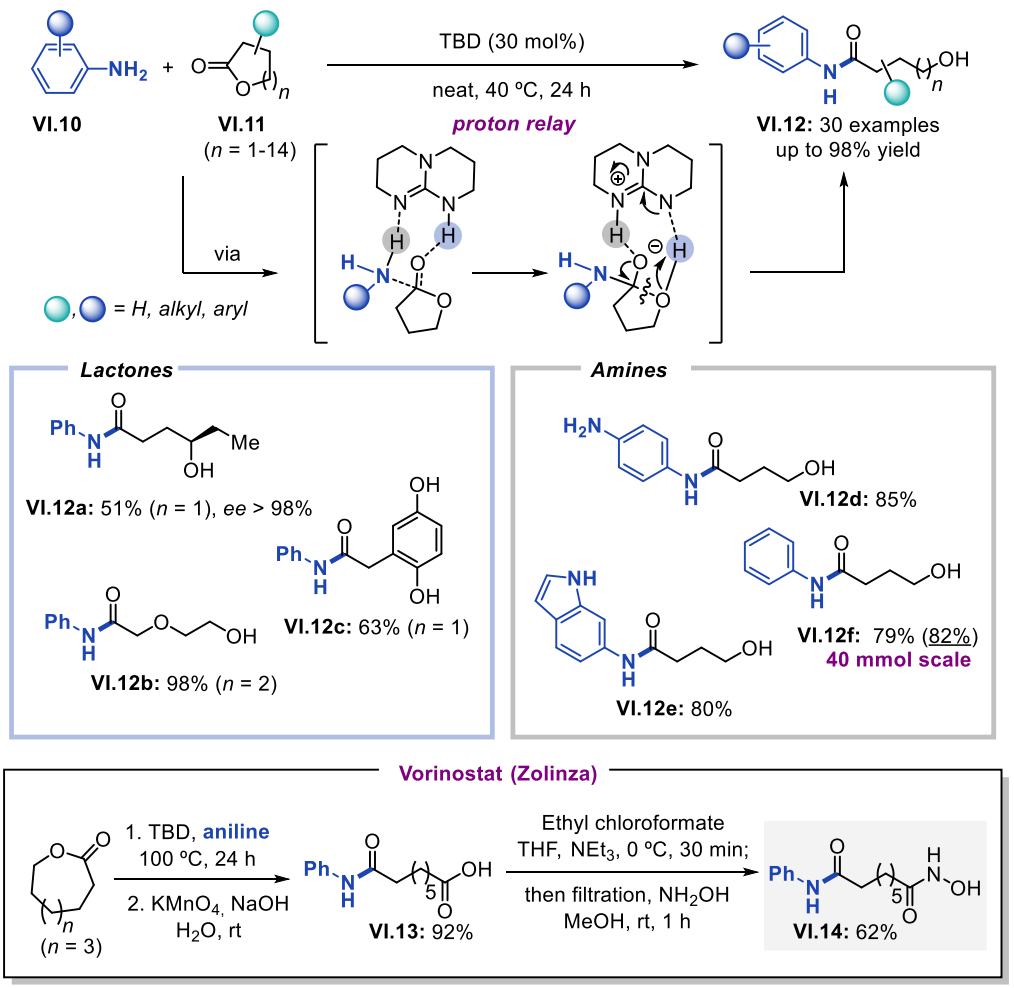
In this latter case, stereocontrol was exerted by a supporting ligand and both (*E*)- or (*Z*)-stereoisomers were selectively obtained. The use of an *N*-heterocyclic carbene (**SIPr**) favored the (*E*)-allylboronate compounds (**VI.8**), whereas application of a bisphosphine (**P-P**) gave a (*Z*) configured intermediate that cyclized *in situ* to give a boracyclic product (**VI.7**). Subsequent oxidative workup of the borylated allylic products provided direct access to valuable (*E*)-1,4-diols (*e.g.,* **VI.9a**)

This work was carried out in collaboration with Dr. Nuria Miralles and Prof. Elena Fernández at University Rovira i Virgili (URV), who performed the borylation studies.[2]

VI.3. Metal-free synthesis of *N*-aryl amides using organocatalytic ring-opening aminolysis of lactones

Amides are very important building blocks in organic synthesis with diverse applications in pharmaceutical, biology and material science, and their formation is thus of fundamental importance. Existing methodologies for amide formation have their inherent limitations, including unfavorable waste profiles, high expense and leaving metal residues in the final products. These features are a growing concern in modern synthetic chemistry. Catalytic ring-opening of non-strained lactones with aromatic amines can offer a straightforward and 100% atom-economical pathway towards relevant *N*-aryl amide scaffolds. However, the electron-deficient nature of aromatic amines and the high thermodynamic stability of non-strained lactones, particularly 5-membered ones such as biomass-derived γ-butyrolactone (γ-BL), represent a huge challenge for the coupling of these reaction partners leading to invaluable *N*-aryl amides, and so far the development of such an attractive catalytic approach has remained elusive.

2 Miralles, N. Gómez, J. E.; Kleij, A. W.; Fernández, E. *Org. Lett*. **2017**, *19*, 6096-6099. This work was highlighted in *Synfacts* **2018**, *14(01)*, 0076. The contribution of JEG was the preparation of the vinyl cyclic carbonate precursors, initial screening in the allylic borylation and discussion of the synthetic and mechanistic details.



Scheme VI-5. Organocatalytic approach towards *N*-aryl amides using lactones and aromatic amines, and the formal synthesis of Vorinostat.

In this work, we reported the first general, metal-free and highly efficient *N*-aryl amide formation **VI.12** from aromatic amines **VI.10** and non-strained lactones **VI.11** under mild operating conditions (40 ºC, neat, open to air), using an organic bicyclic guanidine (TBD) that acts as a proton-shuttle (Scheme VI-5). The process has a broadly applicability towards the conversion of a wide range of lactones **VI.11** with different ring sizes (featuring 5- to 7-, 9-, or 16-membered rings) and an ample variety of electron deficient aromatic amines **VI.10**, leading to the formation of *N*-aryl amides with synthetically useful hydroxyl end-groups **VI.12**.

As an additional advantage of this method, the functional character of this family of *N*-aryl amides allowed for useful post-modification towards relevant, biologically interesting scaffolds, and the formal syntheses of drug-like molecules such as Vorinostat **VI.14** known for the treatment of cutaneous T-cell lymphoma (CTCL), a type of cancer of the immune system.

This project is based on the initial discoveries and optimization studies of Dr. Wusheng Guo, and has been experimentally concluded in collaboration with Dr. Luis Martínez, and computationally supported by Dr. Nuno Bandeira and Prof. Carles Bo (ICIQ) whose input was relevant to the mechanistic features of this reaction.[3]

3 Guo. W.; Gómez, J. E.; Martínez-Rodríguez, L.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *ChemSusChem* **2017**, *10*, 1969-1975. The contribution of JEG was the extension of the product scope, to deliver some of the post-modified compounds and mechanistic discussions of the amide formation manifold.

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