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Asymmetric Transformations under Chiral Brønsted Acid Catalysis: (4+3) Cycloaddition and Allylboration of Imines

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Summary

The use of catalysts able to engage in hydrogen bonding interactions with a given reagent opens up as a useful strategy in the area of organocatalysis. Chiral BINOL-based phosphoric acids and derivatives have demonstrated their proficiency as versatile catalysts for a wide range of synthetic transformations. In this context, our group has started to use those strong Brønsted acids to catalyze different organocatalytic reactions.

The present manuscript compiles the study and development of diverse enantioselective organocatalytic reactions. In this context, investigations were directed to the use of allenamides as oxyallyl cation precursors in the (4+3) cycloaddition with a wide range of electron-rich dienes, catalyzed by BINOL-based chiral Brønsted acids. Under the optimal conditions a complete regioselective reaction furnishes 8-oxabicyclo[3.2.1]octane scaffold with four new stereogenic centers in high yields and excellent stereoselectivities.

Additionally, as a part of a short stay in the laboratories of Prof. Andrei V. Malkov in Loughborough University and a later collaboration between both research groups, the optimization of the kinetic resolution of racemic secondary allyl boronates has been studied with the aim to use these enantiopure allyl boronates in the allylation reaction of primary imines *via* chirality transfer. This leads to the formation of chiral homoallylic primary amines which are very interesting chiral building blocks.

Resumen

El uso de catalizadores capaces de involucrarse en interacciones mediante enlaces de hidrógeno con un determinado reactivo abre una nueva y útil estrategia en el área de la organocatálisis. Los ácidos fosfóricos quirales derivados de BINOL han demostrado su gran capacidad versátil en un gran número de transformaciones sintéticas. En este contexto, nuestro grupo se ha iniciado en la utilización de este tipo de ácidos de Brønsted fuertes para catalizar diferentes reacciones organocatalíticas.

El presente manucrito compila el estudio y desarrollo de diversas reacciones organocatalíticas enantioselectivas. En este contexto, las investigaciones fueron dirigidas al uso de alenamidas como precursores de cationes oxaalílicos en la cicloadición (4+3) con una gran variedad de dienos ricos en electrones catalizado por ácidos de Brønsted quirales derivados del BINOL. Bajo las condiciones óptimas se consigue una reacción completamente regioselectiva para dar estructuras tipo 8-oxabiciclo[3.2.1]octano con cuatro nuevos centros estereogénicos con altos rendimientos y excelentes estereoselectividades.

Adicionalmente, como parte de una estancia breve en los laboratorios del Prof. Andrei V. Malkov en la Universidad de Loughborough y una posterior colaboración entre ambos grupos de investigación, se estudió la optimización de la resolución cinética de alilboronatos secundarios racémicos con el fin de utilizar los alilboronatos enantiopuros en la reacción de alilación con iminas mediante transferencia de quiralidad para obtener aminas primarias homoalílicas quirales como estructuras interesantes.

Laburpena

Hidrogeno-loturen bidez nahasteko gai diren katalizatzaileak erreaktibo jakin batekin estrategia berri eta baliagarri bati hasiera eman diote organotakalisi arloan. Transformazio sintetiko askotarako eraginkor eta erabilera anitzeko katalizatzaileak direla egiaztatu dute azido fosforiko kiralak. Testuinguru honetan, gure taldea Brønsted azido gogor hauekin hasi da lanean erreakzio organokatalitiko ezberdinak katalizatu ahal izateko.

Eskuidatzi honek erreakzio enantioselektibo organokatalitiko ezberdinen ikasketa eta garapena biltzen ditu. Testuinguru honetan, alenamiden erabilerara bideratu zen ikerketa katioi oxalilikoen aurrendari bezala lan dezakete elektroi aberatsak diren dieno ugariekin BINOL deribatuen Brønsted azido kiralengandik katalizatuta den (4+3) zikloadizio erreakzioa. Erreakzioa guztiz erregioselektiboki funtzionatzen du lau zentru estereogeniko berri dituzten 8-oxabiziklo[3.2.1]oktano estrukturak etekin altuekin eta estereoselektibitate bikainekin lortzeko.

Bestela ere, egonaldi motz baten emaitzaz Prof. Andrei V. Malkoven laborategian Loughborough Unibertsitatean eta ikerketa talde bien artean ondorengo kolaborazio baten emaitzaz, alilboronato sekundario razemikoen erresoluzio zinetiko baten optimizazioan lan egin zen. Geroago, alilboronato enantiopuruak eta iminak alilazio erreakzioan erabili ziren kiralitate-transferentziaren bidez interesgarriak diren amina primario homoaliliko kiralak lortu ahal izateko.

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Chapter 1

CHAPTER 1

Introduction

1. Asymmetric Organocatalysis
2. Brønsted Acid Catalysis: BINOL-based Brønsted Catalysts
3. Background: Previous Reports of the Group
4. General Objectives of the Present Work

1. ASYMMETRIC ORGANOCATALYSIS

Asymmetric catalysis is one of the most important and efficient methodologies in organic synthesis for the preparation of chiral compounds in a stereoselective manner. Control over the stereochemical outcome of organic reactions has long been recognized by multiple sectors of synthetic chemistry and proof of this is the Nobel Prize to Knowles, Sharpless and Noyori in 2001 for their work on the use of chiral catalysts for highly enantioselective transformations.

Organocatalysis is one of the three general subfields that, along with enzymatic-[1] and metal-catalysis,[2] comprises the whole area of asymmetric catalysis. It is based on the use of substoichiometric amounts of small organic molecules that do not contain any metal atom in their active site to catalyze a wide range of organic transformations. Although asymmetric catalysis has been governed by bio- and metal-catalysis, organocatalysis[3] has gathered importance as it is indicated by the large number of publications during the last two decades.[4]

Although the first examples that illustrate the ability of small organic molecules to catalyze an enantioselective organic reaction were reported several decades ago with the works of Marckwald (1904),[5] Bredig and Fiske (1912)[6] and Pracejus (1960),[7] the area of enantioselective organocatalysis has became a main focus of research only recently. In fact,

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[1] Enzymatic catalysis: (a) *Enzyme Catalysis in Organic Chemistry*, 3rd ed.; .Drauz, K., Gröger, H., May, O., Eds.; Wiley-VCH: Weinheim, 2012. (b) Tao, J.; Zhao, L.; Ran, N. *Org. Process. Res. Dev.* **2007**, *11*, 259. (c) Benkovic, S. J.; Hammes-Schiffer, S. *Science* **2003**, *301*, 1196. (d) Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139.

[2] Metal-catalysis: (a) *Metal Catalyzed Reactions in Water*; Dixneuf, P. H., Cadierno, V., Eds.; Wiley-VCH: Weinheim, 2013. (b) *Homogeneus Catalysis with Metal Complexes*; Temkin, O. N., Ed.; Springer: Berlin, 2012. (c) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004. (d) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

[3] For the first-time introduction of the term "organic catalysis" see: (a) Langebeck, W. *Angew. Chem.* **1928**, *41*, 740. (b) Langebeck, W. *Angew. Chem.* **1932**, *45*, 97. (c) *Die Organiche Katalysatoren und ihre Beziehungen zu den Fermenten*; Langebeck, W., Ed.; Springer-Verlag: Berlin, 1949.

[4] General reviews in organocatalysis: (a) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (b) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (d) Marson, C. M. *Chem. Rev.* **2012**, *41*, 7712. (e) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* USA **2010**, *107*, 20618. (f) *Asymmetric Organocatalysis:From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A., Groger, H., MacMillan, D. W. C., Eds.; Wiley-VCH: Weinheim, 2005. (h) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304. (i) Yang, J. W.; List, B. *Science* **2006**, *313*, 1584. (j) *Stereoselective Organocatalysis. Bond Formation and Activation Modes*; Rios Torres, R., Ed.; Wiley-VCH: Weinheim, 2013. (k) *Asymmetric Organocatalysis in Natural Product Syntheses;* Waser, M., Ed.; Springer: Heidelberg, 2012. (l) *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules;* Vicario, J. L., Badía, D., Carrillo, L., Reyes, E., Eds.; RSC Publishing: Cambridge, 2010.

[5] Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349.

[6] (a) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7. (b) Bredig, G.; Fiske, P. S. *Chem- Ztg.* **1912**, *35*, 324.

[7] Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.

between 1968 and 1997, there were only a few reports showing the use of small organic molecules as catalysts for asymmetric reactions; probably being the most famous the Hajos-Parrish-Eder-Sauer-Wiechert reaction[8] that was established in the context of the intramolecular aldol reaction catalyzed by L-proline, that was used in the preparation of chiral precursors required for the synthesis of steroids (see Scheme 1.1).
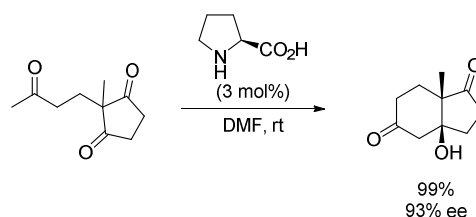
Scheme 1.1

In these early publications there was not a strong emphasis on the potential benefits of using these small organic molecules as catalysts and were focused only on individual transformations. This situation began to change with important contributions to this field such as the enantioselective epoxidation of simple alkenes catalyzed by enantioenriched ketones realized by Shi and Yang,[9] and by the first examples of hydrogen-bonding catalysis in the asymmetric Strecker reaction by Jacobsen and Corey between 1998 and 1999.[10] However, it was not until 2000 when chemists realized that the use of organic molecules as chiral catalysts could become a whole field of research within the area of asymmetric synthesis that occurred with the publication of the key seminal examples by List, Lerner and Barbas III[11] on the L-proline catalyzed aldol reaction and by Ahrendt, Borths and MacMillan[12] on the imidazolidinone-catalyzed Diels-Alder reaction.[13]

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[8]   (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Hajos, Z. G.; Parrish, D. R. *German Patent* DE 2102623, 1971. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496. (d) Eder, U.; Sauer, G.; Wiechert, R. *German Patent* DE 2014757, 1971.

[9]   (a) Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491.

[10] (a) Sigman, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

[11] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[12] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[13] MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

The contribution of List, Lerner and Barbas III was significant because they reported the first enantioselective intermolecular aldol reaction between acetone and a variety of aldehydes catalyzed by L-proline supporting that the mechanism of Hajos-Parrish reaction could be extended to other transformations with higher applications. Mechanistic studies demonstrated that enamine intermediates were present as nucleophiles in the reaction (see Scheme 1.2). At the same year, MacMillan introduced the iminium activation concept in the first enantioselective organocatalytic Diels-Alder reaction catalyzed by a chiral imidazolidinone salt. He reported that the imidazolidinone catalyst would activate α,β-unsaturated carbonyl compounds through condensation furnishing the corresponding iminium ion, which consequently lowered the energy of its LUMO, becoming activated as dienophile towards the Diels-Alder cycloaddition with electron-rich dienes (see Scheme 1.2).
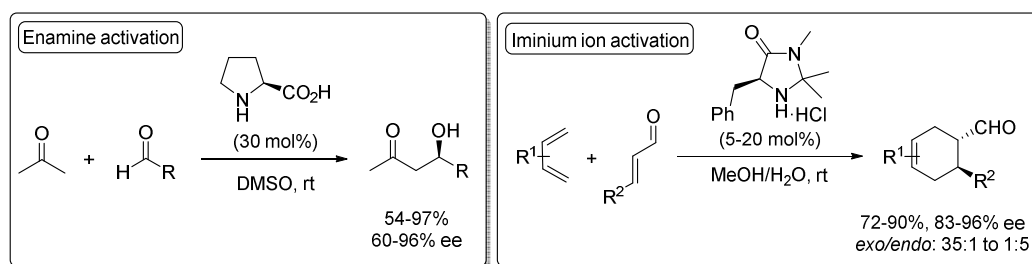
Scheme 1.2

After these seminal works, the field has experienced an impressive growth with the emergence of new activation mechanisms and their application to multiple organic transformations. The number of publications on the topic has impressively increased and organocatalysis is nowadays commonly viewed as the third pillar of asymmetric catalysis, with the other two being biocatalysis and metal catalysis. Other important contributions to this field also took place between the last decades of the 20th century and the first one of the 21st, in which other activation manifolds were also reported such as phase-transfer catalysis,[14] H-bonding catalysis,[15] NHC[16] and the use of chiral Brønsted acids to catalyze asymmetric transformations.[17]

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[14] (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

[15] (a) Sigman, M. S.; Jacobsen, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (c) Sigman, M. S.; Jacobsen, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (d) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

[16] Selected reviews on NHC: (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (b) Dwivedi, S.; Gupta, S.; Das, S. *Curr. Organocatal.* **2014**, *1*, 13. (c) Bugaut, X.; Glorius, F.; *Chem.*

The most important progress for the success of organocatalysis has been the classification of the generic modes of catalyst activation, induction and reactivity. These models can be further used as templates in new synthetic transformations due to their simplicity and broad scope of application. Moreover, this has lead to the development of new catalysts that are useful in a wide range of asymmetric reactions.

There are two main ways to classify organocatalysts; depending on the interaction between substrate and catalyst in the transition state (named *covalent* and *non-covalent* catalysis);[3c] or according to their acid/base reactivity (see Figure 1.1).

Covalent catalysis represents those reactions in which the catalysts activate the substrate forming a covalent bond. This method of activation implies that reversible chemical reactions have to be available for the attaching and detaching of the catalyst to the substrate/final product in order to allow activation and catalyst turnover. Chiral amines or aminocatalysts belong to this group participating in many reactions by the formation of azomethine compound (enamine, iminium ion or iminium-radical cation, also known as SOMO catalysis).[18] *N*-heterocyclic carbene[16] or those involving the formation of ylides and phosphinium salts[19] are other important catalysts. On the other hand, *non-covalent catalysis*, is based on weaker interactions between the catalyst and the substrate. One of the most important activation mechanism is that involving the formation of catalyst-substrate complexes by the formation of hydrogen bonds.[20] The formation of chiral ion pairs[21] and the use of tertiary amines as chiral Brønsted base catalysts[22] are also other important methodologies included in this group.

Soc. Rev. **2012**, *41*, 3511. (d) Enders, D.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (f) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

[17]   (a) Rueping, M.; Parmar, D.; Sugiono, E. *Asymmetric Brønsted Acid Catalysis*; Wiley-VCH: Weinheim, 2016. (b) Akiyama, T. Hydrogen-Bond Catalysis or Brønsted-Acid Catalysis? General Considerations. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009.

[18]   For reviews in aminocatalysis: (a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632. (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (d) List, B. *Chem. Commun.* **2006**, 819.

[19]   Selected reviews on chiral phosphine catalysis: (a) Xiao, Y.; Sun, Z.; Kwon, O. *Beilstein, J. Org. Chem.* **2014**, *10*, 2089. (b) Wei, Y.; Shi, M. *Chem. Asian J.* **2014**, *10*, 2720. (c) Xu, L.-W. *ChemCatChem* **2013**, *5*, 2775. (d) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005.

[20]   (a) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009. (b)Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (e) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

[21]   (a) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534. (b) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367. (c) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (d) Jew,
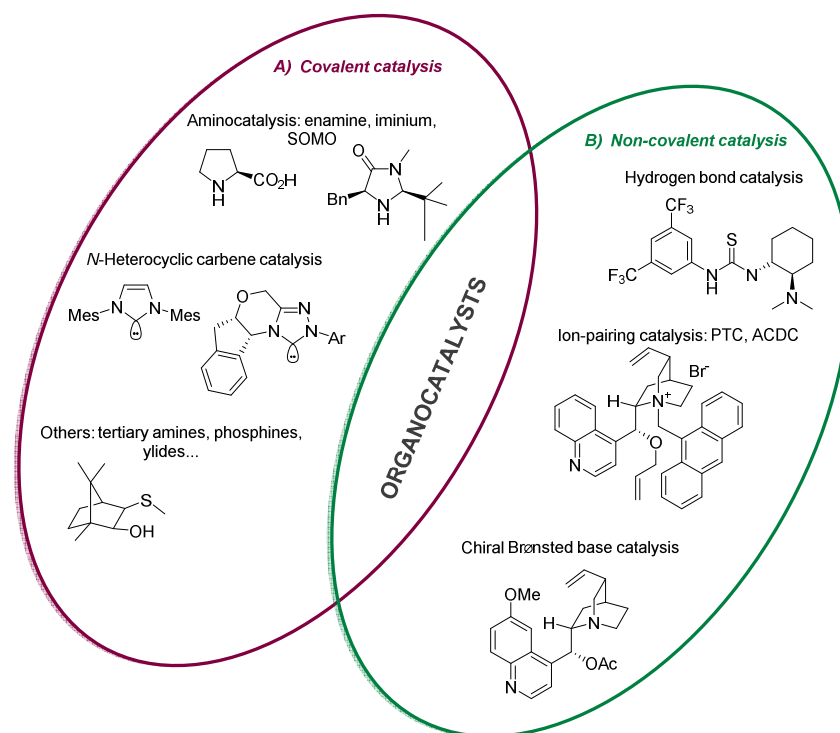
Figure 1.1

Another way to categorize organocatalysts is according to their acid/base reactivity.[23] In this sense, organocatalysts can be classified as Lewis acids, Lewis bases, Brønsted bases and Brønsted acids. Although Lewis acid catalysts are commonly associated to metal catalysis, these are also organic catalysts used to activate electrophiles under this type of acid/base interactions.[24] Electrostatic coordination of the metal-free Lewis acid through Coulomb and dispersion forces to a lone pair of electrons results in the withdrawal of electron density and thereby in the activation of the electrophile toward nucleophilic attack.[25] The most important ones are phase-transfer catalysts (PTC) in which tipically chiral cation-directed catalysts, such as quaternary ammonium

S.; Park, H. *Chem. Commun.* **2009**, 7090. (e) *Asymmetric Phase Transfer Catalysis*; Maruoka, K., Ed.; Wiley-VCH: Weinheim, 2008. (f) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222. (g) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. For ACDC: (h) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518.

22 Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

23 Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.

24 For reviews on Lewis acid organocatalysis: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O´Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c), Shi, Y. *Chem Res.* **2004**, *37*, 488. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (e) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222. (f) Sereda, O.; Tabassum, S.; Wilhelm, R. *Topics Current Chem.* **2009**, *291*, 86. (g) Wang, X.; Lan, Q.; Shirakawa, S.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 321.

25 *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*; Peters, R. Ed.; Wiley-VCH: Weinheim, 2015.

or phosphonium salts, have been used in reaction between two substances located in different immiscible phases where a hydrophobic conterion assist the transport phenomenon.[26] Analogously, Lewis base catalysts can be use to enhance the nucleophilicity or the electrophilicity of a reagent. These activate the substrate *via* nucleophilic addition which undergoes a reaction and then releases the product and the catalyst for further turnover. Different modes of activation depend on the selected Lewis base converting the substrates either into activated nucleophiles (e.g. enamine catalysis) or electrophiles (e.g. iminium catalysis).[18] The crucial effect of Lewis acids and Lewis bases on the reactivity is associated with changes in frontier orbital energies of the reaction components and consists of a lowering of the energy of the LUMO of the electrophile and an increase of the energy of the HOMO of a nucleophile, respectively. On the other hand, Brønsted bases operate through a partial deprotonation of a pronucleophile substrate providing new species with improved nucleophilicity due to the formation of an ion-pair that maintains the chiral environment during the reaction.[22] Finally, Brønsted acid activation takes place through the protonation of the substrate or *via* H-bonding interactions for the activation of the electrophile.[27] The weak nature of these interactions is capable to decrease the electronic density of the electrophile favouring the nucleophilic attack.

In the following section methodologies involving Brønsted acid activation will be presented due to their direct relationship with the research presented in this manuscpript.

[26] (a) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367. (b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (c) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090.

[27] Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

2. BRØNSTED ACID CATALYSIS: BINOL-DERIVED CHIRAL BRØNSTED CATALYSTS

As mentioned, Brønsted acids interact with the substrates (a Lewis base) releasing electronic density and favouring the activation towards nucleophilic attack. These have demonstrated that are highly efficient and versatile catalysts for relevant synthetic transformations.[28] Brønsted acids are classified into two categories; weak Brønsted acids, such as ureas,[29] thioureas[30] and diol derivatives,[31] which are also called H-bonding catalysts; and on the other hand, stronger Brønsted acids, such as phosphoric acids, sulfonic acids and related derivatives.

The use of catalysts incorporating multiple hydrogen bond donors opens up as a useful strategy resulting in an increase of enthalpic binding affinities between the catalyst and the substrate which provide better organization in the transition states and as a consequence, better stereoselectivities. Thioureas have emerged as one of the most efficient classes of catalysts working under H-bonding activation, with a superior ability than ureas due to the higher N-H acidity and lower tendency to self aggregation.

The first example of chiral Brønsted acid catalysis was reported by Jacobsen in the enantioselective Strecker reaction catalyzed by a chiral thiourea and represented a real breakthrough in the field, demonstrating the enormous power of H-bonding activation.[32] Computational studies showed that the thiourea catalyst was able to interact with the imine electrophile by formation of a double H-bonded network, which resulted in a rigid transition state that in the presence of bulky substituents at both the amino acid position and the 3-position of the salicylimine moiety accounted for the high enantioselectivity observed (see Scheme 1.3). This seminal work indicated that a chiral Brønsted acid enables discrimination between the enantiotopic faces of an imine substrate *via* hydrogen bonds, opening a new way in

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28 Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

29 Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, *12*, 1919.

30 For reviews on chiral thiourea catalysts: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418.

31 Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

32 (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

enatioselective catalysis without the use of chiral metal catalysts. Later in 2003 Schreiner used thioureas as catalysts for diastereoselective Diels-Alder reactions.[33]
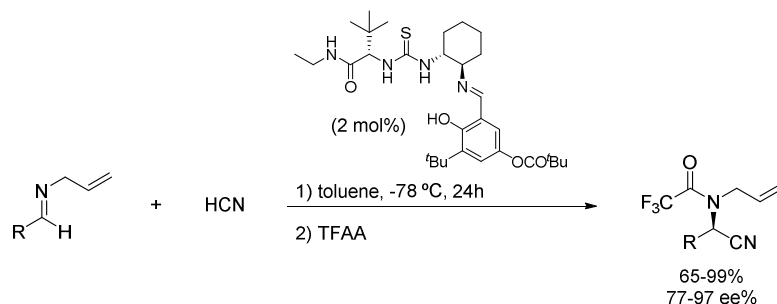
Scheme 1.3

Rawal reported the use of TADDOL as chiral Brønsted acid catalyst on the enantioselective hetero-Diels-Alder reaction.[34] He showed that a simple chiral diol uses H-bonding to catalyze an important family of [4+2] cycloaddition reactions between aminosilyloxy dienes and different aldehydes. Diols functions in the same way as Lewis acids, by activating the carbonyl group through hydrogen bonding. After treatment with acetyl chloride to remove the TBS group and the dimethylamino groups, dihydropyrones were obtained in excellent enantioselectivities and yields (see Scheme 1.4).
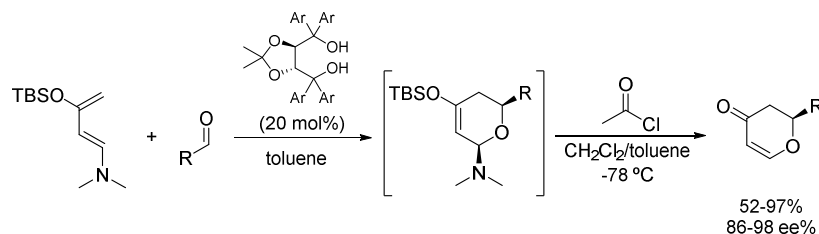
Scheme 1.4

The use of BINOL as chiral Brønsted acids in the enantioselective asymmetric Morita-Baylis-Hillman reaction between cyclohexenone and aldehydes has been demonstrated by Schaus.[35] The catalyst serves to promote the conjugate addition step of the reaction, and then remain hydrogen-bonded to the resulting enolate in the enanioselectivity-determining aldehyde

[33]   (a) Schreiner, P. R.; Wittkopp, A. *Chem. Eur. J.* **2003**, *9*, 407. (b) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

[34]   Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

[35]   McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.

addition step. Presumably, the chiral Brønsted-acid-stabilized enolate formed after addition of the trialkylphosphine would act as the nucleophile in the addition reaction.
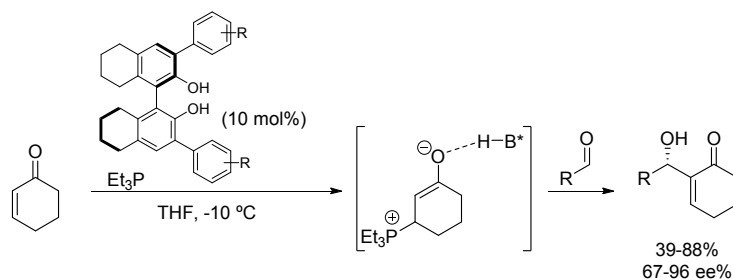
Scheme 1.5

These landmark works have strongly influenced on the development of chiral Brønsted acid catalysis. However, the acidity of the thiourea and alcohol functionalities is rather weak; and consequently, the activation capacity of these catalysts is low.[36] Due to the necessity of stronger Brønsted acids for activating wider range of substrates and compensate this limitation, Terada and Akiyama have evaluated different organic acids that are shown in Figure 1.2, which incorporated strong acidic functionalities.

sulfonic acids
high acidity, free rotation

carboxylic acids
low acidity, free rotation

sulfinic acids
free rotation
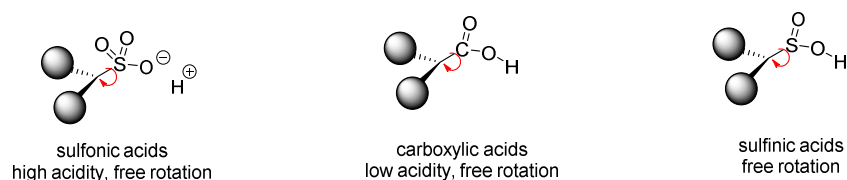
Figure 1.2

Initially, sulfonic acids were surveyed but due to their too strong acidity they probably could not keep H-bonding interactions between a protonated substrate and the conjugated base. These would generate non stable ionic pairs, which would lead to diastereomeric TS and low enantioselectivities. Carboxylic and sulfinic acids have appropriate acidity; however, it would be

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36 Thiourea and urea: Bordwell, F. G.; Algrim, D. J.; Harrelson Jr., J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903. Aliphatic alcohols: (a) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424. (b) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295. pK_a values: For (thio)urea: (c) Li, X.; Deng, H.; Zhang, B.; Li, J. Y.; Zhang, L.; Luo, S. Z.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 450. (d) Jakab, G.; Tancon, C.; Zhang, Z. G.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724. For squaramides: Ni, X.; Li, X.; Wang, Z.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 1786. For DIOL derivatives: Ni, X.; Li, X.; Li, Z.; Cheng, J.-P. *Org. Chem. Front.* **2016**, *3*, 1154. For TADDOL derivatives: (e) Seebach, D.; Beck, A. K.; Bichsel, H.-U.; Pichota, A.; Sparr, C.; Wünsch, R.; Schweizer, W. B. *Helv. Chim. Acta* **2012**, *95*, 1303. (f) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O´Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524.

difficult to provide and efficient chiral environment due to their free rotation around the single bond. Phosphoric acids were found to be interesting due to the possibility to introduce two substituents at the phosphorous atom three atoms away from the acidic proton. This means that a chiral environment can be design closer than in the case of sulfonic, carboxylic or sulfinic acids. Under these premises, Akiyama and Terada put their attention on phosphoric acids due to their structural and chemical features and in 2004 independently presented BINOL-derived phosphoric acids in Mannich reactions.[37] They were selected as chiral sources due to their axially chiral molecule having C_2-symmetry which is crucial in the catalytic design because it supposes that the same catalyst molecule is generated when the acidic proton migrates to the phosphoryl oxygen. They showed an adequate acidity to generate stable electrostatic interactions and due to their chiral environment, the acidic group is more restricted (see Figure 1.3). A chiral *pocket* is formed and free rotation is avoided when the phosphorous atom and the BINOL framework are connected by two P-O bonds. There is also the possibility to change stereoelectronic effects introducing diverse subtituents (G) on the ring system conferring different chiral environments as necessity. However, the most innovative characteristic is probably its bifunctionality; the phosphoryl oxygen (P=O) contains two free electron pairs giving to the molecule Brønsted base functions making phosphate group with acid and base properties.
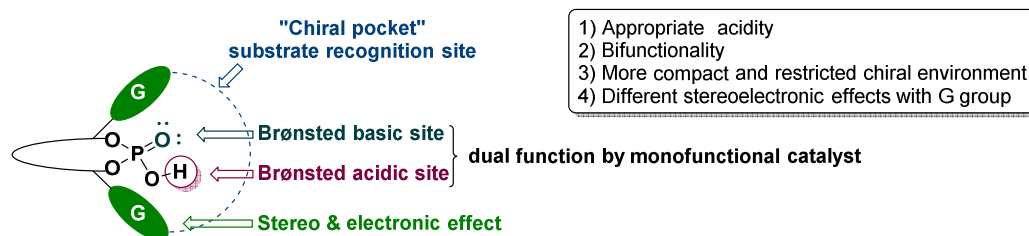

Figure 1.3

There is an important relationship between the catalytic activity and the acidity of the phosphoric acid and surprisingly, pK_a studies are relatively scarce. A general study was published by O´Donoghue and Berkessel with some pK_a´s in DMSO of chiral phosphoric acids and *N*-triflylphosphoramides.[37f] They concluded that the differences in acidity between the different catalysts were not large and that the relative acidity of the catalyst may not be the only factor that influences their catalytic performance. However, it has to be pointed out that measurements of

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37   (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

pK_a values of highly acidic acids in DMSO can provide almost indentical pK_a values (near zero) depending on the experimental procedure employed.[38] A solution came from Rueping and Leito in 2013 when they reported a full study on establishing an acidity scale for the most widely used Brønsted acids which were conducted by using UV/Vis spectrophotometric methods in MeCN.[39] In addition, Cheng and Li reported a theoretical study on the acidities of BINOL phosphoric acids and other related derivatives.[40] From the measurements that were conducted in MeCN it was found that these type of BINOL-based Brønsted acids could be classified on three distinct groups of varying acidity depending on their structure, namely phosphoric acids, *N*-sulfonyl phosphoramides and sulfonyl imides (Figure 1.4). Hydrogenated versions of parent catalysts are also commonly used and it is usual to find several transformations with these catalysts.
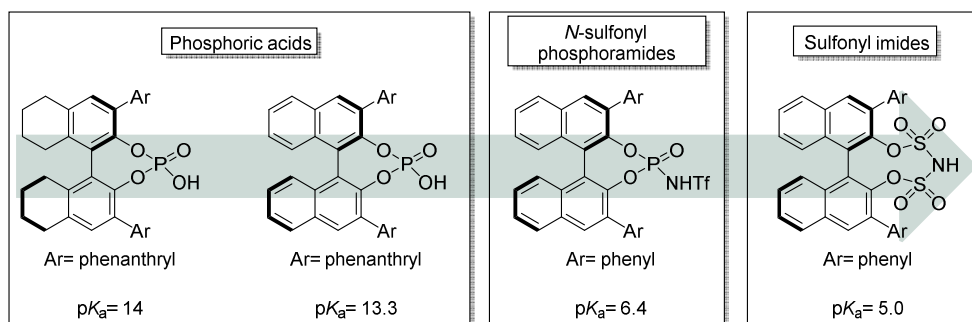
Figure 1.4 pK_a values in MeCN

The mechanism involved in the activation of the electrophile by this type of BINOL-based strong Brønsted acids is a subject of intense debate and in many cases it has not clearly established. In principle, there are three possible ways for the Brønsted acid to interact with the substrate through Brønsted acid/Brønsted base interactions identified as mono-, dual- and bifunctional activation (see Figure 1.5). For mechanisms including the monoactivation manifold the reaction proceeds through a single H-bonding interaction between the catalyst and the substrate. In the case of dual activation, there are additional interactions with the electrophilic substrate that offer higher stabilization of the intermediates. This can imply the formation of a Brønsted acid-substrate complex involving the participation of the phosphoryl oxygen of the catalyst as H-bonding acceptor, forming a second hydrogen bond with a Brønsted-acid site at the

38 Koppel, I. A.; Koppel, J.; Pihl, V.; Leito, I.; Mishima, M.; Vlasov, V. M.; Yagupolskii, R. W.; Taft, R. W. *J. Chem. Soc. Perkin Trans. 2* **2000**, 1125.

39 Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

40 Yang, C.; Xue, X.-S.; Jin, J.-L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 7076.

substrate, establishing a network of two H-bonding interactions between the catalyst and the electrophilic reagent or the exclusive participation of the proton and two Brønsted basic sites of the substrate in a bidentate fashion. Finally, bifuncional activation is probably the mechanistic pathway that covers the largest proportion of this catalysis and implies the activation of both the electrophile and the nucleophile by the catalyst.
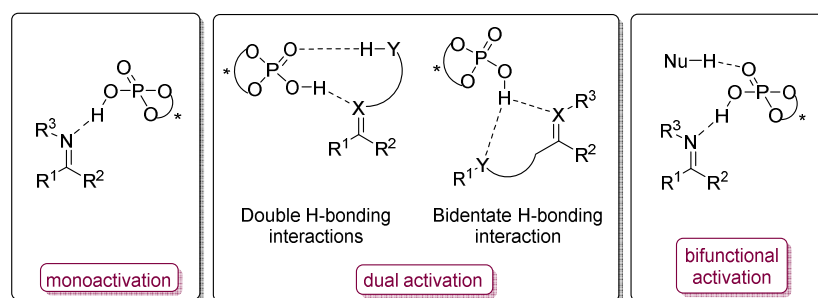

Double H-bonding interactions   Bidentate H-bonding interaction

monoactivation   dual activation   bifunctional activation

Figure 1.5

A good example of a phosphoric acid-catalyzed reaction in which the catalyst operated through the monoactivation manifold is the report by Terada in the context of aza-Friedel-Crafts reaction between *N*-Boc imines and methoxyfuran (see Scheme 1.6).[41] The mechanistic proposal involves the formation of the substrate-catalyst complex through the aforementioned single H-bonding interaction followed by nucleophilic attack of furan. According to the model proposed by Goodman,[42] configuration of E imine is maintained in the transition state and the geometry of the complex would try to avoid steric *clashing* between the Boc group and the large 3,3´-substituents of the BINOL moiety. Addition of 2-methoxyfuran will take place through the less hindered *Re*-face affording the major enantiomer shown in Scheme 1.6.
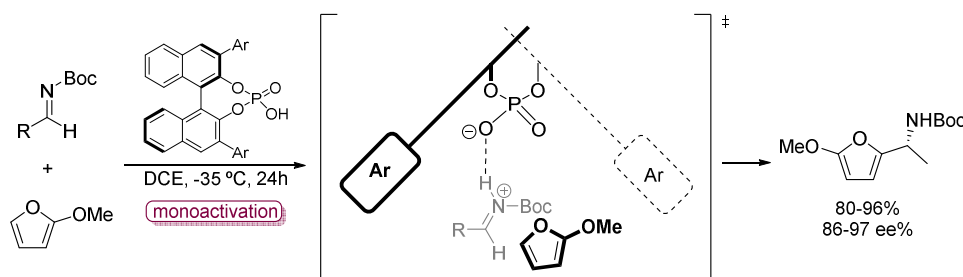
Scheme 1.6

41   Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

42   Reid, J. P.; Simón, L.; Goodman, J. M. *Acc. Chem. Res.* **2016**, *49*, 1029.

Motivated by the desire to activate a wider range of substrates, Yamamoto developed a new type of catalysts which are more acidic than phosphoric acids.[43] They introduced the strongly electron-withdrawing group triflylamide into the phosphate moiety becoming very powerful catalysts due to their higher acidity (see Figure 1.5) and therefore being able to activate unreactive substrates in the presence of phosphoric acids.[44] In this context, an example of a *N*-triflyl phosphoramide catalyzed activation of electrophiles through the monoactivation approach is the conjugate addition of indoles to β,γ-unsaturated-α-ketoesters reported by Rueping.[45] The investigation was started with the use of weak acids such as carbonic acids or diphenyl phosphate, but no reaction was observed resulting in the use of catalytic amounts of *N*-triflylphosphoramide crucial for the formation of the final product (see Scheme 1.7).
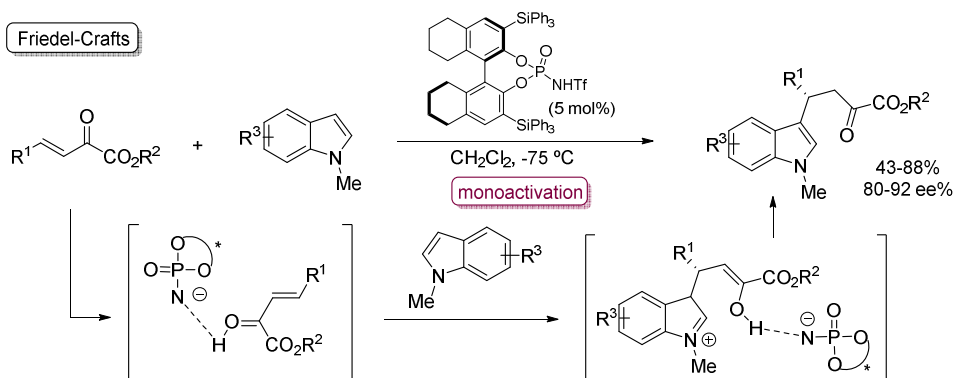
Scheme 1.7

A good example of a chiral phosphoric acid activating the substrate through dual activation can be seen in enantioselective Mannich-type reaction reported by Akiyama and co-workers.[37a] In this report, 2-hydroxyphenyl imines reacted enantioselectively with silyl ketene acetals in the presence of a catalytic amount of a BINOL-based chiral phosphoric acid to give *syn*-Mannich products (see Scheme 1.8). It was found that the *N*-2-hydroxyphenyl substituent of the aldimine was essential to fix its geometry giving the reaction in order to obtain a range of *syn*-diastereoisomers generally in high yields and enantioselectivities. The proposed dual

43 Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

44 (a) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *125*, 11783. (b) Johnston, J. N. *Angew. Chem. Int. Ed.* **2011**, *50*, 2890. (c) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem. Int. Ed.* **2011**, *50*, 6706. (d) Cheon, C.-H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043.

45 Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 593.

activation manifold involved the participation of the acidic proton of the catalyst by protonation of the imines nitrogen and the 2-hydroxy group would form a hydrogen bond with the phosphoryl oxygen to generate a zwitteronic nine-membered cyclic transition state which is attacked by the silyl enol ether. It was also reported that the transition state corresponding to the *si*-facial attack is sterically less favoured than the *re*-facial alternative due to sterically repulsive interaction between 3,3´-aryl substituents and approaching nucleophile.
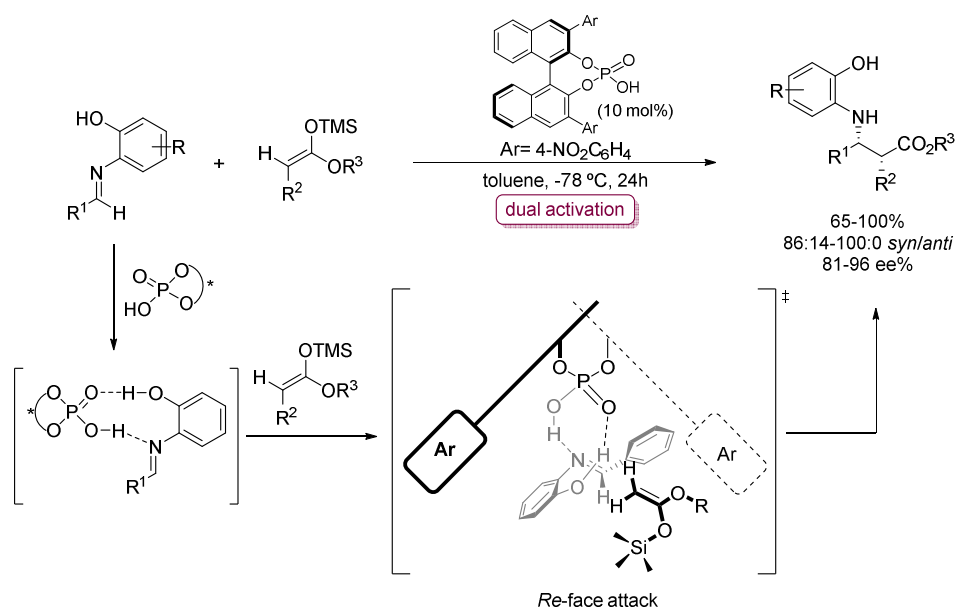
Scheme 1.8

In a similar approach, Terada demonstrated that glyoxylates can also undergo an *anti*-selective hetero-Diels-Alder reaction with dienes to give dihydropyrans.[46] The glyoxylate aldehyde participates in a dual activation mannifold where the aldehyde proton is proposed to be acidic enough to interact with the Lewis basic site of the catalyst and, at the same time, an interaction between the oxygen atom of the aldehyde and the acidic proton on the catalyst would occur generating a rigid substrate-catalyst complex. On one hand, different 3,3´-substituents on the catalyst demonstrated that the reaction proceeded via *exo*-alignment depending on the steric demand of the catalyst leading to *syn* selectivity (see Scheme 1.9). The use of non-bulky groups such as phenyl groups at the 3 and 3´ positions of the catalyst and the steric repulsion between

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46   Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882.

the diene substituents and glyoxylate in the *endo* transition state allow the diene to occupy an *exo* orientation. On the other hand, facial selectivity is determined by the steric hindrance between the diene substituents and the phenyl group of the catalyst, thus lead the attack of the diene through the *Si*-face of the glyoxylate.
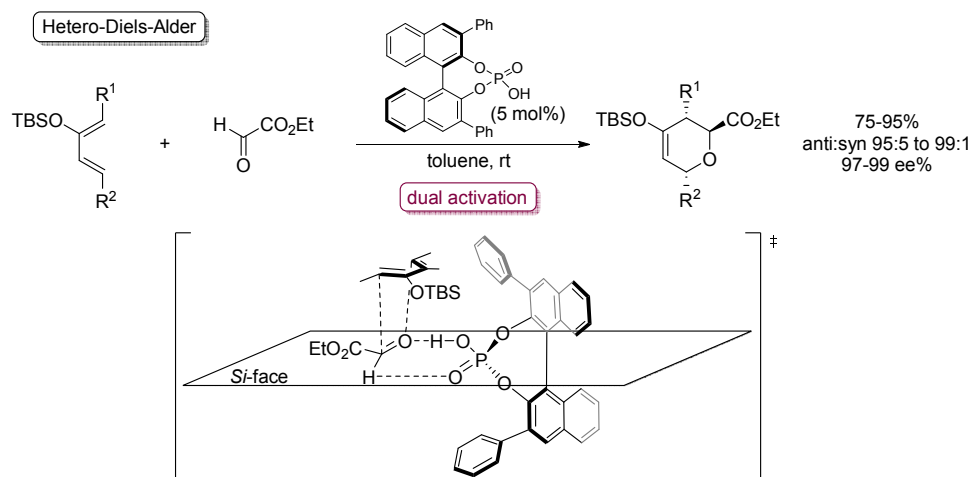
Scheme 1.9

The dual activation by bidentate H-bonding interaction is exemplified with the enantioselective Nazarov cyclization with α-alkoxyketones catalyzed by chiral Brønsted acids to generate cyclopentenones reported by Rueping.[47] In this work, the necessity of *N*-triflyl phosphoramides as more acidic Brønsted acids was observed; the acidic proton of the catalyst is involved in a bidentate interaction between the alkoxy and the carbonyl group of the substrate as it is shown in Scheme 1.10. Subsequent conrotatory 4π electrocyclization leads to an oxyallyl cation intermediate which forms an enolate through the elimination of a proton. Successive protonation of this enolate should results in the formation of the final product and regenerates the catalyst.
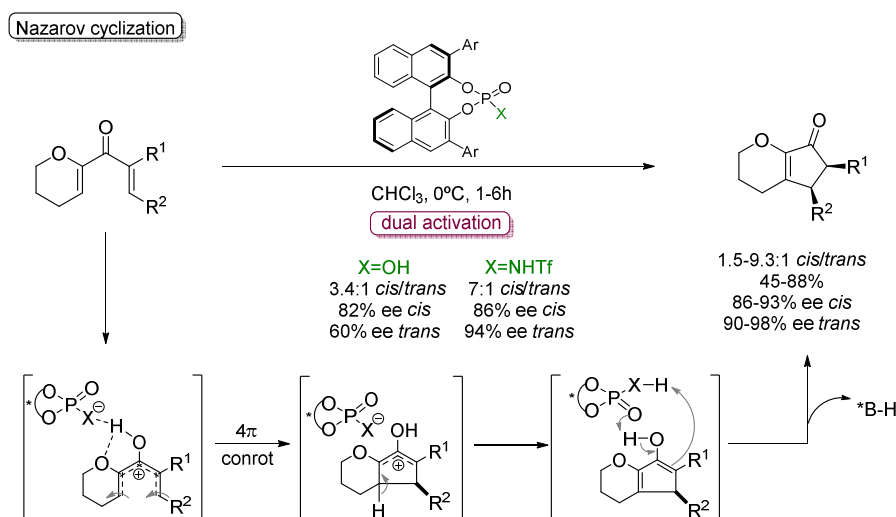
Scheme 1.10

In spite of these previous selected examples of mono- and dual activation manifolds, bifunctional activation covers the largest proportion of BINOL-derived Brønsted acid-catalyzed transformations. As it is mentioned before, this involves the participation of the phosphate moiety as a bifunctional entity that interacts with the electrophile by donating the acidic proton and simultaneously activates the pronucleophile by the participation of the phosphoryl oxygen as Brønsted basic site. A good example of this behaviour is shown in Scheme 1.11. Terada and co-workers showed their results simultaneously with Akiyama in the presence of Brønsted acids in a Mannich reaction between acetyl acetone with *N*-Boc proteceted imines (see Scheme 1.11).[37b]

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47   Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097.

Thus, the phosphoric acid catalyst electrophilically activates the imine through the acidic proton, and the Brønsted basic phosphoryl oxygen interacts with the O-H proton of the enol tautomer leading to secondary amine products enantioselectively in high yields. The protective group of the imine was found to be crucial to achieve a high enantioselectivity observing that with a low steric demand of the protecting group the ee was reduced. Later, Goodman and Simón[48] explained the final stereochemistry of the reaction reporting a model for the enantioselectivity of reactions with imines catalyzed by BINOL-phosphoric acids catalysts which is applicable for other reactions. The model appears to work in all 40 cases evaluated and requires only of the transition state *E/Z* configuration and the choice between type I and type II pathways. For the lowest energy transition structure of reactions with many nucleophiles, the nitrogen substituents of the imine is directed toward the empty side of the oxygen to which it is H-bonded (type I). Type II pathway has a higher energy as a consequence of additional steric interactions due to imine substituent is directed toward the bulky group of the catalyst. This model explains the enantioselectivity obtained for many nucleophilic addition to imines.
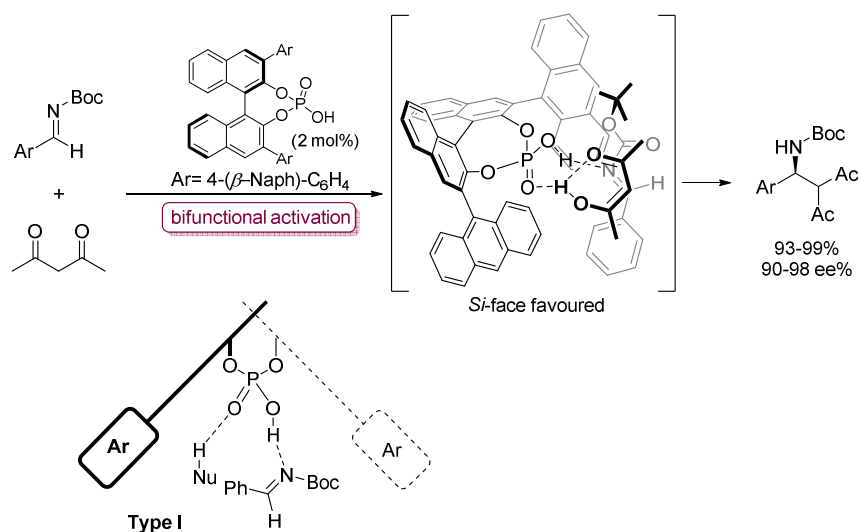
Scheme 1.11

48   Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

Another representative reaction that shows this excellent performance of phosphoric acids as bifunctional catalyst is the transfer hydrogenation[49] of imines or imine equivalents in the presence of Hantzsch esters as hydride sources.[50] In this sense, the first enantioselective chiral phosphoric acid-catalyzed hydrogen transfer reaction of imines with a Hantzsch ester was reported by Rueping in 2005 (see Scheme 1.12).[51] Activation of ketimine by protonation through the catalyst was proposed to take place, leading to the formation of an iminium/phosphate ion pair intermediate; and subsequent activation of the hydride donor would occur *via* H-bonding interaction with the acidic N-H moiety of the dihydropyridine substrate. Goodman[52] and Himo[53] have investigated the origin of the enantiocontrol with generic transition state that can also be used to explain other BINOL-derived phosphoric acid-catalyzed reductions of imines with Hantzsch esters (see Scheme 1.12). Calculations revealed that the less stable (*Z*)-iminium intermediate proceeded to react through the lowest energy transition state due to shortest H-bond distance between the iminium cation and the phosphate anion, and that the (*Z*) geometry confers more compactness to the former, which is crucial to enter into the binding pocket of the catalyst. The most favourable attack takes place on the *Re* face of the iminium ion, while other posibilities present important steric repulsions between catalyst and reactants.

Scheme 1.12

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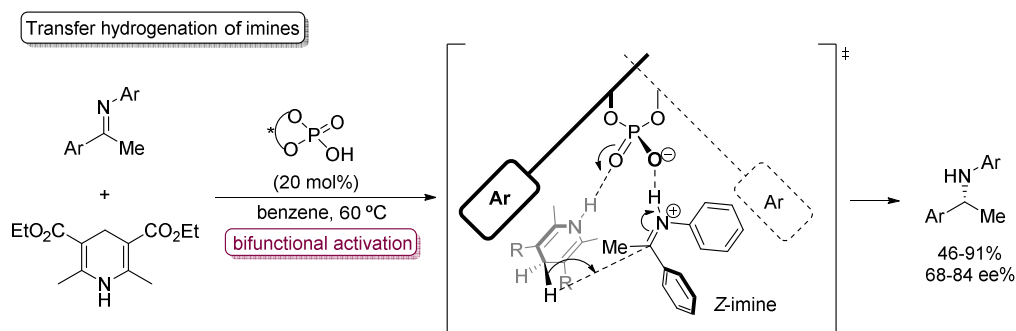
[49] (a) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084. (b) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750.

[50] Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.

[51] (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, 2367.

[52] Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.

[53] Marcelli, T.; Hammar, P.; Himo, F. *Chem. Eur. J.* **2008**, *14*, 8562.

The bifunctional activation manifold can also operate in other mechanistically different reactions such as in the enantioselective allylation of aldehydes with allylboronates shown in Scheme 1.13 reported by Antilla.[54] These reactions proceed via cyclic, six-membered ring chairlike transition states involving the interaction of the carbonyl group with the boron atom. Mechanistic insights suggested that the reaction involves both H-bonding interaction from the P-O-H group to the pseudoaxial oxygen of the cyclic boronate (the nucleophile) and a stabilizing interaction from the phosphoryl oxygen to the formyl hydrogen of the aldehyde (the electrophile).[55] This second stabilizing interaction provides rigidity in the transition state that could be responsible for the high levels of enantioselectivity observed. The reaction is favoured by *Re* face over *Si* face due to the unfavorable steric interaction between the pinacol ester methyl groups and the large aromatic group of the catalyst which disfavors the TS*Si* coffering the (*R*)-homoallylic alcohols.

Scheme 1.13
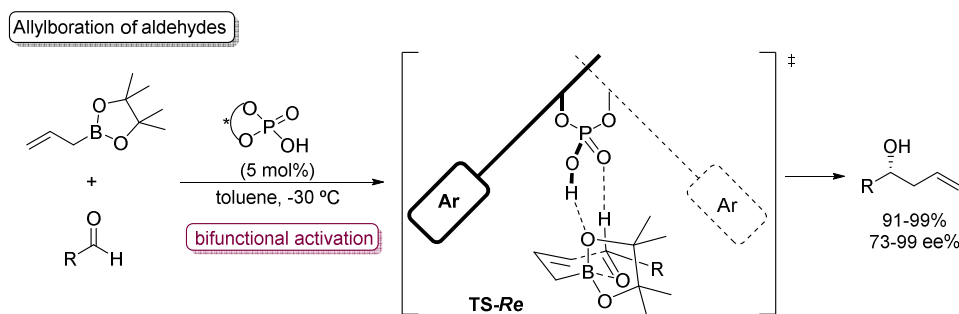
However, it has to be pointed out that in addition to these three possible ways for a Brønsted acid to activate the electrophile discussed before, there is a fourth possibility that has been more recently proposed and developed. This implies the possibility for the formation of an ion pair after the catalytst protonates the electrophilic substrate. This additional mode of activation is defined as counterion catalysis and involves the capacity of the chiral phosphate counteranion to exert stereoinduction of the reaction occurring at the protonated substrate. In this sense, it must be taken into account that the formation of a chiral contact ion pair between the chiral acid and the substrate will depend on the difference in pK_a between the chiral Brønsted

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54 Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.

55 (a) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1208. (b) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 6142. (c) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716.

acid catalyst and the substrate during the activation of the electrophile and that this will determine the equilibrium between the formation of a hydrogen-bonded or an ion-pair species.[56] In particular, Rueping and Gschwind have been able to demonstrate that NMR spectroscopy is the method of choice to distinguish between both activation modes of hydrogen bonding and ion pairing in Brønsted acid catalysis.[57] The study was performed with diphenyl phosphate and ^{15}N-labeled imines observing the variations in ^{1}H-NMR spectra under different reaction conditions. It was found that the ratio between hydrogen bonding and ion pairing can be manipulated readily by simply introducing substituents with different electronic properties.

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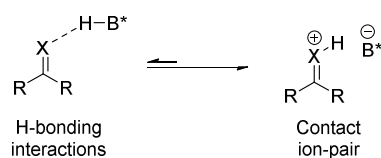
56   Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.

57   Fleischmann, M.; Drettwan, D.; Sugiono, E.; Rueping, M.; Gschwind, R. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6364.

A good example of this activation pattern is the intramolecular allylic alkylation of substrate phenols reported by Rueping that leads to the formation of chromenes under *N*-triflyl phosphoramide catalyst.[58] The process exhibits high compatibility with the presence of a wide range of substituents at the aromatic rings in the substrate. The transformation was proposed to proceed *via* protonation of the allylic alcohol which subsequently dehydrates to yield a carbocation which is associated with the phosphoramide anion in a chiral contact ion pair assisted by hydrogen-bonding interaction with the phenol moiety. The allyl carbocation is formed in a preferred anti,anti configuration, stabilized by intramolecular π-π stacking interactions as well as by intermolecular electrostatic interactions with the catalyst.
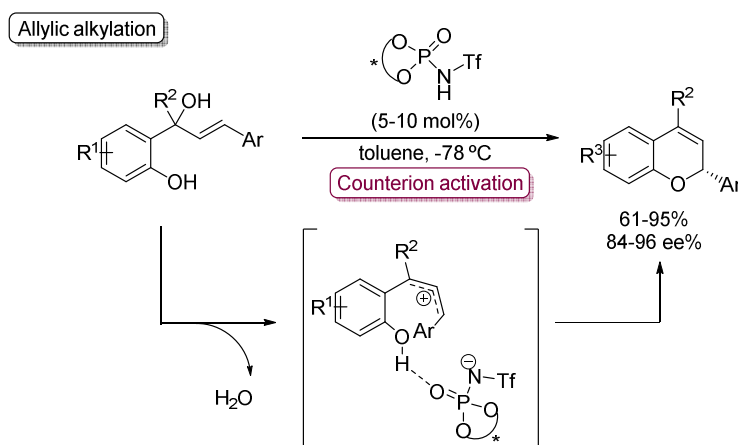
Scheme 1.14

N-acyl iminium ions are another class of reactive electrophiles that have been used under the counterion activation manifold. In particular, γ-lactams were used by Huang as *N*-acyliminium precursors in the enantioselective N-H functionalization of indoles (see Scheme 1.15).[59] The chiral phosphoric acid was involved in the generation of a chiral conjugate base/*N*-acyl iminium ion pair by protonation of the γ-lactam in a reversible process which has demonstrated by Deuterium-labelling experiment. Better understanding of the mechanism was

58   Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.

59   Xie, Y.; Zhao, Y.; Qian, B.; Yang, L.; Xia, C.; Huang, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 5682.

obtained from in situ FTIR experiments observing that the enol-type *N*-acyiliminium ion was most likely involved in the contact ion pair which subsequently the free hydroxy group will capture the conjugate Bronsted base by intermolecular H-bonding. Assisted by the conjugate base, the acidic N-H group of the indole will react with the cyclic *N*-acyliminium ion through *Re*-face nucleophilic addition.

Scheme 1.15
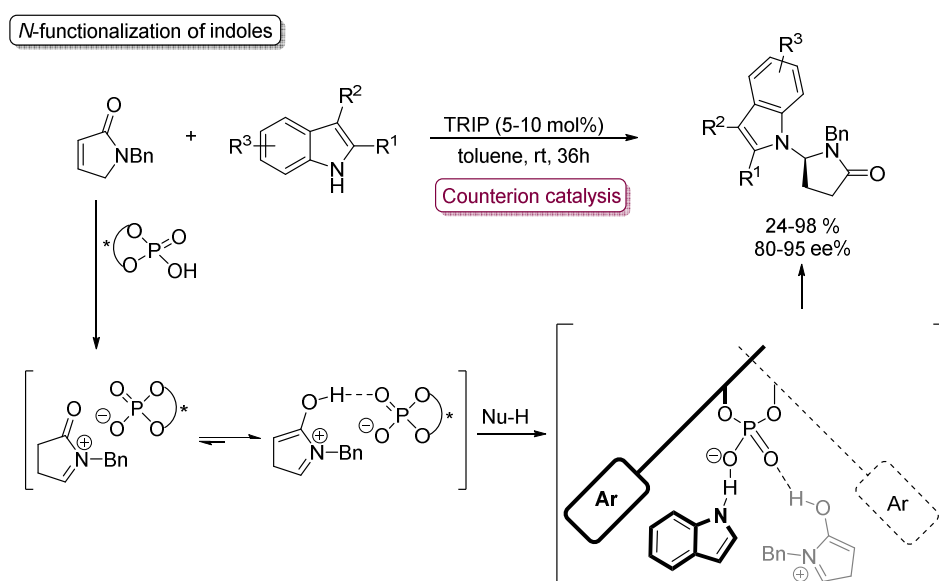
An alternative, yet analogous approach to this type of activation is the strategy kwon as Asymmetric Counteranion Directed Catalysis (ACDC).[21h] This methodology refers to "the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst". A good example of this strategy is reported by List who established the first steps on the field in a enantioselective epoxidation of α,β-unsaturated enals catalyzed by phosphate amine salt derived from a trifluoromethyl-substituted dibenzylamine and phosphate with *tert*-butyl hydroperoxide as oxidant observing high yields, and stereoselectivities (see Scheme 1.16).[60] The reaction is thought to proceed through the conjugate addition of *tert*-butyl hydroperoxide to the iminium-ion intermediate, and therefore the formation of the β stereocenter can be assumed as a case of ACDC without significant stabilization. The effect of TRIP in the formation of the α stereocenter

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[60]   Wang, X.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 1119.

is proven by the high enantioselectivities obtained with β,β-disubstituted enal bearing two identical substituents. In this case, the initial addition of the hydroperoxide to the chiral iminium-TRIP ion pair will not generate a stereocenter, and the departure of *tert*-butanol from intermediate **II** and formation of the C-O bond will become the enantiodetermining step leading to the formation of chiral iminium-TRIP ion pair **III**. Enantioselectivities are only possible if the achiral intermediate **II** is generated in a chiral conformation through the influence of phosphate anion but chirality must be induced *via* H-bonding interaction due to the neutral nature of the **II** intermediate.[61] The potential of the reaction was proved with the improvement on the obtained results compared with those achieved with diarylprolinol silyl ether catalyst,[62] so this system provided the proof of principle for the feasibility of ACDC.

Scheme 1.16
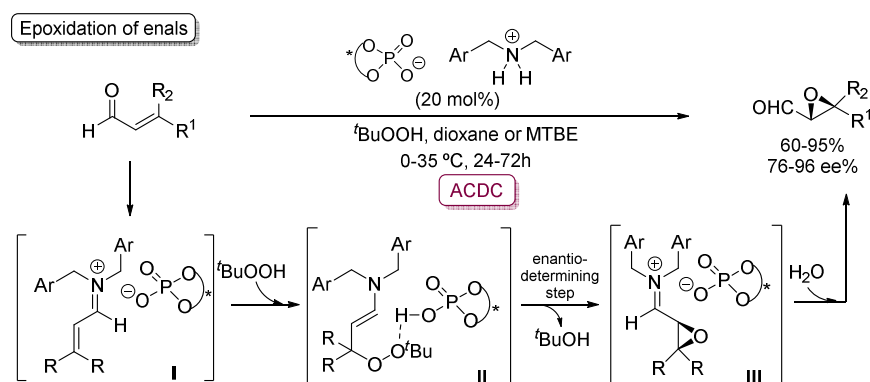
In summary, BINOL-derived chiral Brønsted acids have shown to be highly efficient for a wide range of transformations forming C-C, C-H and even C-X bonds in enantioselective fashion. Their utility is not only limited to their acidic character, they have become powerful counterions for an increasing list of reactions. However, we are far from understanding of how the catalysts function, for that reason experimental and computational studies are required for further progress in the field.

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61   Merten, C.; Pollok, C. H.; Liao, S.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 8841.

62   Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

3. BACKGROUND: PREVIOUS REPORTS OF THE GROUP

Our research group has been focussed in the development of new methodologies in asymmetric synthesis. Originally, the chiral auxiliary strategy was widely used to obtain the required stereochemical control in a number of contributions to enolate chemistry,[63] and conjugate addition reactions.[64]

More recently, the interest of the group moved forward to asymmetric organocatalysis, especially in **aminocatalysis**, which suppose the activation of the corresponding substrate *via* condensation with a primary or secondary amine generating an azomethine intermediate (enamine, iminium salt or their vinylogous versions). First steps in this field were taken in the context of *enamine activation* with one example of a Michael reactions between aldehydes and β-nitroacrolein dimethyl acetal (see Scheme 1.17).[65] The obtained Michael adducts were directly transformed into highly functionalized enantioenriched pyrrolidines through simple transformations.[66]
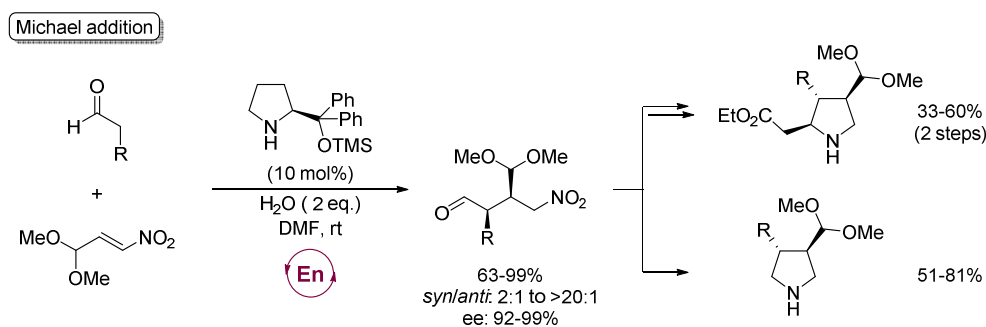
Scheme 1.17

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[63] Latest aldol reaction: (a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460. Latest Mannich reaction: (b) Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, 4065. Latest electrophilic amination reaction: (c) Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2002**, *13*, 745. Aziridine ring opening reaction: (d) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

[64] Conjugated additions: (a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404. (b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. Aza-Michael reactions: (c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790. (d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588. 1,4-Addition/α-alkylation tándem reaction: (e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535.

[65] Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135.

[66] Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357.

Simultaneously, the *iminium activation* approach has been applied using chiral secondary amines as catalysts in a wide range of transformations comprising the β-functionalization of aldehydes and α,β-unsaturated ketones (see Scheme 1.18). In this sense, the group started developing organocatalytic enantioselective aza-Michael-type reactions using tetrazoles and tetrazolothiones as N-donors.[67] The group also worked in enantioselective conjugate additions employing hydrazones as umpolung acyl anion equivalents, providing a direct access to 1,4-dicarbonyl compounds, or alternatively, using *N*-nitromethylphthalimides as masked hydroxymoyl anion equivalents to get enantioenriched γ-hydroxyiminoaldehydes.[68] In other cases, bis-nucleophilic substrates have been used in cascade processes involving sequential 1,4/1,2-addition that finishes in the isolation of hemiaminal-type products.[69]
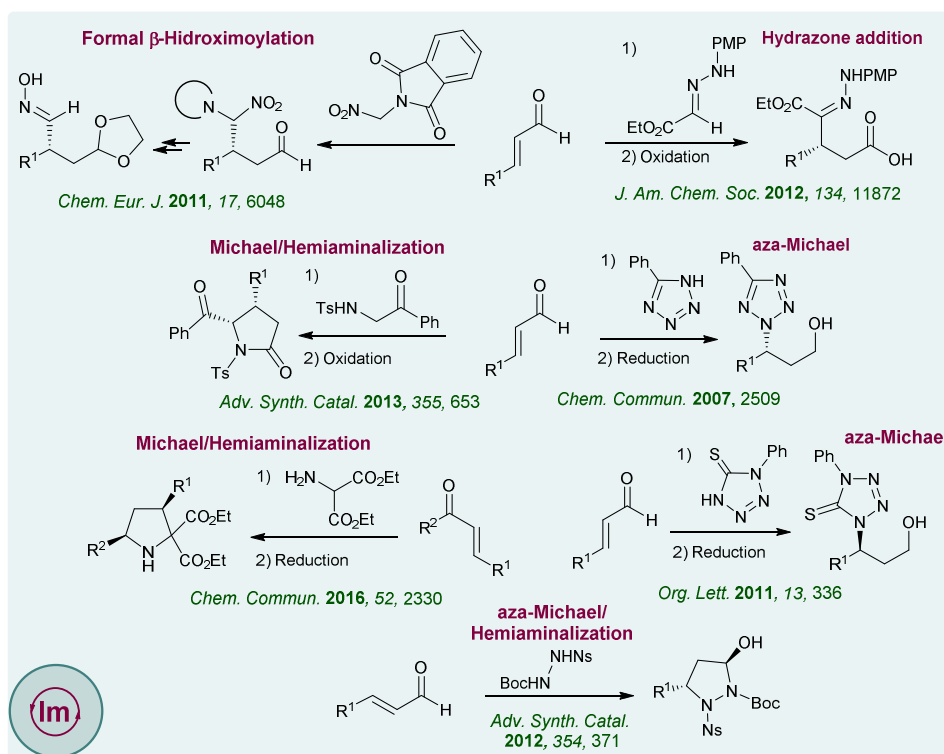
Scheme 1.18

[67] (a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509. (b) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336.

[68] (a) Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872. (b) Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.

[69] Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371. (b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, D.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653. (c) Riaño, I.; Díaz, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330.

The LUMO-lowering effect associated with the formation of an α,β-unsaturated iminium ions (*iminium catalysis*) has also been applied to cycloaddition chemistry where the group developed a (3+2) cycloaddition with azomethine ylides as 1,3-dipoles (see Scheme 1.19).[70] This reaction has demonstrated a great ability to support different substitution patterns on the substrates allowing to report different variants of the initial reaction,[71] and in the application to the synthesis of diverse heterocyclic structures.[72] Accordingly, after a extensive computational study[73] it was established that the process follows a stepwise Michael/Mannich mechanism, initiated by the conjugate additions of the 1,3-dipole over the α,β-unsaturated iminium ion, followed by the generation of a nucleophilic enamine intermediate, which reacts intramolecularly with the azomethine moiety. In a similar way, the combination of *iminium ion/enamine* cascade activation has been applied to promote different transformations, such as oxa-Michael/Aldol/hemiacetalization,[74] Michael/Aldol/dehydration,[75] Michael/Michael,[76] Michael/α-alkyaltion[77] and oxa-Michael-Michael reactions.[78]

[70]   Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[71]   (a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307. (b) Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* **2013**, *45*, 2669. (c) Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313. (d) Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Asymmetric Catal.* **2015**, *2*, 26.

[72]   (a) Iza, A.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E.; Martínez, J. I. *Org. Biomol. Chem.* **2010**, *8*, 2238. (b) Iza, A.; Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2013**, *69*, 8878.

[73]   Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossio, F. P. *Chem. Eur. J.* **2012**, *18*, 7179.

[74]   Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701.

[75]   (a) Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092. (b) Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.

[76]   Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.* **2015**, *2*, 206.

[77]   (a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, 701. (b) Martínez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240.

[78]   Orue, A.; Uria, U.; Roca-López, D.; Delso, I.; Reyes, E.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Sci.* DOI:10.1039/c7sc00009j.
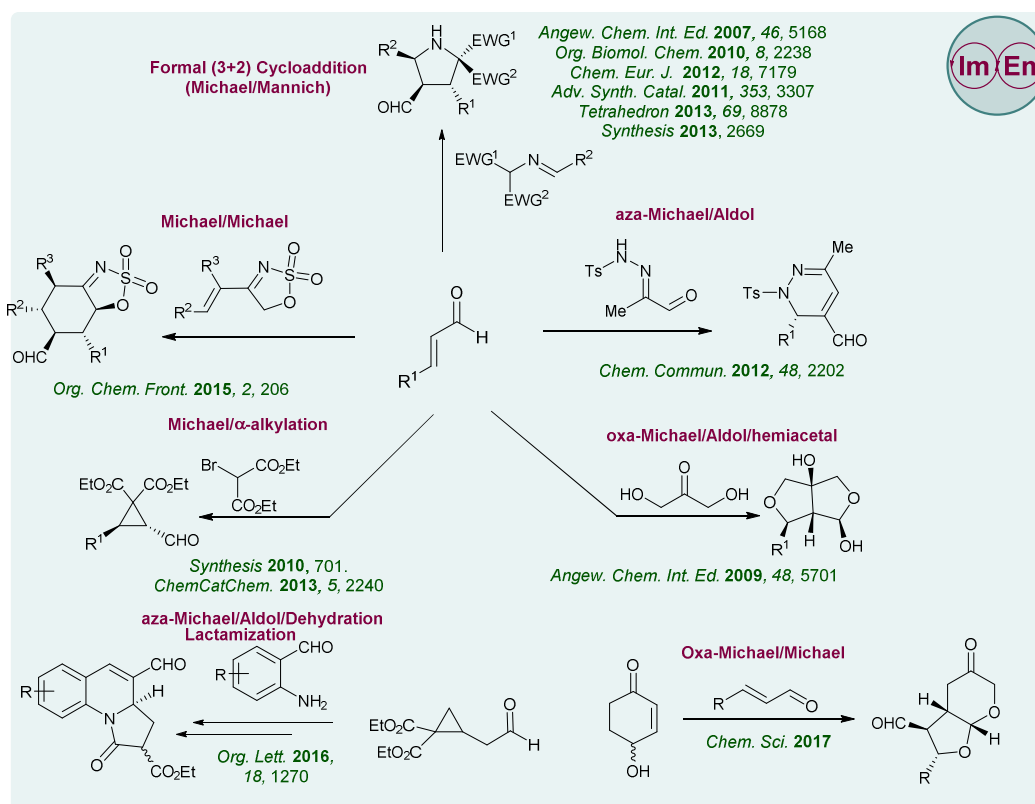
Scheme 1.19

On the other hand, the remote functionalization of unsaturated carbonyl systems has been achieved making use of the combination of enamine and iminium activation modes with the principle of vinilogy. In this sense, our research group has employed the *dienamine activation* manifold to the (2+2) cycloaddition with nitroalkenes[79] and to the (5+2) cycloaddition with oxidopyrylium ylides[80] (see Scheme 1.20). Additionaly, dienamine activation was applied to a cascade Diels-Alder cycloaddition/elimination sequence between enolizable enals and acetoxyhydropyran-5-ones yielding 8-oxabicyclo[3.2.1]octane adducts in excellent yield and stereocontrol.[81] Finally, *trienamine activation* has also been explored using dienals with

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[79] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

[80] (a) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3043. (b) Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L. Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 884.

[81] Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.

interrupted conjugation which are more reactive than the standard ones in the presence of nitroalkenes for a Diels-Alder cycloaddition.[82]
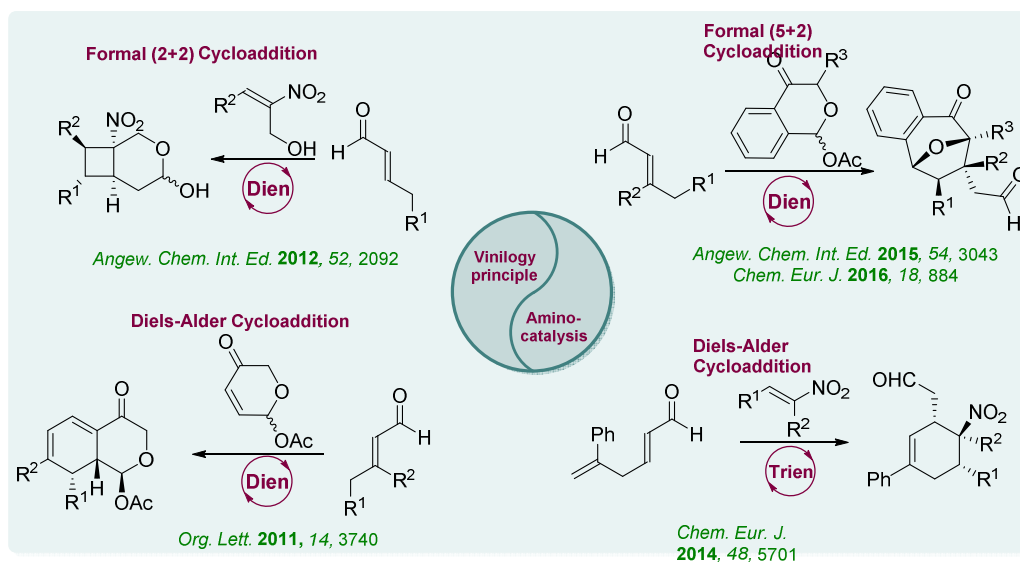
Scheme 1.20

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82   Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.

On the other hand, other different activation modes have been more recenrly explored in our group. In particular, **N-heterocyclic carbene** catalysis has been used in the formation of tertiary propargylic alcohols *via* cross-benzoin reaction between aldehydes and ynones,[83] or in the hetero-Diels-Alder reactions between catalytically generated acyl azolium enolated and alkylideneoxindoles using formyl cyclopropanes as unconventional starting materials undergoing activation by the NHC (see Scheme 1.21).[84]
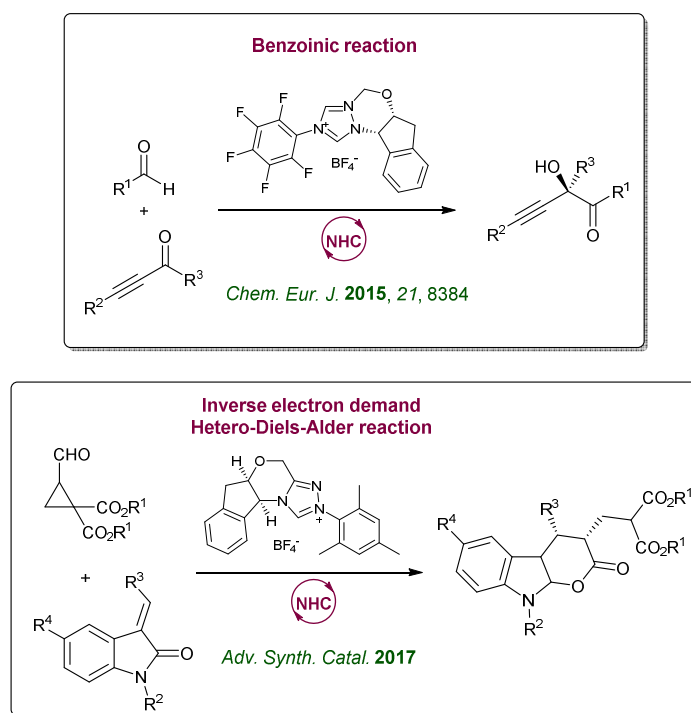
Scheme 1.21

83 Sánchez-Díez, E.; Fernández, M.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Eur. J.* **2015**, *21*, 8384.
84 Prieto, L.; Sánchez-Díez, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Adv. Synth. Catal.* DOI: 10.1002/adsc.201700198.

Alternatively, non-covalent activation mode was also explored in a diastereosivergent Michael/Henry cascade process under bifunctional **Brønsted base/H-bonding** catalysis employing squaramide/tertiary amine-type catalysts (see Scheme 1.22).[85]
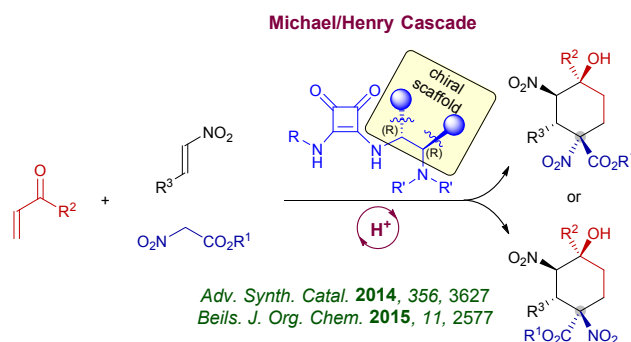
Scheme 1.22

As it is shown, the diverse research activity of the group allows achieving stereocontrol on different reactions using carbonyl compounds as substrates through varied organocatalysis under covalent and non-covalent activation. Despite the progress, in our group there is no previous experience in the use of strong Brønsted acids as organocatalysts which is the central subject of this research work.

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85 (a) Martínez, J. L.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627. (b) Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beils. J. Org. Chem.* **2015**, *11*, 2577.

4. GENERAL OBJECTIVES OF THE PRESENT WORK

The work presented in this manuscript was developed as a new field in the research of the group with a common objective, the development of new organocatalytic reactions applied to the enantioselective synthesis of functionalized products. In particular with this project, we wished to explore the possibility of using BINOL-based chiral Brønsted acids as organocatalysts to promote new transformations. The research was divided into two different part, including a chapter detailing the work performed in the context of a short stay at University of Loughborough under the supervision of Prof. A. V. Malkov.

1. Brønsted Acid Catalysis: Enantioselective Oxidative (4+3) Cycloaddition between allenamides and furans. As part of our ongoing program dedicated to the development of organocatalytic cycloaddition reactions we direct our efforts in a (4+3) cycloaddition reaction. In particular, it is known that oxyallyl cations react with electron rich dienes under this type of reactivity pattern, providing a direct access to seven-membered carbocyclic structures. Thus, we decided to apply this reactivity under Brønsted acid catalysis as it is shown in Scheme 1.23.
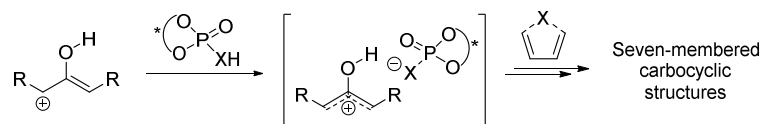
Scheme 1.23

2. Brønsted Acid Catalysis and Chirality Transfer: Enantioselective allylation of imines with allyl boronates.

Prof. Andrei V. Malkov has developed a kinetic resolution of chiral racemic secondary allyl boronates in the allylation of aldehydes catalyzed by chiral phosphoric acids (see Scheme 1.24).[86]
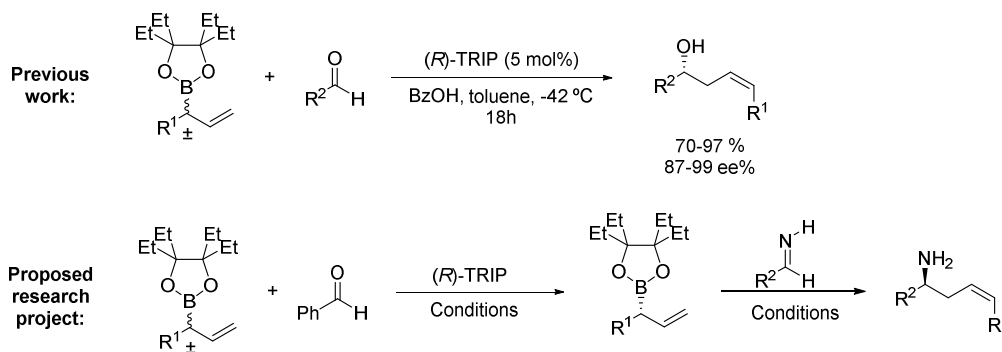
Scheme 1.24

The objective of the present work is the use of the chiral secondary allylboronates obtained by resolution in the reaction mentioned before as chiral reagents in the 1,2-addition to imines to obtain enantiopure homoallylic amines (see Scheme 1.24). In particular, we will also focus in the use of primary imines as challenging reagents that lead directly to *N*-unprotected products. This project was started at Malkov´s group in Loughborough University and followed in the University of the Basque Country in a context of collaboration between both research groups.

86 Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5338.

Chapter 2

CHAPTER 2

Enantioselective (4+3) Cycloaddition between Allenamides and Furans

1. Introduction: (4+3) Cycloadditions with Oxyallyl Cations
2. Specific Objectives and Work Plan
3. Results and Discussion
4. Conclusions

1. INTRODUCTION: (4+3) CYCLOADDITIONS WITH OXYALLYL CATIONS

The development of efficient new methodologies for the synthesis of complex carbo- or heterocyclic molecules has become a very important goal in organic synthesis. Cycloaddition reactions can be especially useful for this purpose as they provide access to the cyclic scaffolds in one step and typically provide products with high functionalization and stereoselectivity. These reactions represent one of the most powerful methods for the synthesis of five and six-membered rings,[1] which are usually prepared by the well-known 1,3-dipolar[2] and Diels-Alder reactions.[3] However, seven-membered rings are more difficult to prepare due to the increased ring strain associated to the formation of the cycloheptene core. The use of cycloaddition reactions to construct seven-membered rings in a straightforward way, from acyclic precursors would allow access to these types of rings.[4] The more common approaches to seven-membered carbo- or heterocyclic compounds through cycloaddition chemistry are based on (5+2)[5] and (4+3)[6] strategies. In the particular case of the (4+3) cycloaddition reaction, it involves the interaction between an allylic cation and a diene, producing the seven-membered ring carbocyclic product after evolution of the carbocationic intermediate (see Scheme 2.1).
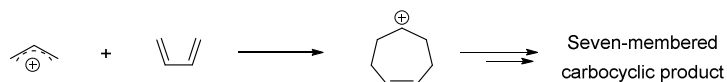
Scheme 2.1 General (4+3) cycloaddition reaction

Allyl cations cover many structural types and variations. Generally, they are stabilized by an atom or group which has the ability to stabilize the positive charge in the final cationic product. In particular, oxygen-stabilized allyl cations are very common cations in (4+3) cycloadditions which allows adding a new function in the final product. In the following section

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1   *Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N. Ed.; Wiley-VCH: Hoboken, 2014.

2   For recent reviews in 1,3-dipolar cycloadditions, see: (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366. (b) Narayan, R.; Potowski, M.; Jia, Z. J.; Antonchick, A. P.; Andrey, P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296.

3   For recent reviews in asymmetric Diels-Alder cycloaddition, see: (a) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902. (b) *Handbook of Cyclization Reactions;* Ma, S. Ed.; Wiley-VCH: Hoboken, 2009. (c) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

4   Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem. Eur. J.* **2006**, *12*, 3438.

5   (a) Clavier, H.; Pellissier, H. Recent Developments in The [5+2] Cycloaddition. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; John Wiley & Sons: Hoboken, 2014. (b) Ylijoki, K. E. O.; Stryker, J. M. *Chem. Rev.* **2013**, *113*, 2244. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189.

6   Mascareñas, J. L.; Gulías, M.; López, F. (4+3) Cycloadditions. In *Comprehensive Organic Synthesis II*; Knochel, P., Molander, G. A. Eds.; Elsevier: Amsterdam, 2014, Vol. 5, pp 595-655.

(4+3) cycloadditions using oxyallyl cations will be discussed due to the relationship with the research project.
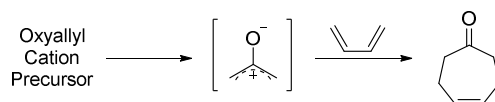
Scheme 2.2

The success of the (4+3) cycloaddition reaction depends on the facility to generate the oxyallyl cation which is going to react with a four-carbon partner. They have been demonstrated to be reactive dienophiles and when those are used, we are able to obtain the interesting cycloheptenone scaffold (see Scheme 2.2) belong to the core of numerous natural products (see Figure 2.1).

Figure 2.1[7]

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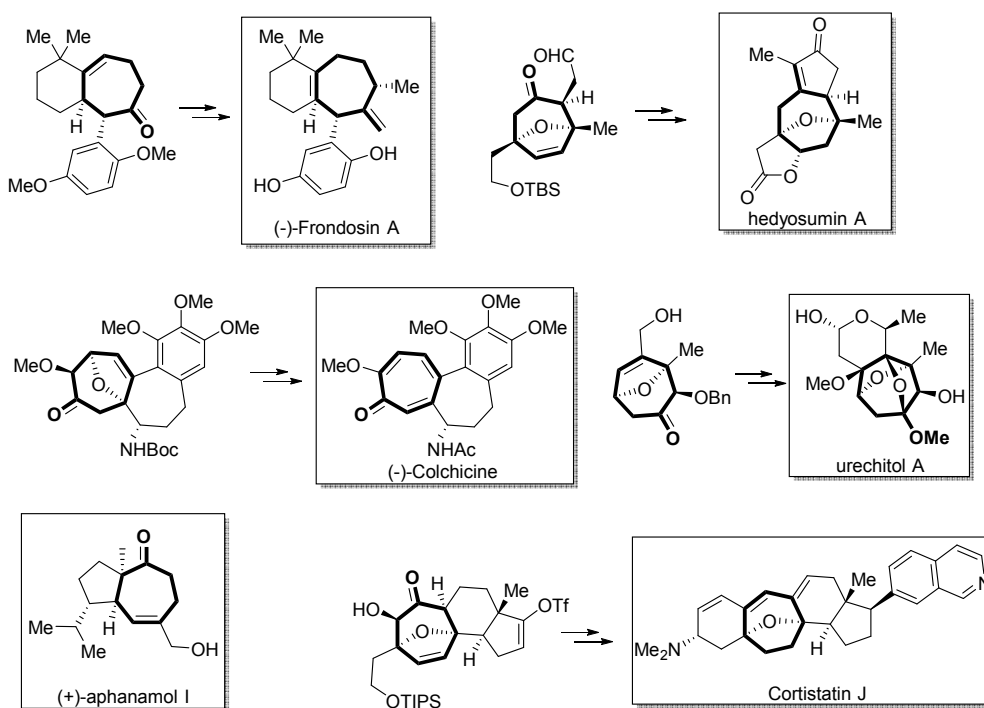
[7]   Frondosin B: Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573. Hedyosumin A: Sun, W.-B.; Wang, X.; Sun, B.-F.; Zou, J.-P.; Lin, G.-Q. *Org. Lett.* **2006**, *18*, 1219. For Colchicine: (a) Lee, J. C.; Cha, J. K. *Tetrahedron* **2000**, *56*, 10175. (b) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 1243. Urechitol A: Sumiya, T.; Ishigami, K.; Watanabe, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5527. Aphanamol I was the first natural product synthesized using

The (4+3) cyloaddition is isoelectronic to the Diels-Alder (DA) reaction involving two electrons from the allyl cation and 4 electrons from the diene in a $[4\pi^s+2\pi^s]$ suprafacial approach. The reactions are symmetry allowed by Woodward-Hoffmann rules and can be explained as an interaction between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the oxyallyl cation (see Figure 2.2).
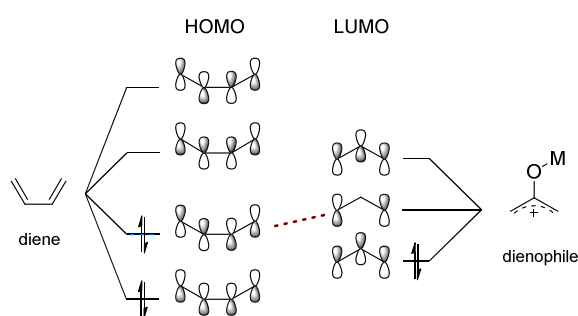
Figure 2.2

In 1984 Hoffmann[8] proposed three types of possible mechanisms for the reaction between a electron rich diene and an oxyallyl cation. Class A pathway belongs to a (4+3) cycloaddition through concerted mechanism; class B is a (4+3) cycloaddition through stepwise bond-formation mechanism; and class C, an electrophilic addition which could be followed by loss of a proton with overall electrophilic substitution at the diene by the intramolecular-nucleophilic capture of the intermediate (see Scheme 2.3).
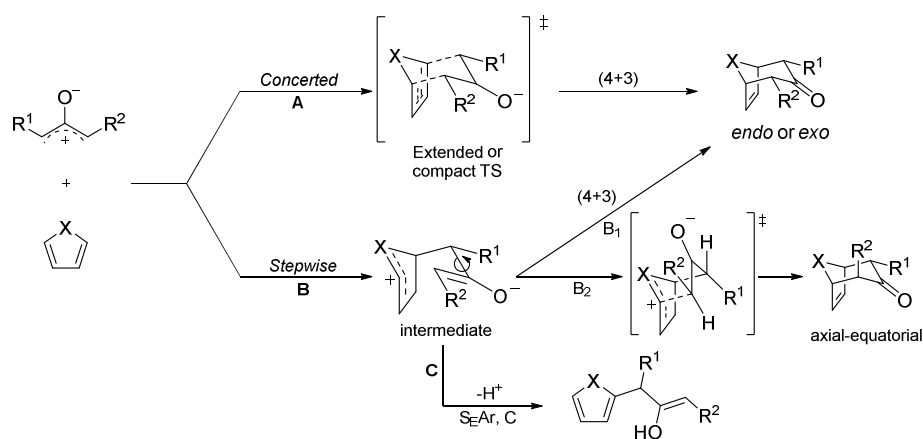
Scheme 2.3

(4+3) cycloaddition strategy: Hansson, T.; Wickberg, B. *J. Org. Chem.* **1992**, *57*, 5370. Cortistatin J: Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12453.

8   Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, *23*, 1.

Type A cyloaddition belongs to a concerted mechanism where the two σ bonds are formed simultaneously. The configuration of the cation remains unalterable during the course of the reaction and therefore, the configuration of the cycloadducts reflects the configuration of the oxyallyl cations.[9] Type B cycloadditions follow a stepwise pathway, in which the first σ bond is formed between the most nuclephilic site of the diene and the most electrophilic site of the dienophile. In this case, the intermediate may lose the configuration during the course of the reaction, thus the configuration of the cycloadduct depends on the stability and lifetime of the intermediate: if the second step is fast, the second σ bond will be formed maintaining the configuration of the cation (B_1) but if it is slow, bond rotation following path B_2. Type C reactions take place *via* the same intermediate but it suffers an electrophilic alkylation leading to the formation of a (3+2)-type of cycloaddition product or alternatively, the diene recovers conjugation by elimination, resulting in the formation of a Friedel-Crafts type adduct. Hoffmann stated that "the reaction of any structurally defined cation can only belong to at most two reaction types" (type A/B or B/C). That excludes the possibility of the reaction taking place by type A mechanism if we observe type C products and vice versa. Later on, Cramer[10] investigated the mechanism using computational methods and suggests that the mechanism depends on the nucleophilicity of the dienes, the electrophilicity of the oxyallyl cations and the electronic properties of oxygen on the allylic moiety.

Oxyallyl cations can adopt different geometries but it is generally considered that there are three types of structures namely W-type, S-type and the least stable U-shaped (seeFigure 2.3). The W-type form represents the lowest energy due to its less sterically congested nature and it is usually proposed for acyclic substrates. The U-shaped conformation is the only one possible in case of cyclic oxyallyl cations.
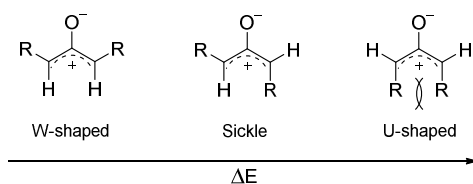
Figure 2.3

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9   Hoffmann, H. M. R. *Angew. Chem. Int Ed.* **1973**, *12*, 819.
10   (a) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523. (b) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176.

The accepted mechanism for the approach of the oxyallyl cation to the diene in the concerted pathway (class A) involves two topologically distinct transition states; a compact *endo* mode (boat-like) or an extended transition state in an *exo* approach (chair-like) (see Figure 2.4). Reactions through compact transition state tend to the formation of diequatorial products; while reactions through extended TS give products with the R^1 and R^2 in diaxial orientation.
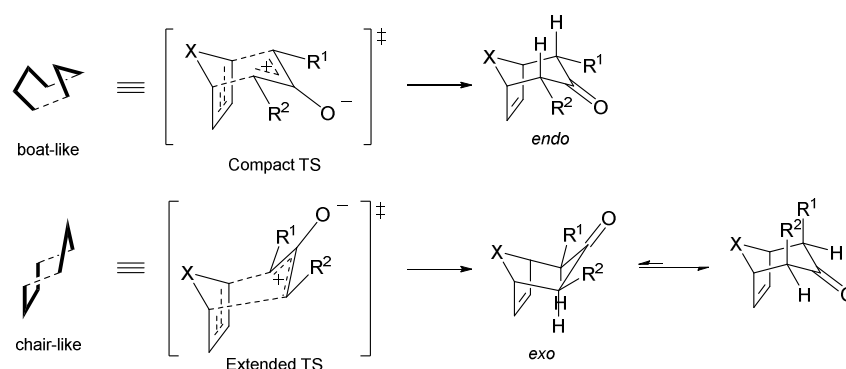
Figure 2.4

A good example of a (4+3) cycloaddition through concerted pathway (class A mechanism) is the one presented by Noyori in 1978[11] in which 2,4-dibromo-3-pentanone reacted with cyclopentadiene in the presence of diiron nonacarbonyl, $Fe_2(CO)_9$. These reductive conditions involve the reaction of α,α´-dihaloketones with the metal-based reducing agent to give a metal enolate, which evolved by loss of the second halide to generate a metal-bound oxyallyl cation. Next, the oxyallyl cation react with cyclopentadiene to yield a mixture of *endo* and *exo* diastereoisomers but confirming that the reaction proceeded through the retention of the particular W-shaped configuration of the oxyallyl cation (see Scheme 2.4).
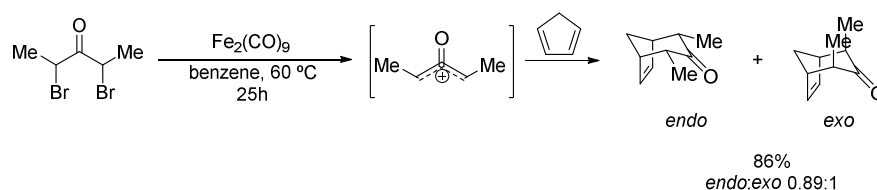
Scheme 2.4

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[11] Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765.

Noyori also presented a similar reaction undergoing the stepwise path (class B) as it is shown in Scheme 2.3.[11] When 2,4-dibromo-3-pentanone reacted with $Fe_2(CO)_9$ in the presence of furan, a mixture in which the two substituents of the oxyallyl cation were arranged in a 1,3-cis and 1,3-anti relative configuration cycloadducts were obtained. Noyori proposed that the oxyallyl cation adopts a W-configuration at the beginning which is lost once the initial intermediate of the stepwise process is generated. The observed differences with the previously mentioned reaction in which cyclopentadiene was employed as the 4C reagent suggests that furan is less reactive towards iron oxyallyls and therefore the formation of the second bond is slow enough to lead to the formation of a 1,3-cis and 1,3-anti mixture of cycloadducts.

90%
0.78:1
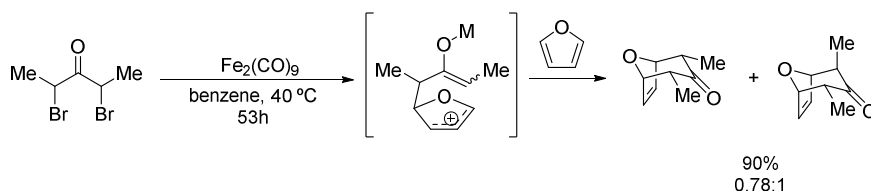
Scheme 2.5

Finally, an example of class C reaction was also reported by Noyori using the same pentanone in the presence of $Fe_2(CO)_9$ and *N*-methylpyrrole obtaining a mixture of regioisomers arising from standard Friedel-Crafts-type reactivity (see Scheme 2.6).[11] The formed intermediate cation after the initial C-C bond formation is so stable that no bond closure steps are energetically favourable.

82%
mixture of regioisomers
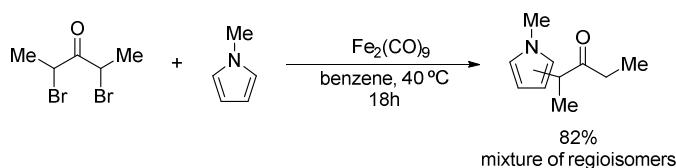
Scheme 2.6

These initial reports together with other key contributions by Hoffmann and Mann could provide the evidence that the electrophilicity of the oxyallyl cation plays an important role, with its configuration determining the stereochemical outcome of the cycloproducts.[12] This high

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[12] (a) Ashcroft, M. R.; Hoffmann, H. M. R. *Org. Synth.* **1978**, *58*, 17. (b) Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611 (d) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

dependence of the reaction mechanism with the nature of the oxyallyl cation is shown in Scheme 2.7, only the least electrophilic *N*-based oxyallyl cation gave cycloaddition products with N-methylpyrrole due to the ionic nature of Na-O bond. The preferentially obtained *endo* product is consistent with a concerted mechanism through compact TS. The more electrophilic dienophiles generated by the presence of Zn/Cu and $Fe_2(CO)_4$ respectively are more susceptible to Friedel-Crafts-type reactivity. When furan was used as diene a similar behaviour was observed demonstrating that more electrophilic oxyallyl cations are more likely to react in a stepwise path to give the axial-equatorial product.

Reductive agent	*endo*	*exo*	axial-equatorial	
Me-N-pyrrole				
Cu/NaI	76%	13%		0%
Zn/Cu	0%	0%		60%
$Fe_2(CO)_4$	0%	0%		82%
furan (O)				
Cu/NaI	91%	9%	0%	
Zn/Cu	81%	10%	9%	
$Fe_2(CO)_9$	44%	0%	56%	
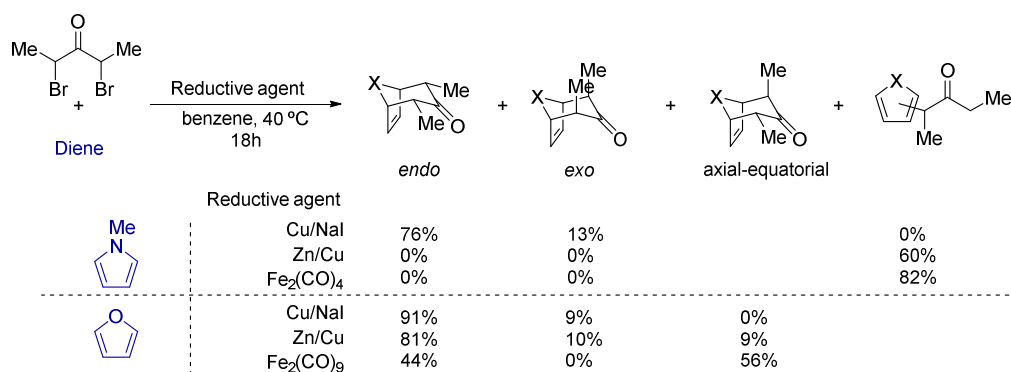
Scheme 2.7

Observing these results, it is also irrefutable the influence of the diene in the outcome of the reaction. Pyrroles behave as poor dienes in cycloadditions due to competing retrocycloaddition to recover aromaticity[13] and resulting in few satisfactory examples in the literature.[14] Furans and cyclopentadienes are the most reactive dienes; cyclohexadienes, anthracenes[15] or fulvenes have also been used resulting in less effective and selective reactions. Acyclic dienes generally provide low yields of cycloaddition products due to the low concentration of *s-cis* conformers.

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[13] (a) Donnini, C. P.; Just, G. *J. Heterocyclic Chem.* **1977**, *14*, 1423. (b) Lee, C. K.; Hahn, C. S.; Noland, W. E. *J. Org. Chem.* **1978**, *43*, 3727. (c) Noland, W. E.; Lee, C. K. *J. Org. Chem.* **1980**, *45*, 4573.

[14] (a) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (b) Davies, H. M. L.; Young, W. B.; Smith, D. H. *Tetrahedron Lett.* **1989**, *35*, 4653. (c) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095. (d) Davies, H. M. L.; Huby, N. J. S. *Tetrahedron Lett.* **1992**, *46*, 6935. (e) Ravisekhara, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10313. (f) Fuchigami, R.; Namba, K.; Tanino, K. *Tetrahedron Lett.* **2012**, *53*, 5725.

[15] Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, *31*, 5329.

As seen from the previous examples, oxyallyl cations are unstable reagents that have to be generated *in situ* from the convenient precursor. In addition to α-haloketones shown before,[6] epoxy enolsilanes are alternative starting materials to generate oxyallyl cations through acid-mediated ring opening of the oxirane moiety. The first use of epoxy enolsilanes as oxyallyl cation precursors for (4+3) cycloaddition was reported by Eguchi and coworkers[16] in the reaction with furan and cyclopentadiene under Lewis acid catalysis (see Scheme 2.8). Although the cycloadducts were produced in low yields and low diastereoselectivities, the reaction could be carried out using a catalytic amount of TESOTf as catalyst. In a later work, Chiu and coworkers[17] demonstrated that the (4+3) cycloadducts could be obtained in good yields performing the reaction at a lower temperature, although without any diastereoselectivity. Slightly better results were obtained using were possible to obtain using epoxy enolsilanes containing bulkier silyl groups.

T= -50 ºC, Yield 12%, *endo:exo* 60:40
T= -94 ºC, Yield 75%, *endo:exo* 55:45
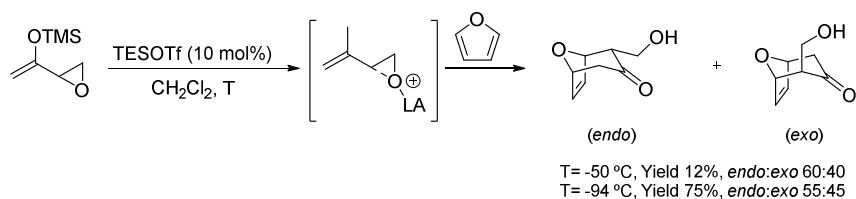
Scheme 2.8

In constrast to the results obtained in intermolecular cycloadditions with epoxy enolsilanes, intramolecular versions afford good yields of the corresponding cycloadducts, and provided as single diastereoisomer in a stereospecific manner. Using a single enantiomer of the epoxy enolsilyl ether optically pure cycloadduct shown in Scheme 2.9 was obtained under the same reactivity as used in Scheme 2.8.[17a] The diastereoselectivity is explained on the basis of a compact transition state adopting preferentially a W-type configuration, thus the cycloaddition is initiated with furan asynchronously with furan through a compact-*endo* transition state in which the tether adopts a chairlike conformation to afford the observed diastereoisomer. This pathway is preferred over the alternative unfavoured *endo* transition state in which the siloxyallyl cation is

16   Ohno, M.; Mori, K.; Hattori, T.; Eguchi, S. *J. Org. Chem.* **1990**, *55*, 6086.
17   (a) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556. (b) Lo, B.; Chiu, P. *Org. Lett.* **2011**, *13*, 864.

in S-type configuration resulting in the isomeric product. This strategy has been applied to the asymmetric synthesis of the pentacyclic framework of stereoidal alkaloid Cortistatins by Chiu.[18]
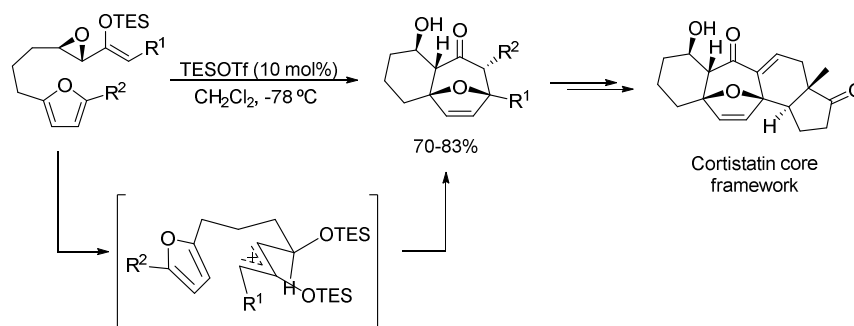
Scheme 2.9

In 2012, an intermolecular asymmetric version of this (4+3) cycloaddition has reported in which the authors confirmed that starting from an enantiopure epoxide the chiral information was directly translated to the absolute stereochemistry of the final product.[19] This result was explained by proposing that the diene intercepts the oxyallyl cation before the cation dissociates to the achiral oxyallyl cation. Computational studies were carried out afterwards which confirmed that the activation energies of the reaction between the chiral oxyallyl cation intermediate and the diene were lower than the barrier required for epoxide ring opening.[20]
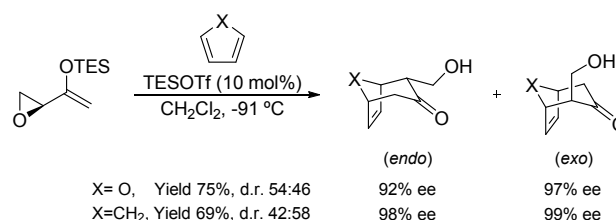
Scheme 1.1

Cyclopropanone diacetals have also been used as oxyallyl cation precursors. These strained carbocyclic reagents undergo spontaneous ring-opening in the presence of a Brønsted acid in order to release ring strain, generating an alkylidene oxyallyl cation-type intermediate. In

18 Liu, L. L.; Chiu, P. *Chem. Commun.* **2011**, *47*, 3416.
19 Lo, B.; Lam, S.; Wong, W.-T.; Chiu, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 12120.
20 Krenske, E. H.; Lam, S.; Ng, J. P. L.; Lo, B.; Lam, S. K.; Chiu, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7422.

particular, Fujita and coworkers[21] showed that these alkylidenecyclopropanone acetals could react with furan in the presence of HCl, producing (4+3) cycloadducts in good yields (see Scheme 2.10).
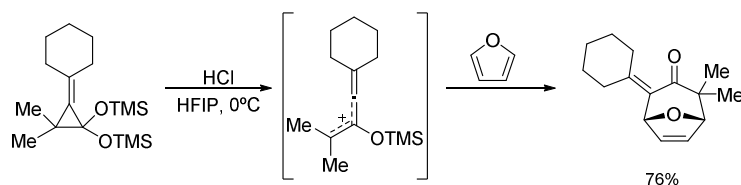
Scheme 2.10

Alternatively, Albizati and coworkers[22] reported that α,α-dialkoxy trialkylsilylenol ethers are also excellent precursors of *O*-stabilized oxyallyl cations through Lewis acid mediated dealkoxylation. In their initial report, they showed the possibility to promote the (4+3) reaction with furans in a regio- and diastereoselective fashion using using substoichiometric amounts of TMSOTf as Lewis acid promoter (see Scheme 2.11).
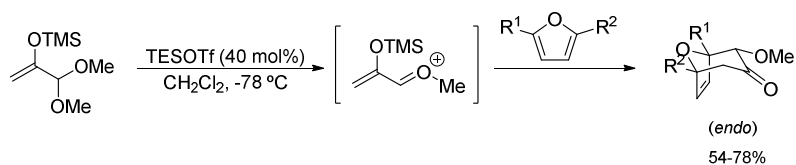
Scheme 2.11

21   Fujita, M.; Oshima, M.; Okuno, S.; Sugimura, T.; Okuyama, T. *Org. Lett.* **2006**, *8*, 4113.
22   Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109.

Hoffmann extended this work through the use of a chiral allyl acetal as the oxyallyl cation precursor developing an asymmetric variant (see Scheme 2.12).[23] These chiral allyl acetals in the presence of TESOTf as Lewis acid promoter, generate a chiral oxyallyl cation intermediate which reacts diastereoselectively with furan providing the final product in good yields. Cycloaddition takes place with high leves of diastereoselectivity through an *endo* transition state. In addition, facial selectivity levels depend on the choice of aryl group at the acetal stereogenic center. When a 2-naphthyl group was chosen, the (4+3) cycloadduct was formed as single diastereoisomer. Houk and Harmata[24] examined the reaction using density functional theory calculations and they predicted that these cycloadditions take place *via* stepwise fashion due to electrostatic stabilization after the formation of the first σ bond. In addition, stereoselectivity is controlled by two main factors: minimization of steric repulsion between the allyl group of the cation and the methyl group of the chiral auxiliary; and by stabilizing CH-π interaction between furan and the aryl group. This model could also predict the differences in selectivity observed when a phenyl and 2-naphthyl substituents were placed at the chiral auxiliary.
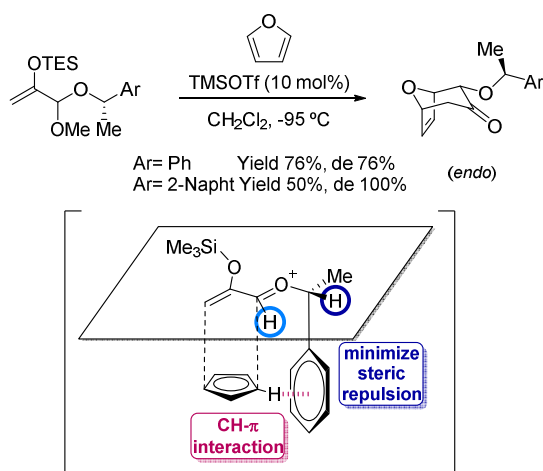
Scheme 2.12

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[23] (a) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1266. (b) Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 684.

[24] Krenske, E. H.; Houk, K. N.; Harmata, M. *Org. Lett.* **2010**, *12*, 444.

Vinyl oxocarbenium species[25] are also available from other precursors like α-silyloxy-α,β-unsaturated carbonyls. Harmata[26] demonstrated that 2-(triisopropylsilyloxy)propenal reacts with different dienes in the presence of catalytic amounts of Sc(OTf)₃ to afford the corresponding cycloadducts in good to excellent yields and in some cases with full diastereoselectivity (see Scheme 2.13). The potential of this type of precursors was demonstrated by Funk[27] who reported the total synthesis of (±)-cortistatin J using α-silyloxy-α,β-unsaturated carbonyl derivatives in an intramolecular version.

72-90%
d.r. 75:25 to 100:0
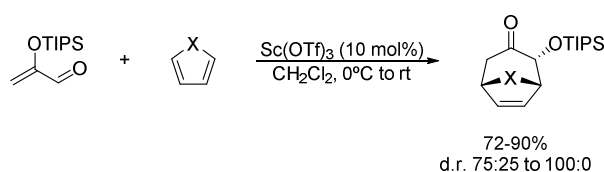
Scheme 2.13

Allenamides are also other effective precursors for the preparation of nitrogen-stabilized oxyallyl cations. These are converted into the key oxyallyl cations through regioselective epoxidation that generates an alkylidenepoxide intermediate that undergoes subsequent ring opening in the presence of a Lewis acid. This methodology has been extensively studied by Hsung reporting the first use of 1-amidoallenes as source of *N*-substituted oxyallyl cations in (4+3) cycloadditions with a variety of furans (see Scheme 2.14).[28] Hsung incorporated a chiral oxazolidinone as chiral auxiliary in the allene moiety which evolved to the *N*-substituted oxyallyl cation after a regioselective epoxidation of the most electron-rich alkene. This intermediate could be readily trapped by the presence of a high excess of furan leading to the final cycloadduct diastereoselectively and with completely *endo* selectivity in the presence of ZnCl₂ as Lewis acid promoter. Dimethyldioxirane (DMDO) was found to be the most useful protocol in epoxidizing chiral allenamide at low temperatures. When the reaction was promoted with cyclopentadiene, the final product was obtained *endo* and diastereoselectively but with an important loss on the reaction yield. Based on experimental data, Hsung and Houk have reported a mechanistic model

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[25] For review on cycloadditions of vinyl oxocarbenium ions: Harmata, M.; Rashatasakhon, P. Tetrahedron 2003, 59, 2371.

[26] Harmata, M.; Sharma, U. *Org. Lett.* **2000**, *2*, 2703.

[27] Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451.

[28] Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174.

based on DFT-theoretical calculations to explain the stereoselectivities of this cycloaddition.[29] Authors revealed that the most stable oxyallyl cation intermediate presents (*E*) configuration in order to minimize electronic repulsions between the oxazolidinone carbonyl and the oxyallyl oxygen. The study reported that this arrangement in maintained in the TS and that the incorporation of the Lewis acid decreases the activation barrier of the cycloaddition but does not change the conformation of the intermediate. The facial selectivity was explained by the presence of a stabilized C-H-π interaction between the phenyl ring of the chiral auxiliary and the hydrogen atom at C-3 position of the furan. As a consequence, the addition of the furan takes place through the most hindered face of the oxyallyl cation.
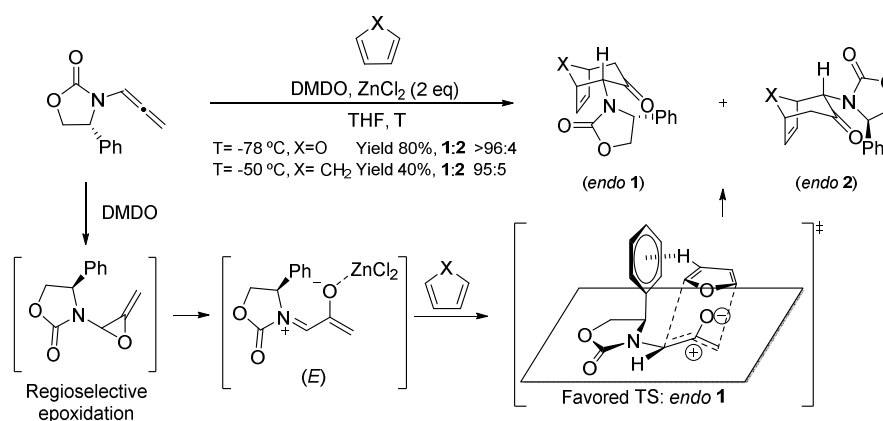
Scheme 2.14

Houk and Hsung also performed the reaction with 2- and 3-substituted furans observing that when 2-substituted furans were used *syn* cycloadducts were formed. However, in the presence of 3-substituted furans, the final product was formed selectively as the *anti* product (see Scheme 2.15).[29] In the same work, they also reported that the aforementioned C-H-π interactions also aid to understand the stereoselectivity of the reaction. In both cases, the major diastereoisomer is derived from the attack of the furan to the more hindered face of the cation, favored by C-H-π interactions. For 2-substituted furans, *syn* cycloadducts are formed selectively, because this arrangement enables the stronger bonding interaction in the TS to involve the less-hindered (C-5) carbon and the more nucleophilic site of the oxyallyl cation. 3-substituted furans

29   Antoline, J. E.; Krenske, E. H.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2011**, *133*, 14443.

undergo cycloaddition preferentially in the *anti* geometry, in order to avoid steric clash between the 3-substituent and the phenyl ring.

Scheme 2.15
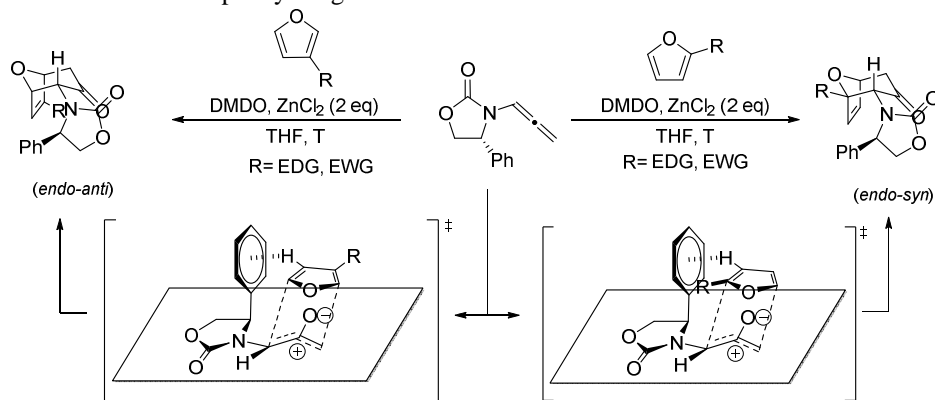
The group of Hsung has also reported an efficient intramolecular version of these (4+3) cycloadditions with allenamides as oxyallyl cation precursors.[30] They reported the first intramolecular (4+3) cycloaddition using nitrogen-stabilized chiral oxyallyl cations *via* epoxidation of *N*-tethered allenamides (see Scheme 2.16).[30b] The epoxidation became very selective at low temperatures for the allenic double bond leading to the formation of the corresponding oxyallyl cation, the subsequent intramolecular reaction gave the desired final products as single diastereomers. The reaction was also tested under Lewis acid catalyst but it did not have any influence on the stereochemical outcome. On the basis of stereochemical assignments, Hsung proposed an approach to intramolecular (4+3) cycloaddition where the cation adopts the most stable W-conformation and proceeds through *exo* transition state. Both oxygen atoms are proposed to be unaligned in view of the fact that Lewis acids did not have any influence on the reaction.

Scheme 2.16

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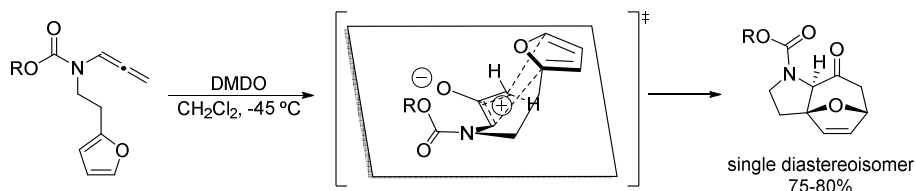
[30]   (a) Rameshkumar, C.; Hsung, R. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 615. (b) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694. (c) Lohse, A. G.; Hsung, R. P.; Leider, M. D.; Ghosh, S. K. *J. Org. Chem.* **2011**, *76*, 3246.

Finally, heteroaromatic betaines such as those used in dipolar (5+2) cycloadditions, can also participate in (4+3) cycloadditions with a suitable diene.[31] Cha and coworkers[32] applied this methodology to generate a cyclic *N*-stabilized oxyallyl cation which reacted with cyclopentadiene at room temperature providing the corresponding *endo* cycloadducts in moderate yield. Cha could perform the reaction on large scale and applied it in a sequence of transformation applied towards the synthesis of to prepare the tricyclic core of Sarain A, a molecule which is reported to display modest antibacterial, insecticidal and antitumor activities.[33]
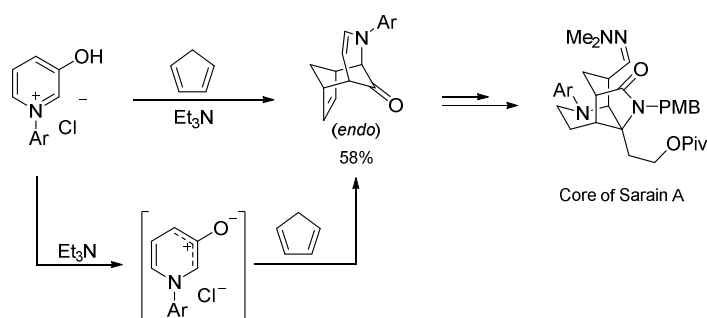
Scheme 2.17

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[31] (a) Dennis, N.; Ibrahim, B.; Katritzky, A. R. *J. Chem. Soc.-Perkin Trans. 1* **1976**, *21*, 2307. (b) Mok, K. L.; Nye, M. J. *J. Chem. Soc. Chem. Commun.* **1974**, *15*, 608.

[32] (a) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017. (b) Lee, H. I.; Sung, M. J.; Lee, H. B.; Cha, J. K. *Heterocycles* **2004**, *62*, 407.

[33] Caprioli, V.; Cimino, G.; De Guilio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol. B.* **1992**, *103B*, 293.

There is a lack of catalytic (4+3) cycloadditions in the literature and even rarer enantioselective versions; in fact, only two examples of catalytic enantioselective (4+3) cycloadditions have been reported up to date. One of these reports made use of the iminium activation approach to activate the oxyallyl cation reagent and the other realied on a Cu(II)/bis-oxazoline chiral Lewis acid as catalyst. Next, these are presented in-depth.

In 2003, Harmata[34] presented the first enantioselective version of (4+3) cycloaddition using silyloxy pentadienals as oxyallyl cation precursors. Silyloxy pentadienals react with the MacMillan catalyst to generate an iminium ion intermediate shown in Scheme 2.18. The addition of 2,5-disubstituted furans lead to the final cycloadduct as a single *endo* diastereomer in moderate to good yields and good enantioselectivities. The reaction performed well with methyl, ethyl and propyl substituents at this position of the furan ring but the complete diastereoselectivity and enantioselectivity was lost when phenyl groups were used. The reaction with 2-substituted furans did not take place observing only the Friedel-Crafts type alkylation product which could suggest a stepwise process.
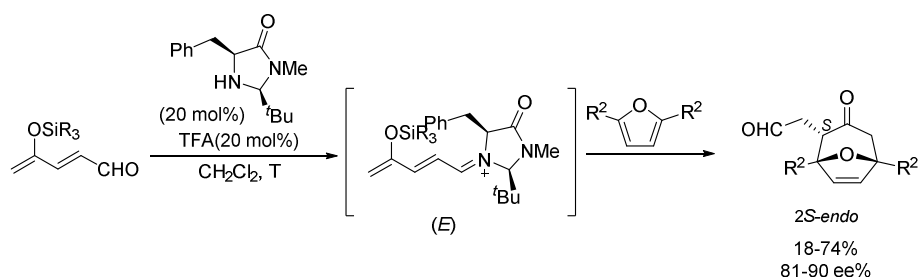
Scheme 2.18

Prior to the determination of the absolute configuration, Harmata assumed that the mechanism that explains the enantioselectivity would follow the earlier proposed model by MacMillan for imidazolidinone-catalyzed enantioselective Diels-Alder and Michael reactions with α,β-unsaturated aldehydes and ketones. However, Sun and Xu applied this methodology in the synthesis of (+)-englerin A and (–)-orientalol F and they deduced the absolute configuration comparing the optical rotations to their final products to those of authentic samples.[35] They

34   Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

35   (a) Sun, B.-F.; Wang, C.-L.; Ding, R.; Xu, J.-Y.; Lin, G.-Q.; *Tetrahedron Lett.* **2011**, *52*, 2155. (b) Wang, C.-L.; Sun, B.-F.; Chen, S.-G.; Ding, R.; Lin, G.-Q.; Xy, J.-Y.; Shang, Y.-J. *Synlett* **2012**, *23*, 263. (c) Wang, C. L.; Sun, B.-F.;

realized that Harmata had anticipated a mechanism that explains the formation of the opposite enantiomer. The addition should take place through *syn* face of the iminium ion. For that reason, in 2014 Harmata and Krenske investigated the mechanism under DFT calculations.[36] The most stable conformation for the iminium ion was reported to be (*E*) isomer; however, some involvement of *Z* transition states may occur, and this would slightly reduce the enantioselectivity.[37] The addition through the *syn* face of the first step is understood trough conformational changes within the iminium cation that occur upon interaction with the diene. In the proposed TS, diene is far enough from the benzyl group and *tert*-butyl group of the catalyst that creates no steric clashes with these groups. To accommodate *syn*-face approach by the furan, SiR_3 group would accommodate in the *anti* face of the iminium intermediate. They demonstrated that the role of SiR_3 is crucial in transmitting chiral information from the catalyst to the bond-forming site.
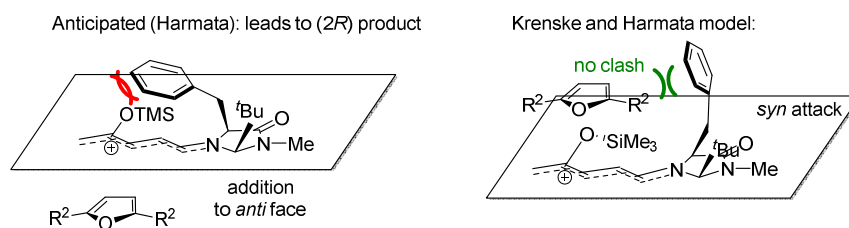
Figure 2.5

Later on, Hsung reported an enantioselective version using chiral Lewis acid catalysis (see Scheme 2.19).[38] The cycloaddition was performed with achiral oxazolidinone-derived allenamides in the presence of a Cu(II)/bis-oxaline chiral Lewis acid, that promoted the *in situ* formation of the oxyallyl cation which, by oxidation with dimethyldioxirane (DMDO) reacted with dienes with *endo* selectivity and with modest to good enantioselectivities. The use of molecular sieves in the reaction led to higher yields. The use of furan led to endo product with excellent yield and enantioselectivity (see Scheme 2.19). The reaction was also carried out with cyclopentadiene but lower enantioselectivities were achieved due to a more reactive diene that

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Chen, S.-G.; Ding, R.; Lin, G.-Q.; Xu, J.-Y.; Shang, Y.-J. *Synlett* **2012**, *23*, 1266. (d) Wang, J.; Chen, S.-G.; Sun, B.-F.; Lin, G.-Q.; Shang, Y.-J. *Chem. Eur. J.* **2013**, *19*, 2539.

36   Krenske, E. H.; Houk, K. N.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 744

37   Seebach, D.; Gilmour, R.; Grošelj, U.; Deniau, G.; Sparr, C.; Ebert, M.-O.; Beck, A. K.; McCusker, L. B.; Šišak, D.; Uchimaru, T. *Helv. Chim. Acta* **2010**, *93*, 603.

38   Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

contributes to a great amount of background reaction.[39] Hsung proposed a working model to explain the obtained stereoselectivity based on mechanistic analysis for asymmetric catalysis employing C_2-symmetric ligands. In this model, it could be observed that the attack through the *Si* face of the oxyallyl cation would be sterically unfavoured due to the interaction between the furan and the phenyl rings, while the *Re* face would predominate.
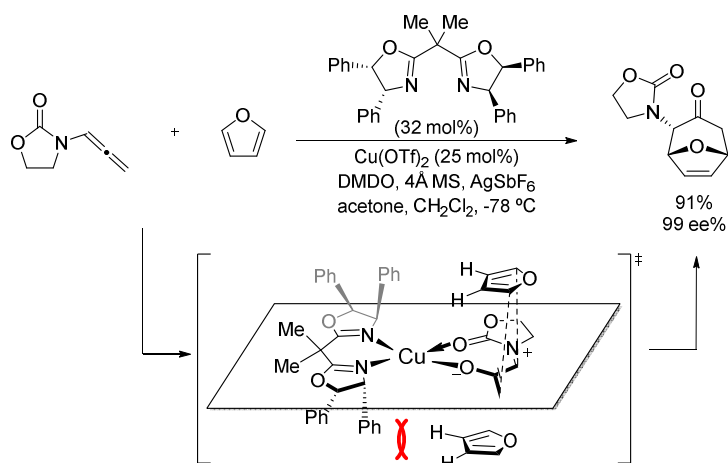
Scheme 2.19

The reaction with 2,5-dimethylfuran provided low enantioselectivities but, in contrast, the use of both 2-methylfuran and methyl furylcarboxylic ester provided excellent regioselectivities in favor of the *syn* isomer with moderate to high enantioselectivities. Reactions with 3-substituted furans were successful, leading to cycloadducts with high enantioselectivities in favor of the *anti* regioisomer as major product (see Scheme 2.20).
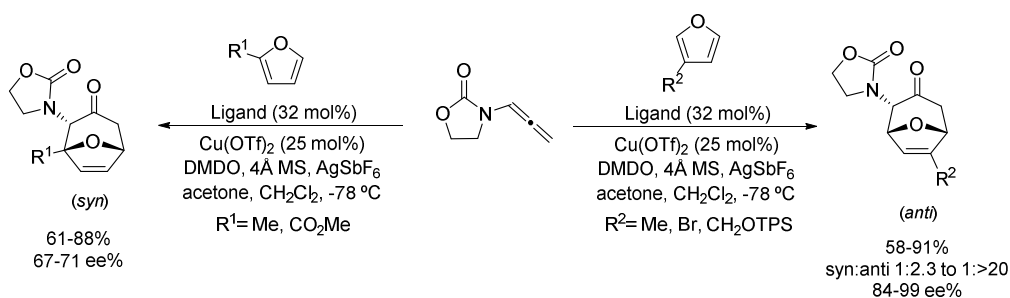
Scheme 2.20

39   Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

The selected examples illustrate the different research activity to get oxyallyl cations and to involve these in (4+3) cycloadditions. It is evident that there is a lack of examples of catalytic (4+3) cycloadditions and when speaking about catalytic enantioselective versions, the literature is limited to the two examples disclosed previously. This encouraged us to confront this challenge.

2.   SPECIFIC OBJECTIVES AND WORK PLAN

As stated in the previous section, despite the fact that the (4+3) cycloaddition reaction using oxyallyl cation as the 3C component is a powerful tool to assemble seven-membered rings; there is an evident lack of catalytic and enantioselective versions that enable the access to enantiopure adducts through this highly useful approach. In consequence, we decided to direct our efforts to the development of an organocatalytic enantioselective version of the (4+3) cycloaddition between oxyallyl cations and electron rich dienes employing Brønsted acid catalysis as the methodological approach to activate the reagents and to achieve stereocontrol (see Scheme 2.21).
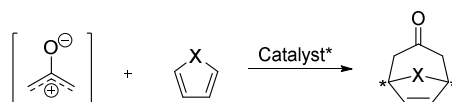
Scheme 2.21

Our hypothesis is shown in Scheme 2.22 and relies on the ability of chiral Brønsted acids to favour the formation of the oxyallyl cation intermediate through ring-opening of an alkylideneoxirane intermediate that is generated upon regioselective epoxidation of an allenamide. Moreover, the chiral Brønsted acid should also be able to transfer its stereochemical influence during the (4+3) cycloaddition process. In particular, BINOL-based Brønsted acids will be surveyed to catalyze this (4+3) cycloaddition.
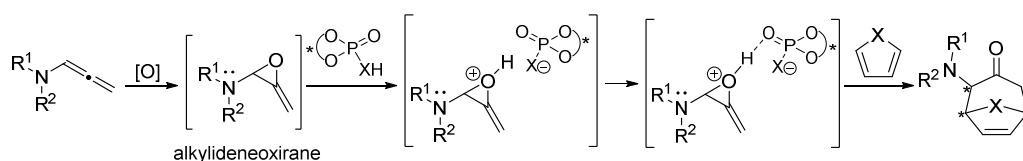
Scheme 2.22

Considering all this aspects, the following work plan was designed:

1.   Proof of concept

Firstly, we need to evaluate the ability of postulated Brønsted acids to catalyze the process and to induce enantioselectivity in the (4+3) cycloaddition between allenamide and furan in the presence of an oxidant that should be compatible with the catalytic system (see Scheme 2.23).
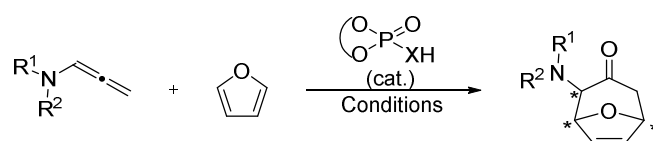
Scheme 2.23

2.   Optimization of the reaction conditions

Once the viability of the reaction has been established, structural requirements to be met by the allenamides give the best performance under these Brønsted acid-catalyzed conditions will have to be identified. In particular, R^1 and R^2 will be modified with electronically different groups until the allenamide that performs best is indetified (see Scheme 2.23). Next, the reaction between furan and the most suitable allenamide will be chosen as model system, with the aim to identify the chiral Brønsted acid that provides the best performing one in terms of yield and enantiocontrol. Some catalyst will be tested and once the best performance is identified, other experimental variables like solvent, additives, concentration or temperature will be evaluated (see Scheme 2.24).
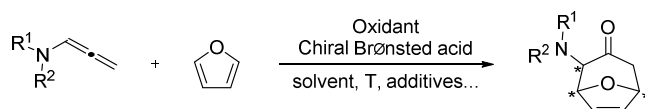
Scheme 2.24

3.   Scope of the reaction

With the optimal conditions in hand, several allenes with different substitution patterns as well as different dienes will be evaluated in order to explore the scope and limitations of the reaction (see Scheme 2.25).
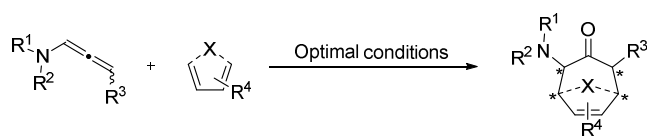
Scheme 2.25

3. RESULTS AND DISCUSSION

Once the synthetic methodologies and literature examples on this topic have been presented and after establishing the specific objectives and a work plan, the most relevant results obtained will be presented and subsequent discussed.

3.1 Proof of concept

We began our work applying the conditions reported previously by Hsung[38] that involved the use of allene **1a** containing a 2-oxazolidinone moiety in the presence of dimethyldioxirane (DMDO) as the oxidant and an excess of furan **2a**. An achiral acid such as diphenyl phosphate was incorporated as catalyst and the reaction was evaluated at two different temperatures (see Scheme 2.26). Initially the reaction was carried out at room temperature observing a very poor conversion into the final products. When the reaction was carried out at -78 ºC a promising reaction yield was achieved. These results indicated the necessity of working at low temperatures probably due to the volatility and unstable properties of DMDO at temperatures over -20 ºC. It has to be highlighted that when the reaction was performed without catalyst at -78 ºC, the reaction underwent with a 27% yield indicating that we had to deal with a high degree of background reaction.
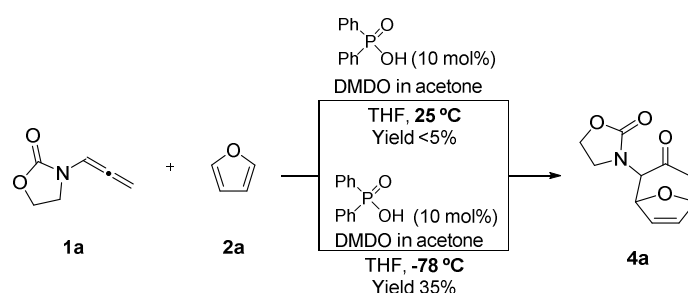
Scheme 2.26

The use of DMDO as oxidant presents some disadvantages that we wanted to overcome.[40] In particular, DMDO has to be freshly prepared previous to its use which would be in solution in available solvents; it must be storage at temperatures below -20 ºC away from light and its lifetime is around 2-6 days at these temperatures. Thus, other different types of oxidants were

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[40] (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Yang, Z.; Yu, P.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 4237.

evaluated such as hydroperoxides (*t*BuOOH, H_2O_2), peracetic acid or *m*-chloroperbenzoic acid. However, none of the oxidants gave the desired cycloadduct. In fact, in all cases the starting allene was recovered.

3.2   Optimization of reaction conditions

Once the possibility of carrying out the reaction in the presence of a Brønsted acid catalyst by using DMDO as the oxidant to generate the key oxyallyl cation intermediate from an allenamide-type substrate, we evaluated the effect of different BINOL-based chiral Brønsted acids on the reaction. In particular, several commercially available chiral phosphoric acids (**3a-e**) and *N*-triflyl phosphoramide-based chiral acids (**3f-g**) were surveyed with the results shown in Table 2.1.

Table 2.1 Variations on the reaction under DMDO and different CBA

Entry	Catalyst	Yield[a]	ee[b]
1	**3a**	69	8
2	**3b**	53	5
3	**3c**	45	<5
4	**3d**	65	16
5	**3e**	51	<5
6	**3f**	38	45
7	**3g**	44	20

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product.

When chiral phosphoric acids **3a-e** were used as catalysts (entries 1-5) adduct **4a** was formed in moderate yield but with very poor enantiocontrol. With the most acidic BINOL-based phosphoric acid **3d** we were able to raise the enantiocontrol to a promising 16% ee. Thus, these

results suggested that more acidic catalysts were necessary in the reaction to get better results. In this sense, geometrically different but the most acidic catalyst in the series of phosphoric acids **3e** (entry 5) was evaluated obtaining adduct **4a** in a promising yield but very low enantioselectivity. However, two different BINOL-derived *N*-triflyl phosphoramides were evaluated (entries 6-7) which provided higher enantioselectivities (45% and 20% respectively).

These promising preliminary results encouraged us to carry on further efforts in order to achieve the highest possible yield and stereoselectivity. In this sense, we decided first to evaluate allenamides with different substitution patterns employing catalysts **3f** and **3g** which had provided the best results in our preliminary survey. The reactions were carried out at -78 °C under 5 mol% of catalyst loading with excess of furan (3 eq) and DMDO (2 eq) and the obtained results are shown in Table 2.2.

Table 2.2 Evaluation of the structure of the allenamide precursor

Entry	allene	R^1	R^2	Product	Yield (%)[a]	ee (%)[b]
1	**1b**	Me	Ts	**4b**	34	48
2	**1c**	Ph	Ts	**4c**	17	74
3	**1d**	p-BrC$_6$H$_4$	Ts	**4d**	23	39
4[c]	**1e**	2,4,6-(Me)$_3$C$_6$H$_2$	Ts	**4e**	18	50
5[d]	**1f**	p-MeOC$_6$H$_4$	Ts	**4f**	50	60
6	**1g**	p-MeOC$_6$H$_4$	Ac	**4g**	50	22
7	**1h**	Ph	Boc	**4h**	37	64
8	**1i**	p-BrC$_6$H$_4$	Boc	**4i**	29	71
9	**1j**	p-MeOC$_6$H$_4$	Boc	**4j**	**63**	**68**
10	**1k**	3,4,5-(MeO)$_3$C$_6$H$_2$	Boc	**4k**	38	73
11	**-**	p-(*N*-(Me)$_2$)C$_6$H$_4$	Boc	-	n.r.[e]	-

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product. [c]The reaction was carried out with **3f** catalyst. [d]Absolute configuration was determined by X-ray analysis (see Experimental section). [e]No reaction.

We started the evaluation of different allenamides by studying different R^1 groups while keeping an electron withdrawing group as the other R^2 substituent. Initially, we tested alkyl

(entry 1) and aromatic substituents (entries 2-5). Allenamide **1b** containing a methyl and tosyl group did not afford good results in terms of yield and enantioselectivity and when a phenyl group was placed (entry 2) the enantiocontrol increased to a promising 74% ee, albeit in very low yield. The use of an electron withdrawing aryl substituent (entry 3) afforded lower enantioselectivities than a simple phenyl group, thus allenamides containing an electron-donating aryl substituent together with the tosyl group were subsequently evaluated (entries 4-5). In particular, allenamide **1e** with a mesityl group (entry 4) and **1f** with a *p*-methoxyphenyl substituent (entry 5) were evaluated obtaining the best result with the latter. Alternatively, we tested the performance of *p*-methoxyphenyl substituted allenamides in combination with other different electron withdrawing substituents such as an acetyl group (entry 6) performing the reaction in a very low enantiocontrol. On the other hand, *tert*-butoxycarbonyl-substituted allenamide **1h** performed much better with an increased 67% ee. Finally, other *N*-Boc protected allenamides were surveyed trying to obtain a fine tuning of the electronic properties of the *N*-aryl moiety (entries 8-11). As it happened before, the best results were obtained with the use of the electron donating *p*-methoxyphenyl substituent (entry 9). This push-pull effect on the nitrogen atom seems to be the most suitable system. However, when the more electron-donating 3,4,5-trimethoxyphenyl substituent was incorporated as the aryl substituent (entry 10) the reaction performed poorly in terms of yield and the use of *p*-dimethylaminophenyl substituent in the allenamide moiety resulted in a sluggish reaction presumably because of overoxidation (entry 11).

We could grow a crystal of the obtained cycloadduct **4f** which allowed to establish the absolute configuration which was established by X-ray analysis (see Figure 2.6). The crystallographic analysis showed an (1*R*,2*S*,5*R*) absolute configuration which was extended to the other cycloadducts **4a-k** based on a mechanistic analogy for all reactions.
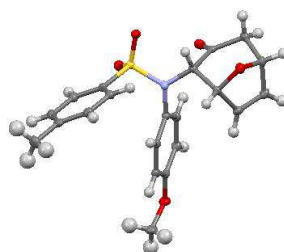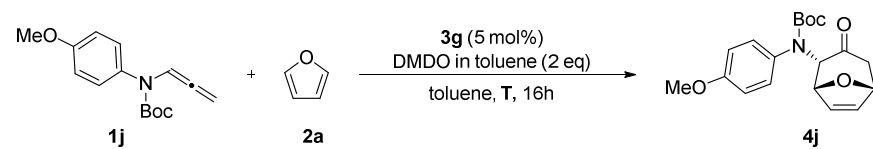
Figure 2.6

Once the structure of the allenamide reagent had been optimized and with catalyst **3g** as the best performing one, we proceeded to study the effect of other parameters on the reaction like solvent, stoichiometric ratio between the different reagents or the incorporation of additives (see Table 2.3). We started by surveying the effect of using more excess of furan (entries 2-3) observing a significant improvement in the yield when 13 equivalents were used. Higher excess of furan did not improve this result. It has to be pointed out that the use of a large excess of diene is usual to find in the previous reports about (4+3) cycloadditions using oxyallyl cations due to the probable oxidation of furan. Finally, we also evaluated the effect of the temperature, demonstrating that when the temperature was higher than -78 ºC (entry 4), poorer enantiocontrol was obtained. However, when we carried out the reaction at -90 ºC (entry 5) the enantioselectivity was not higher compared to the same reaction at -78 ºC.

Table 2.3 Study of the effect of the furan equivalents and temperature on the reaction.

Entry	Furan eq	T /ºC	Yield[a]	ee[b]
1	3	-78	63	68
2	13	-78	**74**	**73**
3	24	-78	70[d]	65
4	13	-40	50	56
5	13	-90	62	67

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product. [c]10 mol% catalyst. [d]Yield was measured by ^{1}H NMR in the crude with TMB as IS.

We next proceeded to study the influence of the solvent in the reaction as it can be seen in Table 2.4. Initially, we tested the reaction in the presence of polar solvents (entries 2-3). The use of a chlorinated solvent such as dichloromethane (entry 2) did not afford better results than those obtained in the original reaction in toluene. Propionitrile was also evaluated obtaining good results in terms of yield and enantioselectivities but not better than in toluene (entry 3 vs 1). An apolar solvent like hexane was also evaluated with no improvement in yield and enantiocontrol. In all these cases we were also able to prepare solutions of DMDO in each of the solvent tested, which means that all these reactions were carried out in a single solvent system. For the evaluation of other solvents in which DMDO solutions can not be prepared, the oxidant was

employed as a solution in toluene in view of the results presented in entry 1. As a consequence, the following experiments were carried out in binary solvent mixtures. In the presence of ethers, the yield of the reaction resulted significantly affected, while maintaining similar enantioselectivities (entries 5-8). The use of nitroethane in the reaction led to similar results to those provided by ethereal solvents (entry 9). However, when we performed the reaction in the presence of ethyl acetate as co-solvent we observed that the enantioselectivity improved significantly (entry 10). We were also able to improve the yield of the reaction using higher excess of DMDO (2.5 equivalents, entry 11) maintaining the enantiocontrol. The reaction was also tested with 3 equivalents of DMDO with no improvement in the yield (entry 12). Moreover, in these cases the reaction could be carried out using furan as the limiting reagent in the presence of a 3-fold excess of allenamide (entry 12) which represents a remarkable improvement compared with 13 equivalents of diene previously required. The use of isopropyl acetate (entry 13) or ethyl formate (entry 14) as co-solvents did not improve the enantiocontrol and led to an important loss in the reaction yield.

Table 2.4 Effect of the solvents and co-solvents on the reaction

Entry	Solvent	Co-solvent	Yield[a]	ee[b]
1	Toluene	-	74	75
2	CH_2Cl_2	-	60	65
3	EtCN	-	68	63
4	hexane	-	60	66
5	toluene	MTBE	21	65
6	toluene	Et_2O	58	68
7	toluene	CpMeO	58	60
8	toluene	THF	39	69
9	toluene	$EtNO_2$	52	63
10	toluene	EtOAc	75	80
11[d]	toluene	EtOAc	**78**	**82**
12[f]	toluene	EtOAc	**71**	**82**
13[d]	toluene	^{i}PrOAc	72[e]	66
14[d]	toluene	Ethyl formate	35[e]	70

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product. [c]Reaction was carried out at -40 ℃. [d]2.5 equivalents of DMDO were used. [e]Yield was measured by ^{1}H NMR in the crude with TMB as IS. [f]The reaction was carried out using 1 eq of furan, 3 eq of allenamide and 6.3 eq of DMDO.

These results agree with some publications[41] by Shimizu and Hoffmann where it was indicated that apolar solvents may induce type B/C mechanisms instead of a concerted A pathway which is the main mechanism operating when polar solvents are used.[41a] Authors explained this change on mechanism by the power of the solvent to stabilize and dissociate the cation/counterion pair. The more polar solvent can fully dissociate the cations making it more electrophilic, while in apolar solvents the cation forms tightly bonded ion-pair with the phosphate ion. The full dissociation favours a concerted pathway while a partial dissociation favours a stepwise manifold starting by the electrophilic addition to the oxyallyl cation/phosphate anion pair.

Finally and with these improved reaction conditions on hand, we decided to reevaluate other catalysts trying to obtain a better performance in terms of enantiocontrol. We prepared electronically structurally different BINOL-based phosphoramides as phosphoric acids and their behavior as catalysts on the (4+3) cycloaddition between **1j** and **2a** was evaluated.

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[41] (a) Shimizu, N.; Tanaka, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1330. (b) Hoffmann, H. M. R.; Chidgey, R. *Tetrahedron Lett.* **1978**, *1*, 85.

Table 2.5 Evaluation of a series of catalysts

Entry	Catalyst	Yield[a]	ee[b]
1	**3g**	**78**	**82**
2	**3h**	33	65
3	**3i**	70	49
4	**3j**	27	<5
5	**3k**	69	-56
6	**3l**	20	25
7	**3m**	40	14
8	**3n**	19	12
9	**3o**	45	70
10	**3p**	28	26

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product.

As shown in Table 2.5, we started by modulating the acidity of the original catalyst **3g** (entry 1 shown for comparison purposes) with the presence of thiophosphate group (entry 2) that led to an important loss of yield and a slight drop in the enantiocontrol. The less acidic partially reduced catalyst **3i** (entry 3) was able to promote the reaction with good yield but with an important loss of enantioselectivity. Next, we decided to evaluate steric effects on 3,3´-positions, starting with catalyst **3j** incorporating the bulky *tert*-butyl dimethyl silyl group (entry 4), that led to an important loss of enantioselectivity. Chiral phosphoric acid **3k** containing a spirobiindane scaffold which is very similar in acidity to **3i** but with different geometrical features afforded the contrary enantiomer of **4j** with poor enantioselectivity (entry 5). Next, BINOL-based phosphoramides with aryl substituents at the 3,3´positions were evaluated. In this sense, catalyst **3l**, **3m** and **3n** with a phenanthrenyl group (entry 6), biphenyl group (entry 7) and p-methoxyphenyl group (entry 8) in 3,3´positions respectively supposed a dramatic loss in the reaction yield and enantiocontrol. The bulky 2,4,6-triisopropylphenyl group known as TRIP catalyst **3o** (entry 9) provided **4j** with a good enantiocontrol but with an important drop in the

yield of the reaction. Finally, bisphosphoric acid catalyst **3p** (entry 10) was evaluated but the results indicate that probably higher acidity was necessary.

Therefore, **3g** remained as the best catalyst to perform the (4+3) cycloaddition reaction. Thus, after a wide range of experimental variables had been explored, we concluded that the optimal conditions for the reaction involved the use of 5 mol% of the chiral Brønsted acid **3g** catalyst, DMDO in toluene as oxidant to generate the oxyallyl cation and 13 equivalents of furan, working in EtOAc as co-solvent in a 0.05M reaction concentration at -78 ºC (see Scheme 2.27).
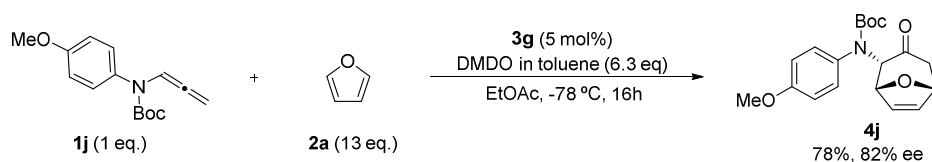
Scheme 2.27

3.3 Scope of the reaction
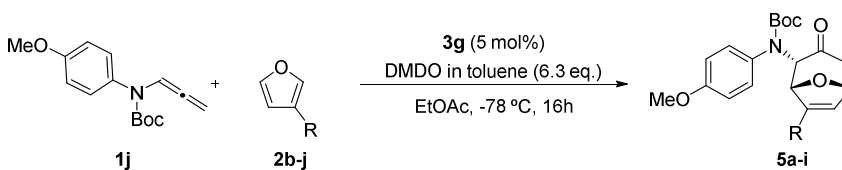
Once the best reaction conditions for carrying out the (4+3) cycloaddition reaction between allenamide **1j** and furan had been established, we decided to extend the methodology to other dienes with different substitution patterns. Initially, we performed the reaction between allenamide **1j** and 3-methylfuran **2b** using the optimized conditions but we obtained the corresponding cycloadduct in a poor 53% yield. However, when the reaction was carried out using furan as the limiting reagent in the presence 3-fold excess of allenamide and 6.3 equivalents of oxidant added portionwise lead to better a reaction yield in a high regioselectivity as it is shown in Scheme 2.28.
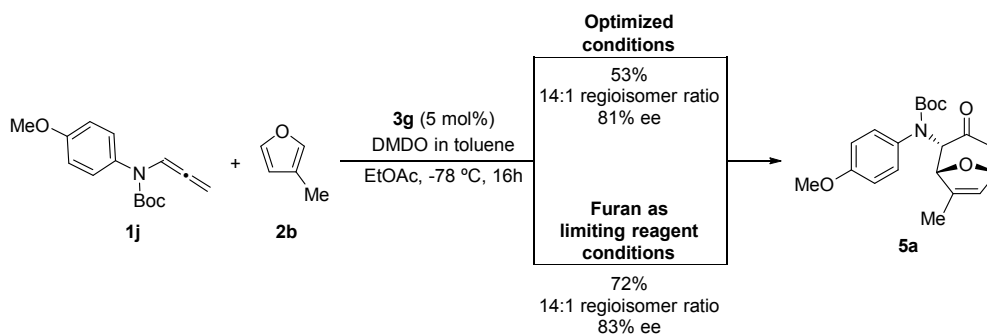
Scheme 2.28

These last conditions were extended to the reaction between allenamide **1j** and a variety of furans (Table 2.6). When 3-methylfuran was used (entry 1) very high enantioselectivity was obtained; while the 3-ethyl derivative (entry 2) slightly drops the reaction yield and enantiocontrol. Furans with longer or bulkier alkyl substituents at this position provides the corresponding adducts with better enantioselectivity, although in low to moderate yield (entries 3-5). Furan **2g** incorporating an olefinic side chain did not give good results in terms of yield very likely because of a competitive oxidation side reaction (entry 6). Finally, when aryl substituents with different electronic properties were introduced at the furan scaffold the reaction performed very poorly (entries 7-9). The same happened when a halogen group or an ester group were incorporated at this position (entries10-11), in which cycloaddition did not take place. In all cases the reaction proceeded diastereoselectively obtaining the *endo* product and also the *syn* regioisomer was obtained as major isomer out of two possible ones.

Table 2.6 Scope of the reaction with 3-substituted furans[a]

Entry	R	Product	Yield	regioisomer ratio[b]	ee[c]
1	Me (**2b**)	**5a**	72	14:1	83
2	Et (**2c**)	**5b**	66	10:1	71
3	o-MeC$_6$H$_4$CH$_2$ (**2d**)	**5c**	45	10:1	85
4[d]	^{i}C$_5$H$_{11}$ (**2e**)	**5d**	40	15:1	76
5	CH$_2$CH$_2$Ph (**2f**)	**5e**	30	18:1	62
6	(Z)-PhCH=CH (**2g**)	**5f**	12	>20:1	86
7	Ph (**2h**)	**5g**	34	>20:1	76
8	p-MeOC$_6$H$_4$ (**2i**)	**5h**	17	>20:1	63
9	p-FC$_6$H$_4$ (**2j**)	**5i**	34	>20:1	57
10	Br	-	n.r.[e]	-	-
11	CO$_2$CH$_3$	-	n.r.[e]	-	-

[a]Reaction carried out in a 0.05 mmol scale of **2b-j**, using 3.0 eq. of allenamide **1j**, 6.3 eq. of DMDO (as solution in toluene) and 5 mol% of **3g** in AcOEt at -78ºC. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis of the pure product. [d]1 eq of allene, 2.5 eq. of DMDO and 2 eq. of furan were used. [e]No reaction.

Other functionalized furans were also prepared and evaluated in the (4+3) cycloaddition reaction (see Table 2.7). The use of *O*-protected 2-(hydroxymethyl)furan derivatives lead to the formation of *endo-syn* products with high yields and enantioselectivities. Remarkably, the use of

O-silyl protected furans, **2m** and **2n** resulted into a highly efficient reaction in terms of both yield and stereocontrol (adducts **5l** and **5m**). We evaluated the use of 3-(hydroxymethyl)furan **2o** but the reaction did not work. We also studied the performance of the reaction using *N*-(*p*-methoxyphenyl)-protected 2-aminomethyl substituted furans (**2p-s**). In this case, using a Boc-protected substrate **2p** provided adduct **5n** in a moderate yield and poor enantioselectivity but changing to an amide as the protecting group led to an important improvement in the performance of the reaction obtaining **5p** with a good 71% ee with *N*-propionamide derived substrate **2r**. When moving to the more bulky pivaloyl derivative **5q**, enantioselectivity was lower and no reaction was observed with N-unprotected aminomethyl substituted furan **2t**.

Table 2.7 Scope of the reaction with functionalized furans[a]

5j[b]	**5k**	**5l**	**5m**	
Yield 57%	Yield 54%	Yield 68%	Yield 70%	n.r.
ee 82%	ee 89%	ee 90%	ee 91%	

5n[b]	**5o**	**5p**[b]	**5q**	
Yield 50%	Yield 78%	Yield 76%	Yield 75%	n.r.
ee 60%	ee 69%	ee 71%	ee 54%	
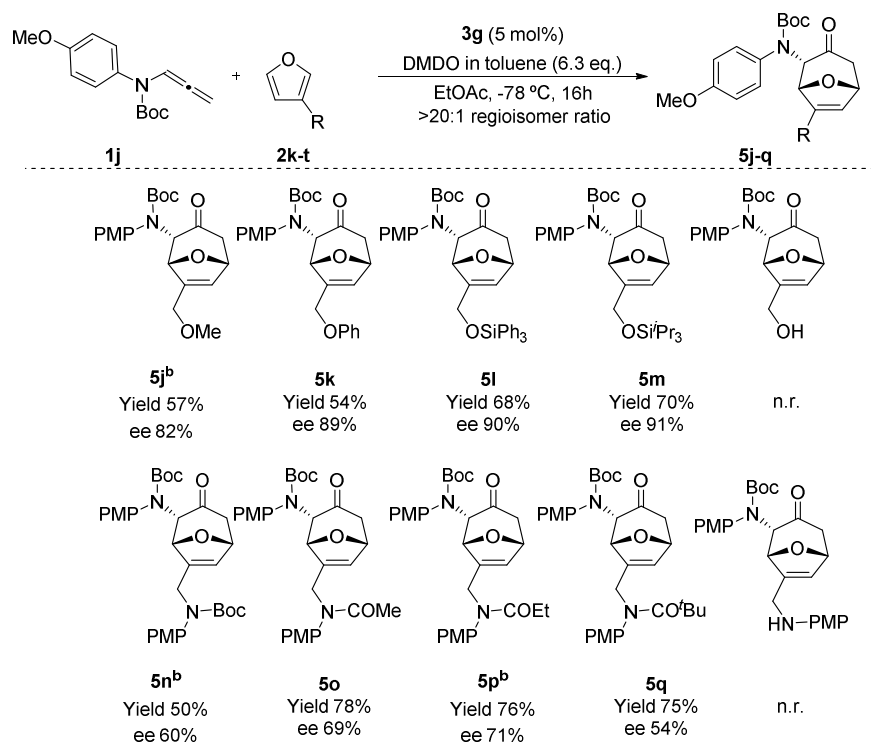
[a]Reaction carried out in a 0.05 mmol scale of **2k-t**, using 3.0 eq. of allenamide **1j**, 6.3 eq. of DMDO (as solution in toluene) and 5 mol% of **3g** in AcOEt at -78°C. [b]1 eq. of allene, 2.5 eq. of DMDO and 2 eq. of furan. Yield of pure product isolated after flash chromatography. ee determined by HPLC analysis of the pure product. n.r. refers to no reaction.

Next we proceeded to evaluate the possibility of carrying out the reaction with 2-substituted furans (see Scheme 2.29). However, none of them provided any (4+3) cycloaddition product. In the case of 2-methylfuran **2u** the Friedel-Crafts type alkylation product was observed,

while for 2,5-dimethylfuran **2v** the starting material was recovered unaltered. The formation of the alkylation product in the reaction with 2-methylfuran might suggest a possible stepwise pathway for this cycloaddition reaction.
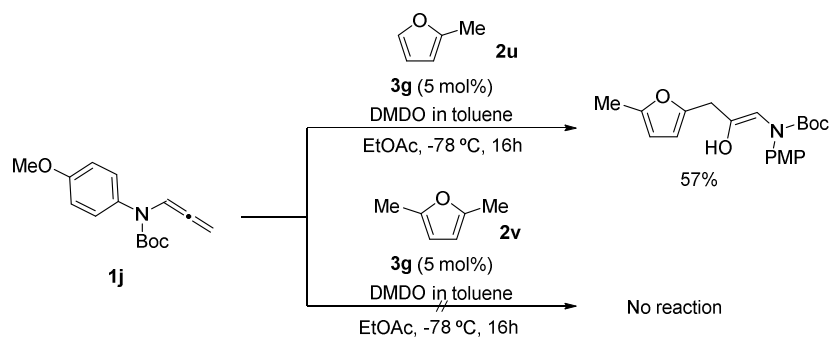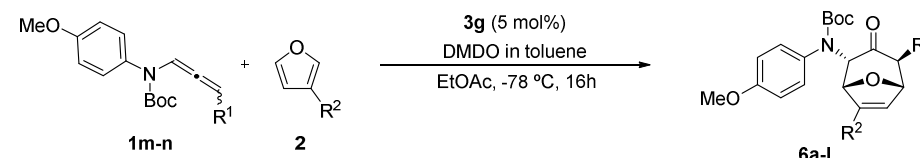
Scheme 2.29

Finally, the reaction was also carried out with more nucleophilic cyclopentadiene **2w** and the more reactive 6,6-dimethylfulvene **2x**. In both cases some cycloaddition product could be isolated in low yields and with complete lack of enantiocontrol (see Scheme 2.30). It has to be mentioned that several pyrroles, tiophenes and acyclic dienes such as Danishefsky´s diene were evaluated with no success.
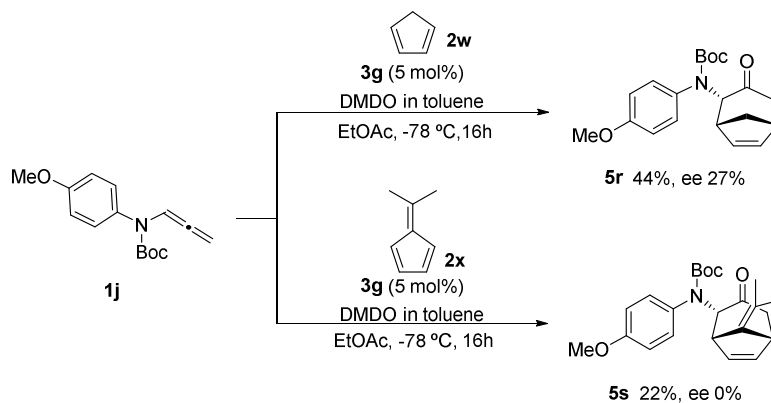
Scheme 2.30

Next, we turned our attention to the use of substituted allenamides as potential substrates in this reaction (see Table 2.8). It has to be highlighted that there are no precedents in catalytical enantioselective (4+3) cycloadditions using substituted allenes in terminal position.

Table 2.8 Scope of the reaction with γ-substituted allenamides and 3-substituted furans[a]

Entry	R¹ (allene)	R² (furan)	Prod.	Yield	regioisomer ratio[b]	ee[c]
1[d]	Me (**1l**)	H (**2a**)	**6a**	67	-	35
2	Me (**1l**)	Me (**2b**)	**6b**	86	15:1	81
3	Me (**1l**)	o-MeC$_6$H$_4$CH$_2$ (**2d**)	**6c**	53	>20:1	73
4	Me (**1l**)	CH$_2$OSiPh$_3$ (**2m**)	**6d**	64	>20:1	90
5	Me (**1l**)	CH$_2$OSi^{i}Pr$_3$ (**2n**)	**6e**	75	>20:1	85
6[d,e]	Et (**1m**)	H (**2a**)	**6f**	64	-	35
7[e]	Et (**1m**)	Me (**2b**)	**6g**	76	10:1	92
8	Et (**1m**)	o-MeC$_6$H$_4$CH$_2$ (**2d**)	**6h**	60	>20:1	87
9	Et (**1m**)	CH$_2$OSi^{i}Pr$_3$ (**2n**)	**6i**	82	>20:1	93
10	Et (**1m**)	CH$_2$CH$_2$Ph (**2f**)	**6j**	73	>20:1	77
11	Et (**1m**)	CH$_2$CH$_2$CO$_2$Et (**2y**)	**6k**	70	>20:1	85
12[e,f]	Et (**1m**)	CH$_2$N-(p-OMeC$_6$H$_4$)(COEt) (**2r**)	**6l**	60	>20:1	68
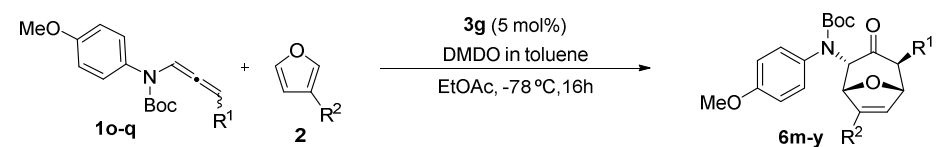
[a]Reaction carried out in a 0.05 mmol scale of **2**, using 3.0 eq. of allenamide **1l-m**, 6.3 eq. of DMDO (as solution in toluene) and 5 mol% of **3g** in AcOEt at -78°C. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis of the pure product. [d]1 eq allene, 2.5 eq of DMDO in toluene and EtOAc, 13 eq furan. [e]1 eq allene, 2.5 eq of DMDO in toluene and EtOAc, 2 eq diene. [e]The enantiomer of catalyst **3e** was used under the same reaction conditions. [f]5 eq. of allene, 12.5 eq of DMDO, 1 eq. diene.

We first tested methyl-substituted allenamides **1m** in combination with furan **2a** but despite the fact that cycloadduct **6a** was isolated in good yield and as a single diastereoisomer, the enantioselectivity was very poor (entry 1). However, other 3-substituted furans performed much better, starting with 3-methylfuran (**2b**, entry 2), 3-benzylsubstituted derivative (**2d**, entry 3) and two *O*-protected hydroxymethyl substituted furans (**2m** and **2n**, entry 4 and 5 respectively). In all these cases the reaction provided moderate to high yields, excellent diastereoselectivities and high ee. Moreover, the reaction also proceeded with high regiocontrol, only observing minor amounts of the other possible regioisomer in the case of 3-methylfuran (entry 2). When we moved to the use of ethyl substituted allenamides **1n** the reaction behaved similarly (entries 6-12). In fact, while the cycloaddition with furan proceeded with poor ee, other substituted furans behaved excellently, furnishing the corresponding adducts with high yields diastereoselectively with high enantiocontrol and regioselectively. Moreover, in this case the reaction also tolerated well the incorporation of other different substitution patterns such as 2-

phenethyl (entry 10), 2-ethoxycarbonylethyl (entry 11) and protected *N*-(*p*-methoxyphenyl)aminomethyl (entry 12) that also performed well in the reaction.

Remarkably, allenamides **1n** incorporating a more bulky cyclohexyl substituent performed much better in all cases as shown in Table 2.9 including the possibility of using the simple furan **2a** as diene (entry 1). The reaction with a variety of 3-substituted furans proceeded in all cases with the highest degree of enantiocontrol observed in all the series and also with good yield and complete *endo* selectivity (entries 1-6). We finally moved to evaluate allenamides **1o** and **1p** (entries 7-13) that incorporate an aryl and a protected hydroxyl group at the lateral chain observing similar results of those observed before.

Table 2.9 Scope of the reaction with γ-substituted allenamides and 3-substituted furans

Entry	R^1 (allene)	R^2 (furan)	Prod.	Yield	r.r.[b]	ee[c]
1[d]	$^cC_6H_{11}$ (**1n**)	H (**2a**)	**6m**	44	-	80
2	$^cC_6H_{11}$ (**1n**)	Me (**2b**)	**6n**	40	>20:1	94
3	$^cC_6H_{11}$ (**1n**)	*o*-MeC$_6$H$_4$CH$_2$ (**2d**)	**6o**	76	>20:1	97
4	$^cC_6H_{11}$ (**1n**)	CH$_2$OSi^{i}Pr$_3$ (**2n**)	**6p**	87	>20:1	99
5	$^cC_6H_{11}$ (**1n**)	CH$_2$CH$_2$Ph (**2f**)	**6q**	70	>20:1	95
6[e]	$^cC_6H_{11}$ (**1n**)	CH$_2$N-(*p*-OMeC$_6$H$_4$(COEt))(**2r**)	**6r**	51	>20:1	96
7[d]	CH$_2$CH$_2$Ph (**1o**)	H (**2a**)	**6s**	30	-	13
8[e]	CH$_2$CH$_2$Ph (**1o**)	Me (**2b**)	**6t**	60	10:1	84
9[f]	CH$_2$CH$_2$Ph (**1o**)	CH$_2$OSi^{i}Pr$_3$ (**2n**)	**6u**	62	>20:1	82
10[d]	CH$_2$CH$_2$OTBS (**1p**)	H (**2a**)	**6v**	37	-	10
11[f,g]	CH$_2$CH$_2$OTBS (**1p**)	Me (**2b**)	**6w**	82	15:1	79
12[f]	CH$_2$CH$_2$OTBS (**1p**)	CH$_2$OSi^{i}Pr$_3$ (**2n**)	**6x**	34	>20:1	83
13[f,g]	CH$_2$CH$_2$OTBS (**1p**)	CH$_2$OSiPh$_3$ (**2m**)	**6y**	73	>20:1	85

[a]Reaction carried out in a 0.05 mmol scale of **2**, using 3.0 eq. of allenamide **1o-q**, 6.3 eq. of DMDO (as solution in toluene) and 5 mol% of **3g** in AcOEt at -78ºC. [b]Regioisomer ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis of the pure product. [d]1 eq allene, 2.5 eq of DMDO in toluene and EtOAc, 13 eq furan. [e]1 eq allene, 2.5 eq of DMDO in toluene and EtOAc, 2 eq diene. [f]5 eq. of allene, 12.5 eq. of DMDO, 1 eq. diene. [g]The enantiomer of catalyst **3e** was used obtaining the opposite enantiomer as major isomer under the same reaction conditions.

At this point, the absolute configuration of the cycloadducts obtained by this protocol was established by single-crystal X-ray analysis of an enantiopure sample of compound **6t**, for which a monocrystalline sample could be obtained (see Figure 2.7). Accordingly to the stereostructure

obtained for this compound, the configuration of all other adducts **6a-y**, was established by assuming the same stereochemical outcome for all reactions between allenamides **1m-q** and furans **2** based on mechanistic analogy.
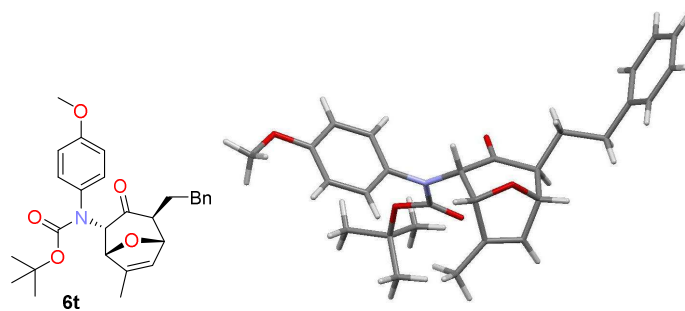
Figure 2.7

3.4   Mechanistic proposal

Based on the obtained stereochemical outcome of the reaction, we present herein a mechanistic proposal that can explain the regio- and stereoselective outcome of the process.
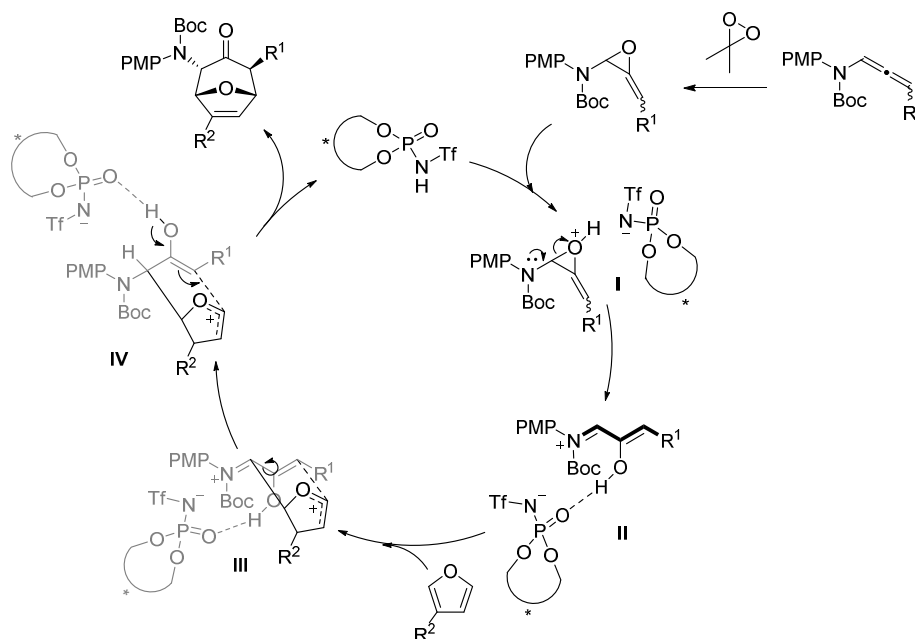
Scheme 2.31 Mechanistic proposal

The reaction would start with the regioselective epoxidation of the more electron rich alkene moiety of the allene in the presence of DMDO, forming the oxirane intermediate **I** which in the presence of chiral Brønsted acid **3g** would lead to the key oxyallyl cation **II**. Once the oxyallyl cation is formed the catalyst would interact *via* H-bonding with the OH moiety and it is also proposed that the phosphate anion would remain close to the iminium cation through ion-pairing interactions, lowering the LUMO of the oxyallyl cation to favour the reaction with the nucleophile. Our proposal relies on a more plausible stepwise mechanism base both in the literature precedent regarding computational studies carried out by Houk and Harmata on related Lewis-acid catalyzed processes[36] and also on the fact that side products arising from Friedel-Crafts type reactivity has been observed in some cases. In this sense, the first σ bond will be formed between the most nucleophilic site on the diene and the most electrophilic site on the cation assisted by the chiral phosphoramide anion forming intermediate **III** which should have a

long enough lifetime to undergo bond rotation before generating the second σ bond to lead to the formation of the final cycloadduct with the observed relative configuration between the two substitution of the oxyallyl cation.

According to the experimental results, a major *syn* regioisomer is obtained in all cases. As it is shown in Figure 2.8, the approximation of the furan to the oxyallyl cation is proposed to be controlled by electronic effects with the most nucleophilic site of the furan and the most electrophilic site of the oxyallyl cation reacting between each other in the first step. The minor regioisomer it is thought to be formed through the background side background reaction because this minor regioisomer has always been obtained as racemic material.
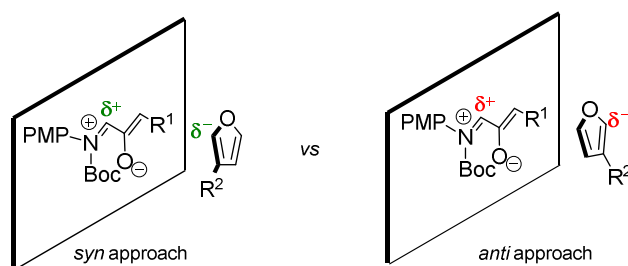
Figure 2.8

On the basis of the experimental results and as it is mentioned before, the catalyst would form a H bond with the dipole and an electrostatic interaction through an ion pair with the iminium cation which lead to a rigid transition state allowing to the furan an approach from the less hindered face (*Si*-face) because of the chiral environment created by the bulky triphenylsilyl substituents of the catalyst (see Figure 2.9). This proposal is agree with the obtained absolute configuration detected experimentally. Finally, it is proposed that *endo* selectivity is favoured due to the preferred alignment of the dipole moments of the furan and the oxyallyl cation which are in opposite directions as proposed by other authors.[42]

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[42] (a) See Ref. 35. (b) Du, Y.; Krenske, E. H.; Antoline, J. E.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Org. Chem.* **2013**, *78*, 1753. (c) See Ref. 30.
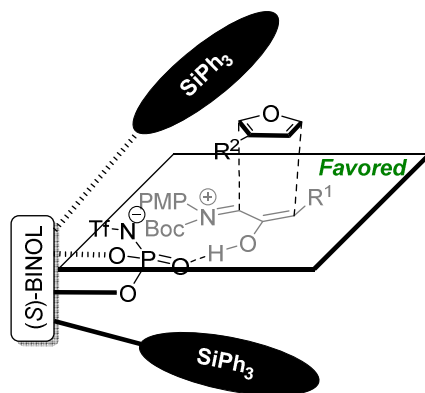
Figure 2.9 Major diastereoisomer

4.   CONCLUSION

Given the results presented in this chapter, the following conclusions can be settled:

- The *in situ* generated oxyallyl cations participate in the organocatalyzed asymmetric (4+3) cycloaddition with furans under Brønsted acid catalysis promoted by substoichiometric amounts of **3g** as the most efficient catalyst.

- The non-stable oxyallyl cations are formed *in situ* after a regioselective epoxidation in the presence of a strong oxidant which epoxidize the most electron-rich alkene.

- The described method provides excellent results with high yields and enantioselectivities with a wide range of allenes and furans containing electron-withdrawing or electron-donating groups.

- Especially mentioned is the applicability of the methodology to γ-substituted allenes, where no precedents are in the literature.

- The cycloadducts are formed with four new stereogenic centers totally *endo* selectively, diastereoselectively, highly regioselectively and enantioselectively.

Chapter 3

CHAPTER 3

Allylation of Imines using Enantiopure Boronates

1. Introduction
2. Specific Objectives and Work Plan
3. Results and Discussion
4. Conclusions

1. INTRODUCTION

The allylation of carbonyl or azomethine compounds is a reaction of great synthetic interest because it enables the direct access to homoallylic alcohols and amines (see Scheme 3.1), which are useful building blocks widely used in the synthesis of natural products and commercial drugs.[1] Stereoselective allylation has attracted a wide interest being the asymmetric addition of allylmetal reagents to aldehydes and imines one of the most used approaches to this type of products.

M= B, Si, Sn, Ti...
X´= alkyl, halide, ether or other anion

X=O, NR´...
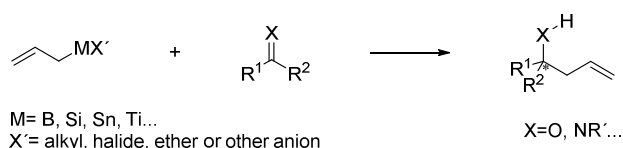
Scheme 3.1

In 1983, Denmark and Webber classified the asymmetric addition for different allylation reagents to C=X bonds into three major types, named Type I, II and III.[2] In the Type I class, allyl-metal reagents undergo reaction through the activation of the carbonyl or imine electrophile involving a closed six-membered chair-like transition state (see Scheme 3.2).[3] The metal acts as a Lewis acid to activate the aldehyde or imine and transfers the allyl fragment to the final product diastereospecificaly, where the (*E*)-allyl fragment provides the *anti*-product and the (*Z*)-allyl fragment affords the *syn* product. Such complete transfer of stereochemical information is explained by a highly organized transition state and theoretical calculations have demonstrated that a Zimmerman-Traxler chair-like transition state pathway is the lowest energy one relative to other possibilities.[4] However, this methodology presents some limitations such as the necessity to isolate diastereomerically pure (*E*) and (*Z*) allylmetal reagents.[5] Allylboron, allyllithium,

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1   For recent reviews: (a) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (c) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303. (d) Hall, D. G.; Rybak, T.; Verdelet, T. *Acc. Chem. Res.* **2016**, *49*, 2489. (d) Diner, C.; Szabó, K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2.

2   Denmark, S. E.; Weber, E. J. *Hel. Chim. Acta* **1983**, *66*, 1655.

3   (a) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236. (b) Vulpetti, A.; Gardner, M.; Gennari, C.; Bernardi, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1993**, *58*, 1711. (c) Gennari, C.; Fioravanzo, E.; Bernardi, A.; Vulpetti, A. *Tetrahedron* **1994**, *50*, 8815. (d) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331. (e) Gajewski, J. J.; Bocian, W.; Brichford, N. L.; Henderson, J. L. *J. Org. Chem.* **2002**, *67*, 4236.

4   Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.

5   (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (c) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

allylaluminate and allyltrihalosilane are reagents that are classified to typically undergo reactions with aldehydes or imines through Type I pathway.

Type I:

X= O, NR
M= B, Li, Al, SiCl₃
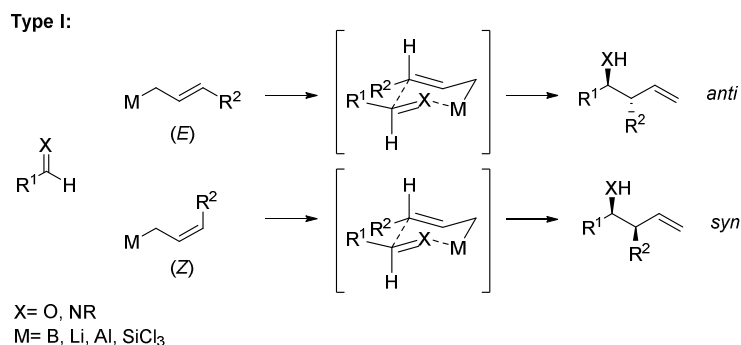
Scheme 3.2

On the other hand, Type II allylations involve the use of non-Lewis acidic metal-allyl nucleophiles (generally allyl trialkylsilanes or allyl trialkylstannanes), which react with the electrophile under the activation of an external Lewis acid, and proceed through an open transition state (see Scheme 3.3). The open transition state leads to the most favorable *syn* product due to minimized destabilizing *gauche* interactions regardless the geometry of the C=C bond of the allylmetal reagent.[6]

Type II:

M= SiR₃, SnR₃

Predominantly syn
independent of starting
allylic geometry
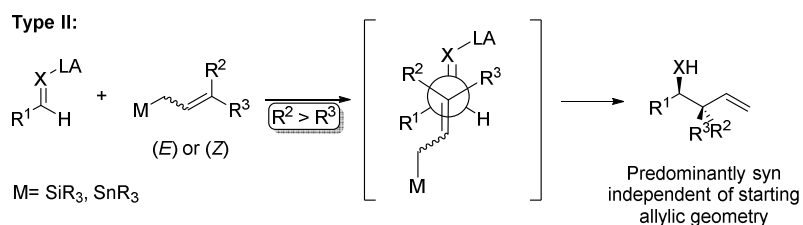
Scheme 3.3

Finally, Type III class allylation involves the use of a Lewis acidic metal-allyl fragment which is able to undergo fast *E-Z* isomerization before undergoing addition to the carbonyl or azomethine electrophile, which takes place preferentially via the (*E*) isomer (see Scheme 3.4). The reaction takes place through closed six-membered chair-like transition state, similar to Type

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6   Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.

I reagents, resulting in the *anti* diastereoisomer.[7] Allylchromium reagents are the most used ones under this reactivity scheme.

Type III:

Scheme 3.4
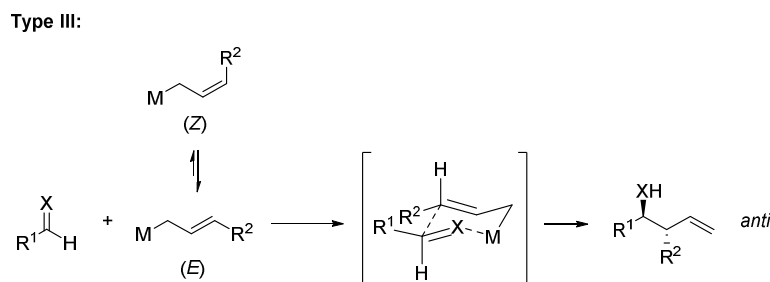
Several excellent methodologies have been reported for carbonyl allylation using a wide range of allylmetal reagents. Among the huge variety of such reagents, allylboron compounds have dominated the field across the years, together with allyltrichlorosilanes.[8] One of the main advantages associated to the use of allylboron reagents is their ease of preparation, broad functional group tolerance, high stability, low toxicity and in overall the excellent operational simplicity associated to their use as nucleophilic reagents.[9]

The allylboration of aldehydes was originally documented in 1964 by Mikhailov and Bubnov, who observed the formation of a homoallylic alcohol product from the reaction with triallylborane with aldehydes.[10] However, it was not until the late 1970s when Hoffmann reported the regio- and diastereospecific nature of the additions of the two isomers of crotylboronate to aldehydes, resulting in the beginnings of this chemistry.[11] Allylic boron reagents react with different carbonyl compounds and derivatives such as imines and other azomethine derivatives. However, their most common use is in nucleophilic additions to aldehydes to produce homoallylic secondary alcohols. In the first 20 years of development,

[7] Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

[8] (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*, Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 299-402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*, Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 403-490. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

[9] Hall, D. G. *Pure Appl. Chem.* **2008**, *80*, 913.

[10] Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964**, 1874.

[11] (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem. Int. Ed.* **1979**, *18*, 306. (b) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309.

works of Brown,[12] Roush,[13] Masamune[14] and Corey[15] were determinant in the chemistry of carbonyl allylboration to become one of the primary methodological tools in stereoselective synthesis (see Figure 3.1). All of those key contributions were based on the use of chiral auxiliaries attached to the boronate to achieve stereocontrol on the final product.[16]

Brown (1983)   Roush (1985)   Masamune (1987)   Corey (1989)
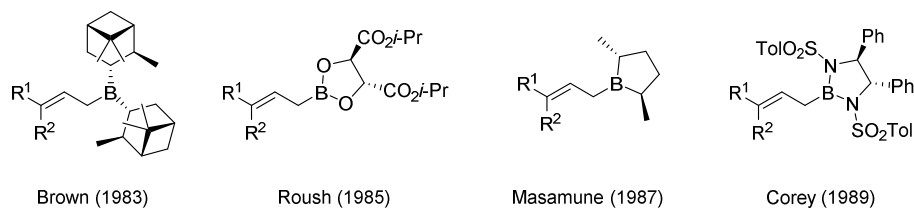
Figure 3.1

In addition to these chiral reagent-based methodologies, asymmetric catalysis also arises as a useful approach to achieve stereocontrol. In fact, one highly explored approach to optically enriched homoallyl alcohols or amines is based on the use of an achiral allyl boronate in the presence of chiral catalyst. A third possible approach to achieve stereocontrol in this reaction is the use of a chiral boron reagent in which the stereochemical information is already placed at the allyl residue that is transferred to the electrophilic carbonyl compound or imine and relies on the capacity to transfer the chirality to the new formed stereocenter (see Scheme 3.5).[17]
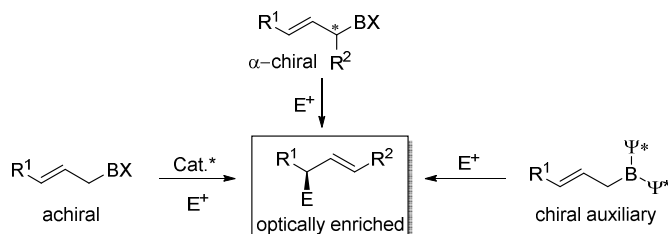
Scheme 3.5

[12] (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (c) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

[13] (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

[14] (a) García, J.; Kim, B.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. (b) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892.

[15] (a) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (b) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878.

[16] (a) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (b) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.

[17] (a) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 2004. (b) Mikhailov, B. M.; Bubnov, Y. N. *Organoboron Compounds in Organic Synthesis*, OPA, Amsterdam B. V., 1984, 571. (c) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (d) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993.

In the following pages, relevant examples of this third approach will be discussed due to their direct relationship with this research.

A good example on the capacity of chiral α-substituted allylic boronates to transfer stereochemical information to the final product was reported by Hoffmann for the synthesis of enantioenriched homoallylic alcohols by addition to achiral aldehydes.[17c] A chirally modified allyl boronate was able to differentiate the two enantiotopic faces of the aldehyde and allow an enantioselective formation of the homoallylic alcohols. These reagent-controlled additions proceed with near perfect transfer of chirality to provide two diastereomeric products (see Scheme 3.6). The obtained (*Z*) and (*E*) homoallylic alcohols were geometrical isomers with opposite stereochemistry at the new stereocentre. Remarkably, the Z/E ratio could be tuned through the rational selectivity of the substituents at the boronate moiety.
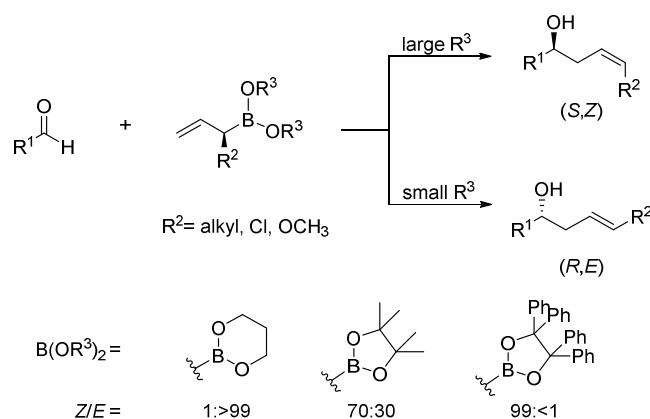
Scheme 3.6

In fact, Hoffmann,[18] Pietruszka and Schone[19] illustrated that the *E*/*Z* ratio of the homoallylic alcohol products in the allylation with secondary alkyl allylboronates was determined by the steric hindrance of the boronate fragment (see Figure 3.2). The *Z*-isomer was more likely generated with larger groups, such as pinacolate or benzopinacolate in the boronate moiety (R^3), due to destabilization of the transition structure (TS2) by a (dominant) *gauche* steric interaction between the boronic ester and the pseudo-equatorial α-substituent (R^2).[18,20] However,

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[18] (a) See Ref. 14c and 14d. (b) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem.* **1985**, *195*, 137.

[19] Pietruszka, J.; Schone, N. *Eur. J. Org. Chem.* **2004**, 5011.

[20] Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12444.

TS1 is also destabilized by 1,3-diaxial interactions when R^2 substituent is oriented in the axial position.[21] This is the reason of poor selectivity observed; the use of Lewis acids to modify the geometry of these transition states, and thus the stereoselectivity, has been studied by the groups of Hall and later Roush.[22] Dipolar effects also influence in the stabilization of the transition state TS1, thus when polar substituents were used (R^2) such as halogen or alkoxy groups, dipolar effects tend to dominate and further favor the transition structure TS1 with the pseudoaxial C-R^2 bond oriented *anti* to the axial B-O bond leading to the formation of *Z* and *E* homoallylic alcohol in modest selectivities.[18b]
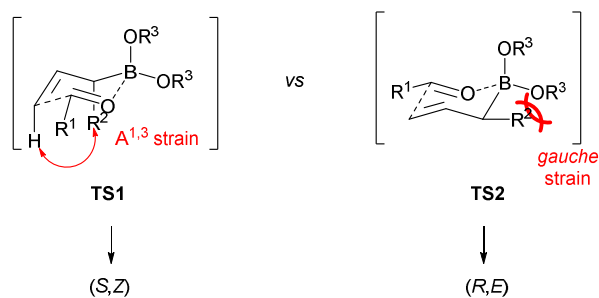
Figure 3.2

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21   Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913.

22   (a) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981. (b) Chen, M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 2706.

The group of Aggarwal has disclosed two different and diastereodivergent methodologies for overcoming this issue with aldehydes, providing densely functionalized homoallylic alcohols in high yields with almost complete diastereo- and enantioselectivity.[23] The first method relies on transforming chiral α-substituted crotylBpin reagents into their corresponding borinic esters *via* sequential treatment with *n*BuLi and trapping the alkoxyde intermediate with TFAA, and subsequently showing high reactivity and selectivity with a range of representative aldehydes (see Scheme 3.7). The reaction is initiated by the addition of *n*Buli to the boronic ester at low temperatures generating the ate complex which might be in equilibrium with the ring opened and coordinately unsaturated borinic ester. Although the equilibrium would lie on the side of the ate complex, the higher reactivity of the borinic ester was expected to be trapped by the addition of TFAA. Addition of aldehyde led to a six-membered chair-transition state obtaining almost complete *E*-selectivity for homoallylic alcohols due to a less sterically environment around boron avoiding clashes between the equatorial α-substituent at the transition state. Evidences of the intermediates were obtained following the course of the allylation reaction by ^{11}B NMR. This strategy has been applied in total synthesis for the preparation of natural products such as (–)-Clavosolide A developed by Aggarwal.[24]
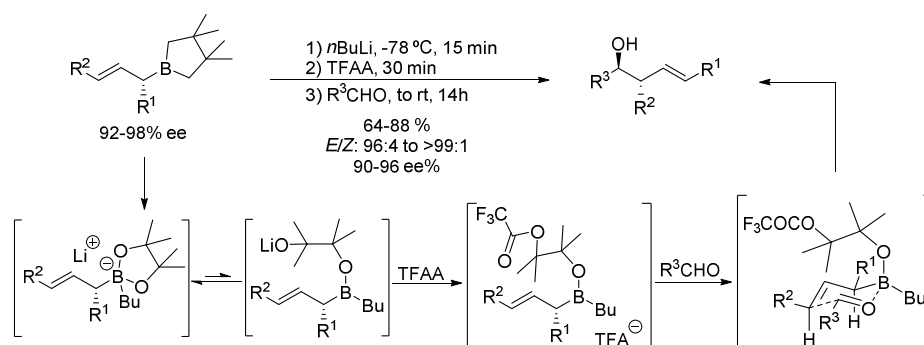
Scheme 3.7

The second approach by this group involves the use of chiral α,α-disubstituted allylic pinacol boronic esters bearing an alkyl group in β-position with a range of different aldehydes.[25] In this case, a bulkier aryl group prefers the axial position of the transition state in order to avoid

23 Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316.

24 Millán, A.; Smith, J. R.; Chen, J. L.-Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 2498.

25 Hesse, M.; Essafi, S.; Watson, C.; Harvey, J.; Hirst, D.; Willis, C.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 6145.

steric clash between both the bulky pinacolate moiety and the adjacent methyl group, giving access to (*Z*)-homoallylic alcohols in complete diastereoselectivity (see Scheme 3.8). Notably, this methodology allows access to enantioenriched homoallylic alcohols with adjacent stereocenters and a tetrasubstituted olefin.
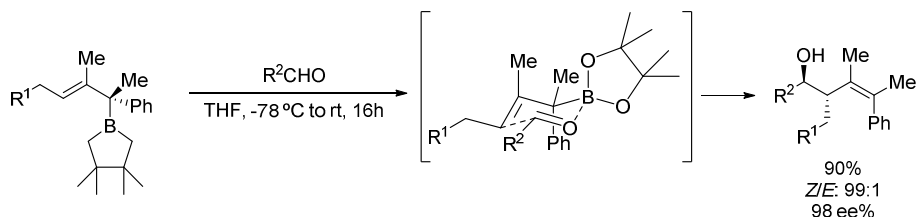
Scheme 3.8

Imines can also undergo allylation reactions with chiral boron reagents which are very attractive way in that they provide a route to homoallylic amines, which as mentioned before, are useful synthetic intermediates in natural product synthesis and drug discovery.[26] However, the addition of allylic boronates to imines is much slower than the additions to the corresponding aldehyde and can often be less selective. This is due to the decreased polarization of the C=N double bond and to the fact that imines are not always configurationally stable and may undergo *E*/*Z* isomerization or even tautomerization to the corresponding enamine in the case of enolizable imines. Nevertheless, and due to the preference of imines to exist in an *E*-geometry, they are expected to have higher activation barriers compared with carbonyl analogues expecting different stereoselectivity due to unfavorable 1,3-diaxial interactions that can occur in the transition state (see Figure 3.3).[27]
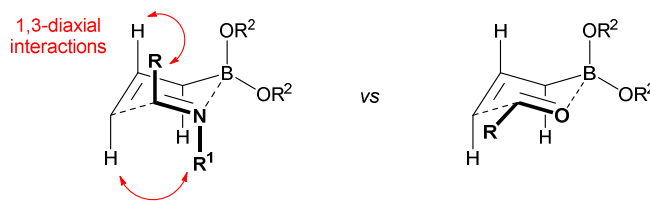
Figure 3.3

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26   (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

27   Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115.

Due to the relation with the present project, allylboration reactions with imines *via* chirality transfer from *C*-chiral allylboronates will be only discusses in the following pages.[28]

An example to accessing homoallylic amines in enantioselective fashion through chiral allylboronate chemistry is shown in Scheme 3.9 and relies on the use of prochiral allenes which in the presence of a palladium catalyst and a chiral ligand form a chiral diboron intermediate that contains both allylboronate and vinylboronate functional groups that subsequently undergo addition to imines, observing excellent levels of chirality transfer.[29] Morken developed a one-pot tandem allene diboration/imine allylation process with *in situ* generated primary imines through reaction of an aldehyde and ammonium acetate. Considering the selectivity achieved in the allene diboration reaction step, the level of chirality transfer in the subsequent allylation reaction often approaches 99%. It has to be highlighted that the enantiomer of the ligand used in the diboration reaction led to (*S*) configuration of the intermediate (R^2=Ph) and the final product was isolated with the (*R*) configuration. As a consequence, it is likely that the allylation reaction proceeds through a transition state structure similar to the one expected for Type I allylmetal compounds.[30] In this model, R^1 group would place in a pseudo-axial position due to the destabilized 1,2-strain present in the diastereomeric transition structure B.

Scheme 3.9

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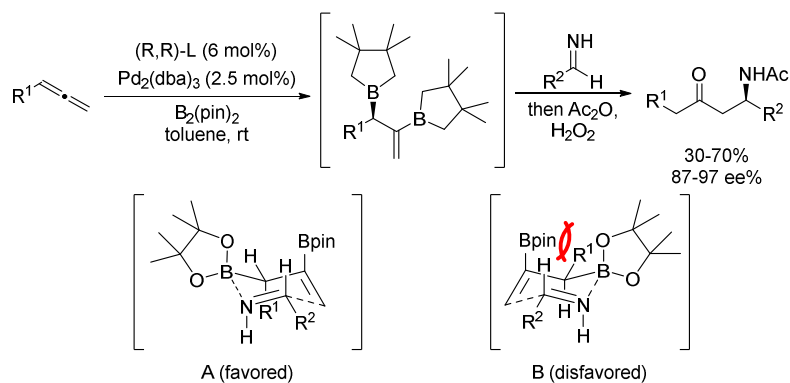
[28] For some examples of allylborations with imines through B-chiral allylic boronates: (a) Chataigner, I.; Zammatio, F.; Lebreton, J.; Villiéras, J. *Synlett* **1998**, 275. (b) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 825. (c) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.

[29] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74.

[30] (a) See Ref. 16e and 16d. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991.

A direct application of chiral allylboration of imines towards the synthesis of relevant heterocyclic structures was reported by Aggarwal,[31] by combining the use of C-chiral allyl boronates with the amination of tertiary potassium trifluoroborates with alkyl azides for the application towards cyclic substrates particularly with certain 2,2-disubstituted piperidines which have emerged as promising neurokinin 1 antagonists that possesses unique antidepressant, anxiolytic and antiemetic properties (see Scheme 3.10).[32]
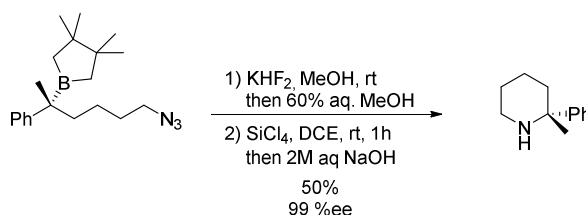
Scheme 3.10

Aggarwal has also reported the possibility of using the traditionally unreactive 3,3-disubstituted allylic pinacol boronic esters[33] in the allylation of imines.[34] As mentioned, this type of boronic esters are not sufficiently reactive to react with ketones and imines by themselves. However, Aggarwal demonstrated the enhanced reactivity of borinic esters in the allylation of aldehydes obtaining high diastereo- and enantioselectivities. Aggarwal showed the versatility of the methodology in the use of challenging imines as electrophiles for the unprecedented construction of two adjacent quaternary stereogenic centers (see Scheme 3.11).
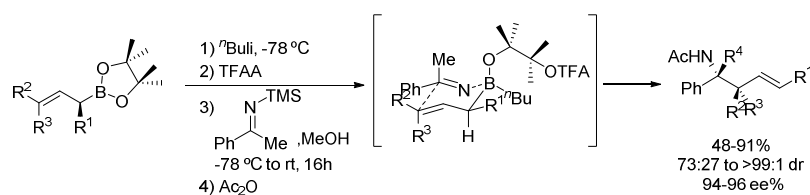
Scheme 3.11

The borinic ester was prepared *in situ* after the sequential addition of *n*Buli to the corresponding boronic ester followed by quenching with TFAA. Next, these boronic esters can

31 Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 1080.

32 Xiao, D.; Lavey, B. J.; Palani, A.; Wang, C.; Aslanian, R. G.; Kozlowski, N.-Y.; Shih, A. T. *Tetrahedron Lett.* **2005**, *46*, 7653.

33 Hoffmann, R. W.; Sander, T. *Chem. Ber.* **1990**, *123*, 145.

34 Chen, J. L.-Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 10992.

react smoothly with different aldimines and ketimines to give *E*-homoallylic amines exclusively in good yields and complete enantiospecificity (see Scheme 3.11). The reaction proceeded better with aldimines than with ketimines in terms of reaction yield. A clear advantage of this methodology is that it is completely stereodivergent allowing the preparation of the four possible stereoisomers by simply changing the *E*/*Z* geometry of the allylboronate and the absolute configuration of its α-stereocenter.

In summary, despite the long history of allylic boronates being used as nucleophiles in the addition reactions to carbonyl compounds and derivatives, it is only in the past few years that their full potential has begun to be fully realized. In particular, the use of enantiopure allylboronates to obtain homoallylic amines through enantiospecific addition has not been very extensively investigated. As it is shown in the different examples presented from the literature, allylation of imines with the α-chiral allylboronates performs with high or excellent chirality transfer as it happens with aldehydes, making this methodology a powerful approach.[35] Despite these significant advances in imine allylboration, some challenges in terms of substrate generality and control of stereoselectivity still remain unexplored.

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[35] (a) Pietruszka, J.; Schöne, N.; Frey, W.; Grundl, L. *Chem. Eur. J.* **2008**, *14*, 5178. (b) Hoffmann, R. W.; Landmann, B.; *Tetrahedron Lett.* **1983**, *24*, 3209. (c) Hoffmann, R. W.; Landmann, B. *Angew. Chem. Int. Ed.* **1984**, *23*, 437. (d) Hoffmann, R. W.; Landmann, B. *Angew Chem. Int. Ed.* **1986**, *25*, 189. (e) Hoffmann, R. W.; Wolff, J. J. *Chem. Ber.* **1991**, *124*, 563.

2.   SPECIFIC OBJECTIVES AND PRECEDENTS IN THE GROUP

The group of Prof. A. Malkov in Loughborough University, where I incorporated in a context of a short stay, had recently reported a novel method for the allylation of aldehydes that involves an efficient kinetic resolution of chiral racemic allyl boronates under chiral Brønsted acid-catalysis.[36] The reaction proceeded through high face- and *Z*-selective fashion, leading to *Z*-homoallylic alcohols as major products (see Scheme 3.12). The reaction tolerated a wide range of aldehydes with a very high *Z*-selectivity (>25:1). In this initial report, emphasis was placed on the synthesis of the homoallylic alcohols as products, but the potential applicability of this approach to resolve the starting allylboronate reagents had not been covered at that moment.
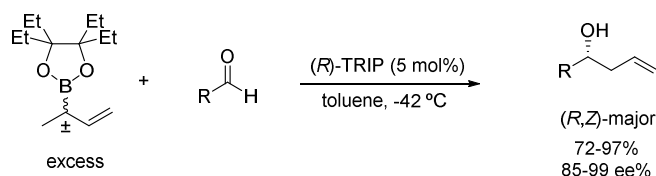
Scheme 3.12

In this context, the aim of the present project is to **establish the conditions for the efficient kinetic resolution of chiral racemic secondary allylboronates** through 1,2-addition to benzaldehyde employing chiral Brønsted acids as catalyst and to **use the resolved chiral allylboronates reagents in the allylation of primary imines** for the synthesis of enantioenriched *N*-unsusbtituted homoallylic amines (see Scheme 3.13).
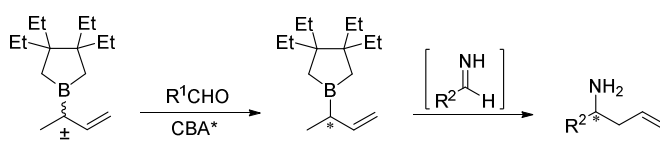
Scheme 3.13

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36   Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5338.

Considering all this aspects, the following work plan was designed:

1.   *Optimization of the Kinetic Resolution step: Enantioselective synthesis of allylboronates*

As it was mentioned, the previous report by the group of Prof. Malkov was not focused in the potential of the methodology to achieve an efficient resolution of the racemic allylboronates that would lead to the isolation of these reagents as enantiopure materials. For that reason, conditions to obtain this enantiopure boronates would be first needed to be optimized working on the allylation of benzaldehyde with boronate **7b** under Brønsted acid catalysis conditions reported initially (see Scheme 3.14).
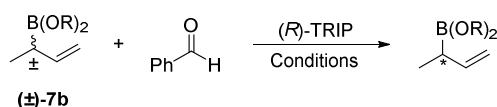
Scheme 3.14

2.   *Allylation of primary imines: Reaction optimization*

Once the optimal reaction conditions for the resolution of the starting boronates are established, we will proceed to explore the use of these chiral substituted allylboronates for the allylation reaction of imines (see Scheme 3.15). In particular, we decided to face the challenge of using primary imines as substrates that would allow the direct obtention of *N*-unprotected homoallyl amines without the need for deprotection.

Scheme 3.15
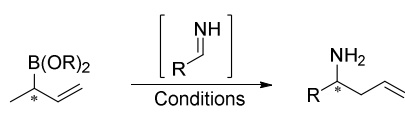
3.   Scope of the reaction: Enantiospecific allylation of imines

Once the optimal conditions for the allylation process using the enantiopure boronate had been established with the model reaction, a variety of imines with different substitution patterns will be evaluated in combination with the enantiopure allylboronate obtained before in order to explore the scope of the reaction (see Scheme 3.16).
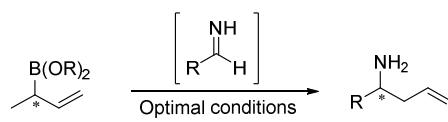
Scheme 3.16

3.   RESULTS AND DISCUSSION

Having reviewed the representative examples found in the literature on this topic and after establishing the specific objectives of the project and a suitable work plan, we will proceed with the discussion of the most relevant results obtained in this part of our research.

3.1   Optimization of the Kinetic Resolution step: Enantioselective synthesis of allylboronates

The starting allylboronates are prepared in a racemic form from the corresponding diol through a one-pot reaction which starts with the formation of the dialkoxyborane intermediate followed by a transmetallation step with crotyl magnesium bromide. The starting diols are either commercially available or prepared following a known procedure that involves the pinacol coupling of 3-pentenone in the presence of samarium iodide (see Scheme 3.17).
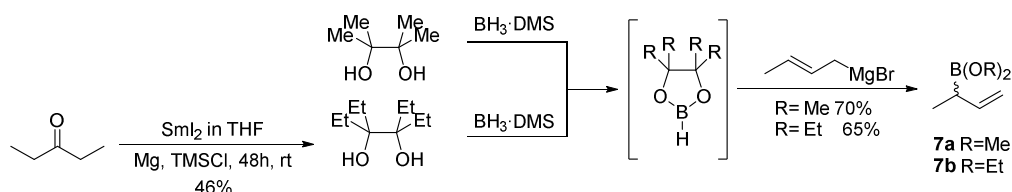
Scheme 3.17

Once the starting materials were prepared, we proceeded to study their kinetic resolution using the conditions reported previously (see Scheme 3.12). Under these reaction conditions and adjusting the number of equivalents of boronate and benzaldehyde to an accurate 2:1 boronate/benzaldehyde relationship, allylboronate (*S*)-**7b** was isolated in 97% ee and in 45% yield out of a maximum of 50% (see Scheme 3.18). The lower reactivity of the the (*S*) enantiomer of the starting material towards the 1,2-addition with benzaldehyde in the presence of (R)-TRIP prhosphoric acid catalyst is in accordance with the mechanistic studies carried out by Malkov.[36]
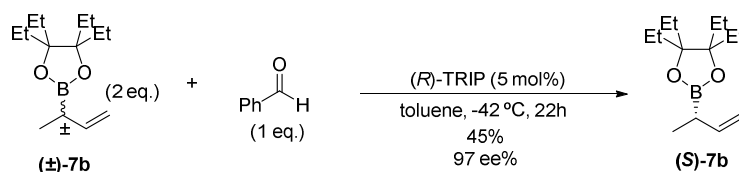
Scheme 3.18

It must be highlighted that the enantiomeric excess of the boronate could not be directly determined at this point. This was carried out by utilizing this enantiopure boronate in a subsequent allylation reaction with benzaldehyde under the conditions reported by Hoffmann that are known to proceed with complete chirality transfer (see Scheme 3.19).[17c]
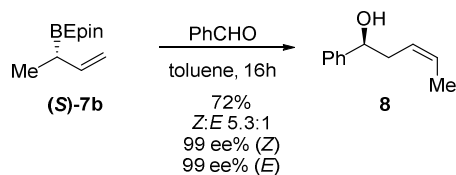
Scheme 3.19

3.2   Allylation of primary imines: Reaction optimization

Once we had optimized the reaction conditions for the kinetic resolution of the racemic secondary allyl boronate, we started with the optimization of the allylation of imines. As model reaction we combined benzaldehyde with ethanolic NH_3 and next, **(±)-7a** as the allylboronate reagent has added (see Table 3.1).[37] The reaction involves the *in situ* formation of the primary imine by condensation of the aldehyde with ammonia and once this reaction is completed the boronate had to be added to the reaction mixture. In an initial prospective study to optimize the yield of the reaction we employed racemic starting materials and in particular, we decided to employ boronate **(±)-7a** because it is much more easily accessible from commercially available starting materials.

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[37]   Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.

Table 3.1 Optimization of the reaction[a]
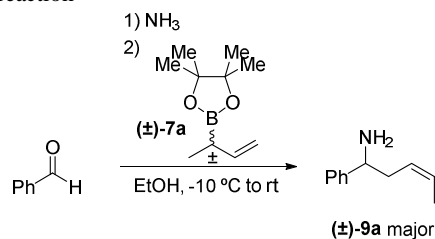
Entry	Boronate eq	Aldehyde eq	NH$_3$ eq	Z/E ratio[b]	Yield (%)
1	1.0	1.2	10	5.3:1	47
2	1.0	1.2	20	5.9:1	52
3	1.0	1.2	30	5.9:1	60
4	1.2	1.0	30	6.1:1	65
5[c]	1.2	1.0	30	**6.5:1**	**75**
6[c]	1.2	1.0	40	6.5:1	74

[a]Aldehyde in ammonia solution in EtOH (2M) was stirred at -10 ºC for 2h. To the solution allylboronate was added dropwise. The mixture was stirred at -10 ºC for 3h and then at rt for 1h before workup. [b]Measured after column chromatography in the ^{1}H-NMR Spectra. [c]Aldehyde in 30 wt% aqueous ammonia and EtOH was stirred at room temperature for 30 min. To the solution was added allylboronate (see Experimental Section for more details).

In our first experiment, the reaction was carried out using a slight excess of benzaldehyde with respect to the boronate reagent, together with 10 equivalents of ammonia (entry 1). Under these conditions the corresponding homoallylic amine (±)-**9a** was isolated in moderate yield but in a very promising 5.3:1 *Z:E* ratio (entry 1). It should be mentioned that some homoallylic alcohol byproduct was also identified in the crude reaction mixture due to a non-complete condensation of the aldehyde with NH$_3$. We next carried out the reaction by increasing the amount of ammonia, observing progressively better yields and also a slight increase in the *Z/E* ratio (entries 2-3). We finally proceeded to carry out the same set of experiments but working in the presence of a slight excess of boronate reagent with respect to benzaldehyde, observing that adduct (±)-**9a** was obtained in 65% yield and a 6.1:1 *Z/E* ratio (entry 4). In a subsequent experiment using aqueous ammonia instead of the ethanolic solution of NH$_3$, and also working at room temperature, we were able to obtain a better yield and a slightly higher *Z/E* ratio in shorter reaction times (entry 5). Increasing the amount of ammonia under these conditions did not end in better results (entry 6).

With these results in hand, we decided to evaluate the reaction using enantiopure boronate (*S*)-**7b** under these optimized conditions (see Scheme 3.20). The reaction proceeded with similar levels of efficiency, providing adduct **9a** in 76% yield, a 8.3:1 *Z/E* ratio and with an excellent

97% enantiomeric excess, which also indicated a complete chirality transfer from the boronate to the final product. It should be mentioned that the enantiomeric excess of **9a** had to be analyzed in the acetylated product because conditions could not be found for the separation of both enantiomers under all HPLC columns available.
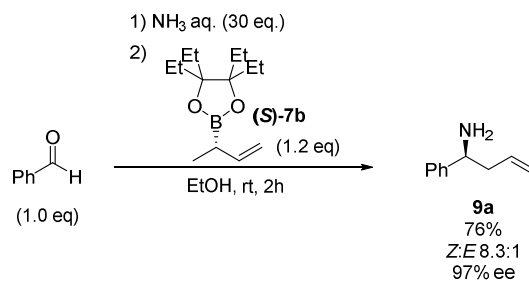
Scheme 3.20

3.3   Scope of the reaction

Once the best conditions for carrying out the allylation of benzaldehyde-derived primary imine and boronate had been established, we decided to extend the methodology to other aldehydes with different substitution patterns as shown in Table 3.2

Table 3.2 Scope of the reaction with substituted aldehydes[a]
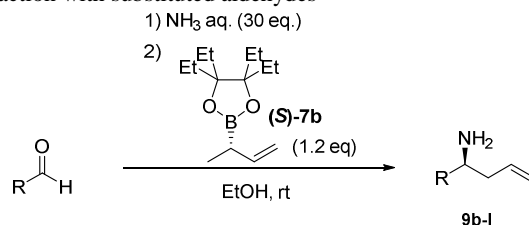
Entry	R	Compound	Z/E ratio[b]	Yield[c] (%)	ee (Z/E)[d] (%)
1	*p*-MeC$_6$H$_4$	**9b**	6.0:1	62	>99/95
2	*p*-OMeC$_6$H$_4$	**9c**	6.4:1	74	98/95
3	*o*-OMeC$_6$H$_4$	**9d**	9.0:1	61	85/73
4	*m*-OMeC$_6$H$_4$	**9e**	5.6:1	59	>99/96
5	*p*-BrC$_6$H$_4$	**9f**	6.0:1	73	98/98
6	*p*-ClC$_6$H$_4$	**9g**	5.5:1	82	99/99
7	*p*-FC$_6$H$_4$	**9h**	5.4:1	61	99/99
8	2-furyl	-	n.d.	<10	-
9	3-furyl	-	n.d.	<5	-
10	CH$_2$CH$_2$C$_6$H$_5$	**9i**	n.d.	73	93/93
11	*n*-heptyl	**9j**	5.6:1	60	96/99
12	*c*-C$_6$H$_{11}$	**9k**	6.3:1	34	91/94
13	*trans*-CH=CHC$_6$H$_5$	**9l**	6.0:1	66	99/n.d.

[a]The reaction was carried out with 1 equivalent of aldehyde, 1.2 eq of boronate **(S)-7b** and 30 equivalents of aqueous solution of ammonia and EtOH. [b]Measured after column chromatography in the ^{1}H-NMR Spectra. [c]Combined yield of the diastereomeric mixture isolated after flash chromatography. [d]Enantiomeric excess of **9b-l** determined by HPLC analysis of the pure product after acetylation or benzoylation to the corresponding product **10b-l**.

As it is shown in Table 3.2, the reaction tolerated well the use of benzaldehyde derivatives with both electron-donating substituents (entries 1-4) and electron withdrawing substituents (entries 5-7) with an important increment in the *E/Z* ratio when *ortho*-substituted aryl groups at the starting aldehyde are applied; although, the enantioselectivity was slightly lower on that case. However, aldehyde derivatives with heteroaromatic substituents (entries 8-9) did not afford the homoallylic amine product. Aldehydes containing alkyl substituents were also tested in the reaction with success (entries 10-12); 3-phenylpropanal lead to high yields and excellent enantiocontrol (entry 10) while the use of an aliphatic aldehyde with a longer alkyl chain suppose a slightly lower yield but still obtaining a high enantiocontrol (entry 11). On the contrary, the utilization of cyclohexanecarboxaldehyde (entry 12) provided adduct **9k** in low yield but with high *Z/E* ratio and excellent enantioselectivity. Cinnamaldehyde also performed well in the reaction with good yields and enantiocontrol (entry 13). In general, it can be seen that

the reaction proceeded with good diastereoselectivity and with an absolute transfer of chirality from the enantiopure boronate to the homoallylic primary amine products with high yields.

As it has mentioned before, the enantiomeric excess of the primary homoallylic amines was not possible to analyze under all HPLC columns available, thus we had to acetylate the final products, and in the case of **9i** and **9k** it was necessary to benzoylate them with a high conversion (see Scheme 3.21).
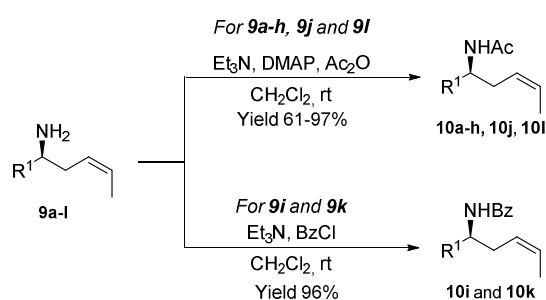
Scheme 3.21

Finally, the absolute configuration of the obtained major diastereoisomer was established by X-Ray analysis of compound **10h**. We could grow a crystal from compound **10h** after acetylation of primary amine **9h**. The crystallographic analysis showed an absolute configuration of (*S*,Z) which was extended to other amines (see Figure 3.4).
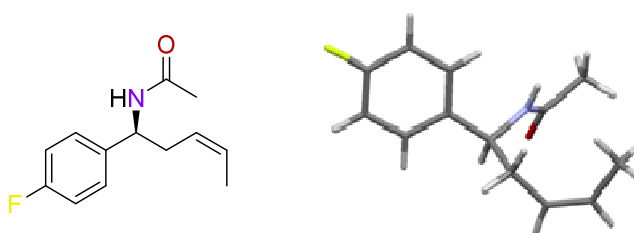
Figure 3.4

3.4 Mechanistic proposal

Based on the obtained stereochemical outcome of the reaction, we present herein a mechanistic proposal that can explain the stereoselective outcome of the reaction. The allylation of imines is thought to proceed *via* cyclic six-membered transition state with a complete transfer of chirality from chiral allylboronate to the newly formed stereogenic center of the amine (see Scheme 3.22). There are four competing transition states for this process and the energy difference will determine the asymmetric induction. When α-substituted group (methyl) is in equatorial position *gauche* destabilizing interactions are present in the transition states **TSII** and **TSIV** which favour the formation of *Z*-homoallylic amines.[38] The spatial disposition of the methyl group with respect to the π-bond will determine the energy and coefficients of the π-orbital, being the most reactive conformation the one in which there is no π-σ* delocalisation as it happens with axial conformation where the dihedral angle between the π-orbital and σ*-orbital belongs to 90º. For transition states **TSI** and **TSII** there are also 1,3-diaxial interactions which favour the formation of (*S*) enantiomer as major *Z*-amine which is in accordance with experimental results. It was assumed that the major enantiomer of *E*-homoallylic amine would be (*R*)-enantiomer due to a more hindered and destabilizing transition state **TSII** which is also in accordance with literature precedents using aldehydes as electrophiles.[17c] When bulky boronic esters are used an increase in geometrical selectivity is expected as it has be mentioned in the introduction of the present Chapter. This is also in agreement with the observed experimental work, when bulkier group like ethyl glycol boronate was used the diastereoselectivity increased with respect to less bulkier group derived from pinacol boronate.
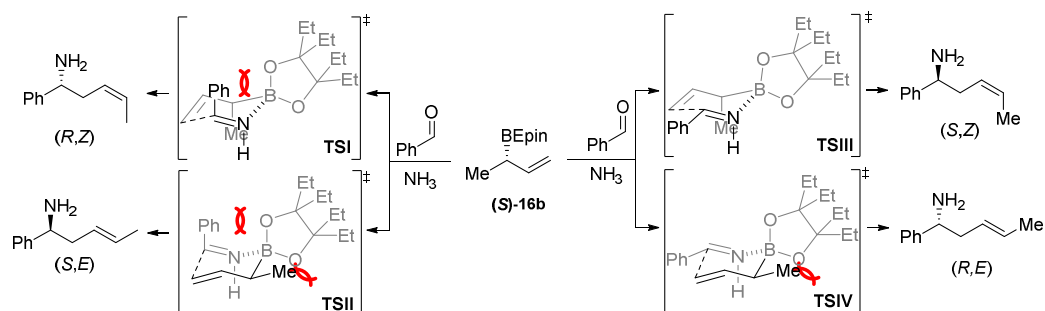
Scheme 3.22

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38 Hoffmann, R. W.; Landman, B. *Chem. Ber.* **1986**, *119*, 1039.

4.   CONCLUSIONS

Given the results presented in this chapter, the following conclusions can be advanced:

- The kinetic resolution of racemic secondary allylboronates through allylation reaction with benzaldehyde under TRIP catalyst has been accomplished with high yield.

- This enantiopure allylboronate has been used in the allylation reaction with primary imines to get enantiopure homoallylic primary amines, which are interesting scaffolds in the synthesis of many natural products.

- The reaction proceeds through *in situ* formation of imines by condensation of the aldehyde with ammonia in ethanol solution. The allylation reaction with enantiopure boronates proceeds with a complete transfer of chirality to give *Z* homoallylic primary amines as major diastereoisomers.

- The allylation reaction with enantiopure boronates proceeds with an absolute transfer of chirality through a six-membered transition state to give *Z* homoallylic amines as major diastereoisomer.

Chapter 4

FINAL CONCLUSIONS

FINAL CONCLUSIONS

The present work gathers different synthetic transformations in which the common feature is the use of BINOL-based Brønsted acid catalysts with the aim to obtain enantiopure products. Experimental results collected during the accomplishment of this work led to the following conclusions.

Enantioselective (4+3) cycloadditions between allenamides and furans. It has been demonstrated that the use of catalytic amounts of a chiral Brønsted acid could promote the enantioselective (4+3) cycloaddition between oxyallyl cations which are *in situ* formed after a regioselective epoxidation of allenamides in the presence of a strong oxidant, and furans as electron-rich diene. Described method provided the *endo* oxabicyclo[3.2.1]octane scaffold in excellent results diastereoselectively and highly regioselective with high yields and enantioselectivities with a wide range of allenes and furans containing different electron-withdrawing or electron-donating groups.

Allylation of imines using enantiopure boronates. The work verified that chiral Brønsted acid could catalyze the kinetic resolution of racemic allylboronates through allylation reaction with benzaldehyde which takes place *via* six-membered chair-like transition state to obtain enantiopure allylboronates that can be used in the allylation reaction with primary imines to get enantiopure homoallylic primary amines. (*Z*)-Homoallylic amines has proven to be the major diastereoisomer after the allylation reaction *via* transfer of chirality with *in situ* formed imines by condensation of the aldehyde with ammonia in ethanol solution and enantiopure boronates.

Chapter 5

CHAPTER 5

Experimental

1. General Methods and Materials
2. Enantioselective (4+3) Cycloadditions between Allenamides and Furans
3. Allylation of Imines with Enantiopure Boronates

1. GENERAL METHODS AND MATERIALS

NMR: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHZ for ^{1}H and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) at indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for ^{1}H NMR, CDCl$_3$, 77.16 ppm for ^{13}C NMR; CH$_3$OH, 4.87 ppm and 3.31 ppm for ^{1}H NMR, CD$_3$OD, 49.1 ppm for ^{13}C NMR; DMSO-d^6, 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR) and coupling constants (J) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR Spectra: s, singlet; d, doublet; t, triplet; q, quartet; app s, apparent singlet; app d, apparent doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dq, doublet of quartets; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals.[1]

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100 in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case.

MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975C quadrupole mass spectrometer under electronic impact ionization (EI) 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%).

HRMS: High-resolution mass spectra on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI$^+$ or ESI$^-$) or on a Micromass GCT spectrometer using chemical ionization (CI).

HPLC: The enantiomeric excess (ee) of the products was determined by High Performance Liquid Chromatography on a chiral stationary phase in a Waters 2695 chromatograph coupled to

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[1]   Kinss, M.; Sanders, J. K. M. *J. Mag. Res.* **1984**, *56*, 518.

a Waters 2998 photodiode array detector. Daicel *Chiralpak AD-H*, *IA*, *IC*, *AY-3* and *Chiralcel OD-3* and *OZ-3* columns (0.46 × 25 cm) were used; specific conditions are indicated for each case.

M.p.: Melting points were measured in a Buchi B-540 apparatus in open capillary tubes and are uncorrected.

Optical rotations $[\alpha]_D^{20}$: were measured at 20 ºC on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. Solvent and concentration are specified in each case.

X-ray: Data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250μm FWHM beam size). The sample was kept at 120 K with a Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount[TM] using Paratone N inert oil and transferred to the diffractometer.

Miscellaneous: Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[2] EtCN was distilled over CaH_2 prior to use. For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 ºC, and allowed to cool under a dehumidified atmosphere.[3] Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel 60 F254). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate dips.[4] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[5] For the removal of the solvents under reduced pressure Büchi R-210 rotatory evaporators were used.

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[2]   Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 7th ed.; Elsevier: Oxford, 2012.

[3]   Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, 1975.

[4]   Stahl, E. *Thin Layer Chromatography*, Springer Verlag: Berlin, 1969.

[5]   Still, W. C.; Kahn, H.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

2. ENANTIOSELECTIVE (4+3) CYCLOADDITIONS BETWEEN ALLENAMIDES AND FURANS

2.1 Synthesis of allenes 1a-p

1a: R^1-R^2 = COCH$_2$CH$_2$CH$_2$; R^3 = H
1b: R^1 = Me; R^2 = Ts; R^3 = H
1c: R^1 = Ph; R^2 = Ts; R^3 = H
1d: R^1 = 4-BrC$_6$H$_4$; R^2 = Ts; R^3 = H
1e: R^1 = 2,4,6-(Me)$_3$C$_6$H$_2$; R^2 = Ts; R^3 = H
1f: R^1 = 4-MeOC$_6$H$_4$; R^2 = Ts; R^3 = H
1g: R^1 = 4-MeOC$_6$H$_4$; R^2 = Ac; R^3 = H
1h: R^1 = Ph; R^2 = Boc; R^3= H
1i: R^1 = 4-BrC$_6$H$_4$; R^2 = Boc; R = H
1j: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R = H
1k: R^1 = 3,4,5-(MeO)$_3$C$_6$H$_2$; R^2 = Boc; R = H
1l: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R = Me
1m: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R = Et
1n: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R= cC$_6$H$_{11}$
1o: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R = PhCH$_2$CH$_2$
1p: R^1 = 4-MeOC$_6$H$_4$; R^2 = Boc; R = TBDMSOCH$_2$CH$_2$

Scheme SI-1. General Overview of the Synthesis of Allenes **1a-p**

Synthesis of Protected Amines SIa-k. Lactam **SI1a** was obtained from commercial sources. **SIb-f**,[6] **SI1g**[7] and **SIh-k**[8] were prepared following the procedure described in the literature. Spectroscopic data were consistent with those reported in the literature.

General Procedure A (GP-A) for the Synthesis of Propargyl Amides, Tosylamides or Carbamates SI2a-k. Products **SI2a-k** were prepared following the procedure described in the literature[9] with some modifications: Corresponding nitrogen derivative **SI1a-k** (10 mmol, 1 eq) was dissolved in dry DMF (0.33 *M*) and cooled to 0ºC and NaH (12 mmol, 60 wt. % in mineral oil, 1.2 eq) was added in one portion. After stirring for 30 min at 0ºC, the corresponding propargyl bromide (14 mmol, 1.4 eq) was added and the mixture was stirred at room temperature for 16 h. The resulting mixture was quenched with a saturated aqueous solution off NH$_4$Cl and extracted with Et$_2$O (3 × 20 mL). The combined organic phases were washed with brine or 5%

6   Kamal, A.; Reddy, J. S.; Bharathi, E. V.; Dastagiri, D. *Tetrahedron Lett.* **2008**, *49*, 348.
7   González-Gómez, A.; Añorbe, L.; Poblador, A.; Domínguez, G.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2008**, 1370.
8   Kumar, K. S.; Iqbal, J.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 6244.
9   Tayama, E.; Sugai, S. *Tetrahedron Lett.* **2007**, *48*, 6163.

aq. solution of LiCl. Products **SI2a-k** was used without further purification in the next step. Spectroscopic data of **SI2a**[10] and **SIb-k**[9] were in agreement with those reported in the literature. Products **SI2l-p** were purified by FC on silica gel (petroleum ether/EtOAc). Spectroscopic data for **SI2l**[11] were in agreement with those reported in the literature.
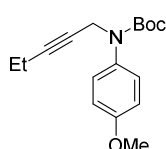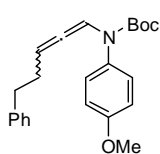
tert-**Butyl (4-methoxyphenyl)(pent-2-yn-1-yl)carbamate, SI2m.** Following *GP-A*, **SI2m** (330 mg, 1.14 mmol, 52%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as colorless oil, starting from *tert*-butyl (4-methoxyphenyl)carbamate (500 mg, 2.2 mmol, 1 eq) in DMF (11 mL, 0.2M), NaH 60 wt. % in mineral oil (100 mg, 2.6 mmol, 1.2 eq) and 1-bromo-2-pentyne (0.32 mL, 3.1 mmol, 1.4 eq). R_f= 0.8 (petroleum ether/AcOEt, 8:2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.84 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 4.27 (t, *J* = 2.0 Hz, 2H, NCH$_2$), 3.78 (s, 3H, OCH$_3$), 2.15 (qt, *J* = 7.5, 2.2 Hz, 2H, CH$_2$), 1.42 (s, 9H, 3×CH$_3$), 1.08 (t, *J* = 7.5 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.8 (C$_{arom}$-O), 154.6 (C=O), 135.3 (C$_{arom}$), 128.0 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 85.4 (**C**≡C), 80.5 (**C**(CH$_3$)$_3$), 75.6 (C≡**C**), 55.4 (OCH$_3$), 40.3 (NCH$_2$), 28.4 (C(**C**H$_3$)$_3$), 13.9 (CH$_3$), 12.5 (CH$_2$). IR (neat): 2976 (C-H st), 1698 (C=O st), 1249 (C-O-C st as), 1026 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 289 (3, M$^+$), 233 (46), 189 (90), 122 (100). HRMS: Calculated for [C$_{17}$H$_{23}$NO$_3$Na]$^+$: 312.1576 [M+Na]$^+$; found: 312.1582.
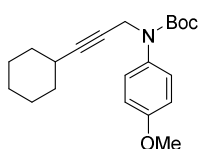
tert-**Butyl (3-cyclohexylprop-2-yn-1-yl)(4-methoxyphenyl)carbamate, SI2n.** Following *GP-A*, **SI2n** (2.67 g, 7.8 mmol, 65%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as colorless oil, starting from *tert*-butyl (4-methoxyphenyl)carbamate (2.68 g, 12 mmol, 1 eq) in DMF (60 mL, 0.22M), NaH 60 wt. % in mineral oil (600 mg, 14.4 mmol, 1.2 eq) and (3-Bromoprop-1-yn-1-yl)cyclohexane[12] (3.38 g, 21.6 mmol, 1.8 eq). R_f= 0.52 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.85 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 4.29 (bs, 2H, NCH$_2$), 3.79 (s, 3H, OCH$_3$), 2.39-2.29 (m, 1H, CH), 1.78-1.56 (m, 4H, 2×CH$_2$), 1.56-1.15 (m, 15H, 3×CH$_3$+3×CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.9 (C$_{arom}$-O), 154.7 (C=O), 135.4 (C$_{arom}$), 128.1 (C$_{arom}$-H), 113.9 (C$_{arom}$-H), 85.3 (**C**≡C), 80.5

10   Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

11   Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

12   Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178.

($\mathbf{C}$(CH$_3$)$_3$), 76.3 (C≡C), 55.5 (OCH$_3$), 40.5 (NCH$_2$), 32.7 (CH2), 29.0 (CH), 28.4 (C($\mathbf{CH_3}$)$_3$), 26.0, 24.8 (CH$_2$). IR (neat): 2930 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1041 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{21}$H$_{30}$NO$_3$]$^+$: 344.2226 [M+H]$^+$; found: 344.2222.
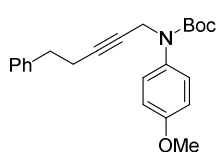
***tert*-Butyl (4-methoxyphenyl)(5-phenylpent-2-yn-1-yl)carbamate, SI2o.** Following *GP-A*, **SI2o** (3.65 g, 10 mmol, 75%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as colorless oil, starting from *tert*-butyl (4-methoxyphenyl)carbamate (2.97 g, 13.3 mmol, 1 eq) in DMF (66 mL, 0.22M), NaH 60 wt.% in mineral oil (640 mg, 16 mmol, 1.2 eq) and prepared (5-bromopent-3-yn-1-yl)benzene[12] (4.16 g, 18.6 mmol, 1.4 eq). R$_f$= 0.37 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.04 (m, 7H, C$_{arom}$-H), 6.83 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 4.28 (t, *J* = 2.2 Hz, 2H, NCH$_2$), 3.80 (s, 3H, OCH$_3$), 2.79 (t, *J* = 7.5 Hz, 2H, C$_{arom}$-CH$_2$), 2.47 (tt, *J* = 7.5, 2.2 Hz, 2H, CH$_2$C≡), 1.44 (s, 9H, 3×CH$_3$).^{13}C NMR (75 MHz, CDCl$_3$) δ 157.9 (C$_{arom}$-O), 154.7 (C=O), 140.8 (C$_{arom}$), 135.4 (C$_{arom}$), 128.6, 128.5, 128.0, 126.3, 113.9 (C$_{arom}$-H), 83.3 (C≡C), 80.6 (C(CH$_3$)$_3$), 77.4 (C≡C), 55.5 (OCH$_3$), 40.4 (NCH$_2$), 35.1 (C$_{arom}$-CH$_2$), 28.5 (C(CH$_3$)$_3$), 21.0 (CH$_2$C≡). IR (neat): 2980 (C-H st), 1695 (C=O st), 1245 (C-O-C st as), 1024 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 167 (46), 151 (100), 108 (85).
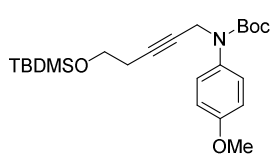
***tert*-Butyl (5-((*tert*-butyldimethylsilyl)oxy)pent-2-yn-1-yl)(4-methoxyphenyl)carbamate, SI2p.** Following *GP-A*, **SI2p** (554 mg, 1.32 mmol, 64%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as colorless oil, starting from *tert*-butyl (4-methoxyphenyl)carbamate (460 mg, 2.1 mmol, 1 eq) in DMF (10 mL, 0.22M), NaH 60 wt. % in mineral oil (100 mg, 2.5 mmol, 1.2 eq) and ((5-bromopent-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane[13] (800 mg, 2.9 mmol, 1.4 eq). R$_f$= 0.68 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.84 (d, *J* = 8.9 Hz, C$_{arom}$-H), 4.28 (t, *J* = 2.2 Hz, 2H, NCH$_2$), 3.78 (s, 3H, OCH$_3$), 3.66 (t, *J* = 7.3 Hz, 2H, CH$_2$C≡), 2.36 (tt, *J* = 7.3, 2.2 Hz, 2H, OCH$_2$), 1.42 (s, 9H, 3×CH$_3$), 0.88 (s, 10H, 3×CH$_3$+CH), 0.05 (s, 6H, 2×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.9 (C$_{arom}$-O), 154.6 (C=O), 135.3 (C$_{arom}$), 128.0, 113.9 (C$_{arom}$-H), 80.9 (C≡C), 80.5 (C(CH$_3$)$_3$), 77.4 (C≡C), 62.1 (OCH$_2$), 55.4 (OCH$_3$), 40.3 (NCH$_2$), 28.4

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(**C**(CH$_3$)$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 23.3 (**C**H$_2$C≡), 18.4 (Si**C**(CH$_3$)$_3$), -5.2 (Si**C**H$_3$). IR (neat): 2934 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1026 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{23}$H$_{37}$NO$_4$SiNa]$^+$: 442.2390 [M+Na]$^+$; found: 442.2386.

General Procedure B (GP-B) for the Synthesis of Allenes 1a-p. Isomerization step was accomplished following a procedure described in the literature:[14] **SI2a-p** (5 mmol, 1 eq) was placed in a two-necked round botton flask and dissolved with THF (0.33M). The mixture was cooled to 0°C and *t*BuOK (1.5 mmol, 30 mol%) was added in three portions and the reaction turned dark. The reaction was monitored by TLC after 16 h and more base was added if necessary. The catalyst was filtered off and the flask was rinsed with Et$_2$O. After the removal of the solvent the residue was purified by FC on silica gel. Spectroscopic data for **1a**,[10] **1b-d**,[16] **1e**,[15] **1f**,[16] **1g**[7] and **1h**[16] were in agreement with those reported in the literature.
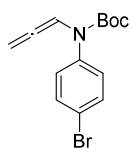
tert-**Butyl (4-bromophenyl)(propa-1,2-dien-1-yl)carbamate, 1i.** Following *GP-B*, **1i** (2.7 g, 8.7 mmol, 62%) was isolated by FC (hexanes/AcOEt, 8:2) on silica gel as a brown solid, starting from **SI2i** (4.4 g, 14.1 mmol) in THF (43 mL, 0.33M) and *t*BuOK (0.48 g, 4.2 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.46 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 7.22 (t, *J* = 6.4 Hz, 1H, NCH), 7.05 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 5.04 (d, *J* = 6.4 Hz, 2H, CH$_2$), 1.44 (s, 9H, 3×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.4 (C=**C**=C), 152.1 (O**C**=O), 138.4 (C$_{arom}$), 131.9 (C$_{arom}$-H), 129.9 (C$_{arom}$-H), 120.8 (C$_{arom}$-Br), 102.0 (NCH), 87.0 (CH$_2$), 82.0 (**C**(CH$_3$)$_3$), 28.3 (CH$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st) 1705 (C=O st), 2976 ((C=C)=C-H st), 1066 (C=C=C st sy) cm^{-1}. MS (EI) m/z (%): 130 (100). HRMS: Calculated for [C$_{14}$H$_{16}$NO$_2$BrNa]$^+$: 332.0262 [M+Na]$^+$; found: 332.0266. M.p.: 97-99°C (hexanes/EtOAc).
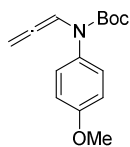
tert-**Butyl (4-methoxyphenyl)(propa-1,2-dien-1-yl)carbamate, 1j.** Following *GP-B*, **1j** (1.36 g, 5.2 mmol, 78%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as yellow oil which solidified after standing, starting from **SI2j** (1.7 g, 6.7 mmol) in THF (20 mL, 0.33M) and *t*BuOK (0.22 g, 2 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.24 (t, *J* = 6.4 Hz, 1H, NCH), 7.03 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.80

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14   Ballesteros, A.; Morán-Poladura, P.; González, J. M. *Chem. Commun.* **2016**, *52*, 2905.
15   Li, X-X; Zhu, L-L; Zhou, W.; Chen, Z. *Org. Lett.* **2012**, *14*, 436.
16   Yang, X.; Toste, F. D. *Chem. Sci.* **2016**, *7*, 2653.

(d, J = 8.9 Hz, 2H, C_{arom}-H), 4.95 (d, J = 6.4 Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 1.40 (s, 9H, 3×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7 (C=**C**=C), 158.5 (C_{arom}-OCH_3), 152.8 (O**C**=O), 132.3 (C_{arom}), 129.2 (C_{arom}-H), 113.9 (C_{arom}-H), 102.6 (NCH), 86.5 (CH_2), 81.5 (**C**$(CH_3)_3$), 55.5 (OCH_3), 28.3 (CH_3). IR (neat): 2980 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 160 (100, [M^+-$C_5H_9O_2$]). HRMS: Calculated for [$C_{15}H_{19}NO_3Na$]$^+$: 264.1263 [M+Na]$^+$; found: 264.1266. M.p.: 55-57ºC (CH_2Cl_2).
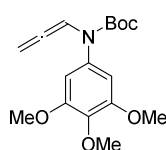
tert-Butyl propa-1,2-dien-1-yl(3,4,5-trimethoxyphenyl)carbamate, 1k. Following *GP-B*, **1k** (2.9 g, 9 mmol, 60%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as yellow oil which solidified after standing, starting from **SI2k** (4.8 g, 15 mmol) in THF (45 mL, 0.33M) and ^{t}BuOK (500 mg, 4.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, J = 6.4 Hz, 1H, NCH), 6.41 (s, 2H, C_{arom}-H), 5.05 (d, J = 6.4 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.81 (s, 6H, 2×OCH_3), 1.46 (s, 9H, 3×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4 (C=**C**=C), 153.0 (C_{arom}), 152.4 (O**C**=O), 137.1 (C_{arom}), 135.0 (C_{arom}), 105.8 (C_{arom}-H), 102.2 (NCH), 86.6 (CH_2), 81.8 (**C**$(CH_3)_3$), 61.0 (OCH_3), 56.2 (OCH_3), 28.4 (CH_3). IR (neat): 2984 (C-H st), 1698 (C=O st), 1257 (C-O-C st as), 1074 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [$C_{17}H_{23}NO_5Na$]$^+$: 344.1474 [M+Na]$^+$; found: 344.1475. M.p.: 81-83ºC (CH_2Cl_2).
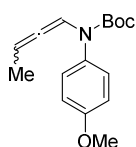
tert-Butyl buta-1,2-dien-1-yl(4-methoxyphenyl)carbamate, 10a. Following *GP-B*, **1l** (430 mg, 1.56 mmol, 53%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as yellow oil, starting from **SI3a** (810 mmg, 2.9 mmol) in THF (9 mL, 0.33M) and ^{t}BuOK (99 mg, 0.88 mmol). R_f= 0.61 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.12 (m, 1H, NCH), 7.05 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.83 (d, J = 8.9 Hz, 2H, C_{arom}-H), 5.34 (qd, J = 6.9, 5.9 Hz, 1H, HC=·=CHN), 3.78 (s, 3H, OCH_3), 1.50 (dd, J = 6.9, 2.8 Hz, 3H, **H**$_3$CCH), 1.43 (s, 9H, 3×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2 (C=**C**=C), 158.2 (C_{arom}-O), 152.8 (C=O), 132.5 (C_{arom}), 129.0 (C_{arom}-H), 113.7 (C_{arom}-H), 101.9 (NCH), 97.4 (HC=·=CN), 81.1 (**C**$(CH_3)_3$), 55.4 (OCH_3), 28.3 (C(**C**$H_3)_3$), 15.6 (H_3**C**C=·=). IR (CH_2Cl_2): 2980 (C-H st), 1701 (C=O st), 1257 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 275 (15, M^+), 174 (47, [M^+-$C_5H_9O_2$]). HRMS: Calculated for [$C_{16}H_{21}NO_3Na$]$^+$: 298.1421 [M+Na]$^+$; found: 298.1421.
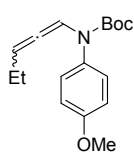
***tert*-Butyl (4-methoxyphenyl)(penta-1,2-dien-1-yl)carbamate, 10b.** Following *GP-B*, **1m** (162 mg, 0.59 mmol, 51%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as yellow oil, starting from **SI3b** (318 mmg, 1.1 mmol) in THF (3.8 mL, 0.33M) and ^{t}BuOK (39 mg, 0.34 mmol). R_f= 0.73 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25-7.18 (m, 1H, NCH), 7.05 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.84 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 5.45 (q, J = 6.1 Hz, 1H, HC=·=CN), 3.79 (s, 3H, OCH$_3$), 1.83 (qdd, J = 7.4, 6.1, 2.9 Hz, 2H, H$_2$CC=·=CN), 1.43 (s, 9H, 3×CH$_3$), 0.79 (t, J = 7.4 Hz, CH$_2$C**H**$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.7 (C=**C**=C), 158.4 (C$_{arom}$-O), 152.9 (C=O), 132.6 (C$_{arom}$), 129.3 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 104.3 (NCH), 103.1 (HC=·=CN), 81.2 (**C**(CH$_3$)$_3$), 55.5 (OCH$_3$), 28.3 (C(**C**H$_3$)$_3$), 23.2 (**C**H$_2$CH$_3$), 12.8 (CH$_2$**C**H$_3$). IR (neat): 2969 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 289 (6, M$^+$), 188 (47, [M$^+$-C$_5$H$_9$O$_2$]). HRMS: Calculated for [C$_{17}$H$_{23}$NO$_3$Na]$^+$: 312.1576 [M+Na]$^+$; found: 312.1580.
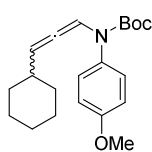
***tert*-Butyl (3-cyclohexylpropa-1,2-dien-1-yl)(4-methoxyphenyl)carbamate, 1o.** Following the *GP-E*, **1n** (1.1 g, 0.37 mmol, 71%) was isolated by FC (petroleum ether/AcOEt, 19:1 to 8:2) on silica gel as yellow oil, starting from **SI3c** (1.5 g, 4.45 mmol) in DMF (15 mL, 0.33M) and ^{t}BuOK (150 mg, 1.3 mmol). R_f= 0.64 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25-7.16 (m, 1H, NCH), 7.04 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.83 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 5.37 (t, J = 5.9 Hz, 1H, HC=·=CN), 3.77 (s, 3H, OCH$_3$), 1.84-1.68 (m, 1H, C$_{cy}$H), 1.66-1.45 (m, 4H, 2×C$_{cy}$H$_2$), 1.44 (s, 9H, 3×CH$_3$), 1.28-0.96 (m, 4H, 2×C$_{cy}$H$_2$), 0.92-0.69 (m, 2H, C$_{cy}$H$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 193.8 (C=**C**=C), 158.4 (C$_{arom}$-O), 152.8 (C=O), 132.5 (C$_{arom}$), 129.4 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 108.4 (NCH), 103.2 (H**C**=·=CN), 81.0 (**C**(CH$_3$)$_3$), 55.4 (OCH$_3$), 38.4 (C$_{cy}$H), 32.4 (C$_{cy}$H$_2$), 32.2 (C$_{cy}$H$_2$), 28.3 (C(**C**H$_3$)$_3$), 26.2 (C$_{cy}$H$_2$), 25.9 (CH$_2$). IR (neat): 2926 (C-H st), 1964 (C=C=C st as), 1701 (C=O st), 1245 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 343 (14, M$^+$), 287 (100), 242 (39, [M$^+$-C$_5$H$_9$O$_2$]). HRMS: Calculated for [C$_{21}$H$_{29}$NO$_3$Na]$^+$: 366.2045 [M+Na]$^+$; found: 366.2039.

General Procedure C (GP-C) for the Synthesis of Allenes 1o-p: Corresponding alkyne **SI2o-p** (1.4 mmol, 1 eq) was dissolved in dry THF (0.2 *M*) and cooled to -78ºC. LiHMDS 1.0 *M* in THF (2.1 mmol, 1.5 eq) was added dropwise to the mixture and stirred at 0ºC for 2 h. The crude was quenched with water (5 mL) and aqueous layer extracted with ether (3 × 5 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the removal of the solvent under reduced pressure, the residue was purified by FC (petroleum ether to petroleum ether/EtOAc 19:1) on deactivated silica gel (acetone) to obtain **1o-p** as an oil.

tert-Butyl (4-methoxyphenyl)(5-phenylpenta-1,2-dien-1-yl)carbamate, 1o. Following *GP-C*, **1o** (295 mg, 0.81 mmol, 58%) was isolated by FC (petroleum ether/AcOEt, 19:1) on deactivated silica gel, starting from **SI2o** (508 mg, 1.4 mmol) in THF (7 mL, 0.2M) and LiHMDS 1.0M in THF (2.1 mL, 2.1 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.15 (m, 4H, 3×C_{arom}-H + NCH), 7.15-7.05 (m, 4H, C_{arom}-H), 6.90 (d, *J* = 6.9 Hz, 2H, C_{arom}-H), 5.49 (q, *J* = 6.3 Hz, 1H, HC=·=CN), 3.81 (s, 3H, OCH_3), 2.62-2.38 (m, 2H, H_2CC=·=CN), 2,17 (qd, *J* = 7.9, 2.5 Hz, 2H, H_2C-C_{arom}), 1.48 (s, 9H, 3×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (C=**C**=C), 158.4 (C_{arom}-O), 152.8 (C=O), 141.6 (C_{arom}), 132.5 (C_{arom}), 129.2 (C_{arom}-H), 128.4 (C_{arom}-H), 128.3 (C_{arom}-H), 125.9 (C_{arom}-H), 113.8 (C_{arom}-H), 103.1 (N**C**H), 102.0 (H**C**=·=CN), 81.1 (**C**(CH_3)$_3$), 55.4 (OCH_3), 35.0 (H_2**C**-C_{arom}), 31.8 (H_2**C**C=·=CN), 28.3 (C(**C**H$_3$)$_3$). IR (neat): 2976 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [$C_{23}H_{28}NO_3$][+]: 366.2069 [M+H][+]; found: 366.2068.
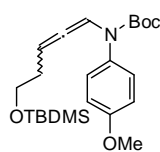
tert-Butyl (5-((tert-butyldimethylsilyl)oxy)penta-1,2-dien-1-yl)(4-methoxyphenyl)carbamate, 1p. Following *GP-C*, **1p** (333 mg, 0.79 mmol, 65%) was isolated by FC (petroleum ether/AcOEt, 19:1) on deactivated silica gel, starting from **SI2p** (509 mg, 1.2 mmol) in THF (6 mL, 0.2M) and LiHMDS 1.0M in THF (1.8 mL, 1.8 mmol). R_f= 0.75 (petroleum ether/AcOEt, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (m, 1H, NCH), 7.04 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.83 (d, *J* = 8.9 Hz, C_{arom}-H), 5.41 (td, *J* = 6.8, 6.0 Hz, 1H, HC=·=CN), 3.78 (s, 3H, OCH_3), 3.49-3.29 (m, 2H, H_2C-O), 2.10-1.98 (m, 2H, H_2CC=·=CN), 1.42 (s, 9H, OC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), -0.01 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2 (C=**C**=C), 158.4 (C_{arom}-O), 152.8 (C=O), 132.5 (C_{arom}), 129.2 (C_{arom}-H), 113.8 (C_{arom}-H), 102.7 (N**C**H), 99.2 (H**C**=·=CN), 81.2 (**C**(CH_3)$_3$), 62.5

(OCH$_2$), 55.4 (OCH$_3$), 33.7 (H$_2$**C**C=·=CN), 28.3 (OC(**C**H$_3$)$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 18.4 (Si**C**(CH$_3$)$_3$), -5.22 (Si**C**H$_3$), -5.24 (Si**C**H$_3$). IR (CH$_2$Cl$_2$): 2955 (C-H st), 1705 (C=O st), 1278 ((Si-)CH$_3$ δ sy), 1245 (C-O-C st as), 1099 (Si-O st), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 167 (100). HRMS: Calculated for [C$_{23}$H$_{38}$NO$_4$Si]$^+$: 420.2570 [M+H]$^+$; found: 420.2570.

2.2 <u>Synthesis of dienes 2a-x</u>

Furan (2a), **3-methylfuran (2b), 2-methylfuran (2u), 2,5-dimethylfuran (2v)** and **6,6-dimethylfulvene (2x)** are commercially available.

3-Ethylfuran (2c). 3-Ethylfuran **2c** was prepared following the described procedure in the literature.[17]. Spectroscopic data for **2c**[17] were in agreement with those reported in the literature.

3-Aryl and 3-Benzyl substituted furans, (2d) and (2h-j)
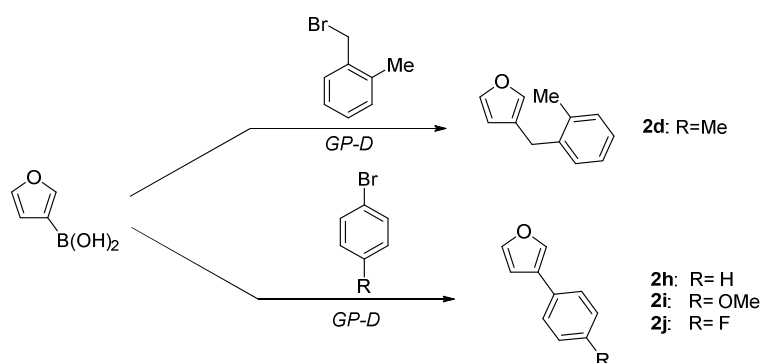
General Procedure D (GP-D) for the Synthesis of Furans (2d) and (2h-j): Suzuki coupling of 3-furanboronic acid with *p*-substituted bromobenzenes or benzyl bromides was prepared following the procedure described in the literature.[18] To a solution of bromide (4.3 mmol, 1 eq) in toluene (9.6 mL, 0.4M) under Ar atmosphere, Pd(PPh$_3$)$_4$ (0.17 mmol, 4 mol%) was added. Then, Na$_2$CO$_3$ (aqueous 2M, 4.8 mL) and a solution of 3-furanboronic acid (5.2 mmol, 1.2 eq) in MeOH (2.4 mL, 2.2M) were added. The reaction mixture was warmed to 80 ºC for 6h. After cooling, CH$_2$Cl$_2$ (10 mL) and Na$_2$CO$_3$ (aqueous 2M, 10 mL) were added. The layers were separated and the combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated. Spectroscopic data for **2h-j** were in agreement with those reported in the literature.[18]

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17 Wiley, R. A.; Choo, H.-H.; McClellan, D. *J. Org. Chem.* **1983**, *48*, 1106.

18 Tofi, M.; Georgiou, T.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2005**, *7*, 3347.
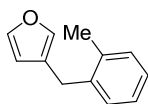
3-(2-Methylbenzyl)furan (2d). Following *GP-D*, **2d** (592 mg, 3.4 mmol, 80%) was obtained as a yellowish oil after purification by FC on silica gel (hexanes to hexanes/EtOAc 19:1) starting from 2-methylbenzyl bromide (0.59 mL, 4.3 mmol) in toluene (9.6 mL, 0.4M), Pd(PPh$_3$)$_4$ (200 mg, 0.17 mmol), Na$_2$CO$_3$ (aqueous 2M, 4.8 mL) and 3-furanboronic acid (0.6 g, 5.2 mmol) in MeOH (2.4 mL, 2.2M). R$_f$= 0.55 (2% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42-7.39 (m, 1H, C$_{heteroarom}$-H), 7.25-7.18 (m, 4H, C$_{arom}$-H), 7.16 (bs, 1H, C$_{heteroarom}$-H), 6.28 (bs, 1H, C$_{heteroarom}$-H), 3.80 (s, 2H, CH$_2$), 2.35 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.1 (C$_{heteroarom}$-H), 139.8 (C$_{heteroarom}$-H), 138.5 (C$_{arom}$), 136.3 (C$_{arom}$), 130.3 (C$_{arom}$-H), 129.3 (C$_{arom}$-H), 126.6 (C$_{arom}$-H), 126.2 (C$_{arom}$-H), 123.8 (C$_{heteroarom}$), 111.4 (C$_{heteroarom}$-H), 29.1 (CH$_2$), 19.5 (CH$_3$). IR (neat): 3102 (C-H st) cm^{-1}. MS (EI) m/z (%): 172 (M$^+$, 100).

(Z)-3-Styrylfuran ((Z)-2g), 3-isopentylfuran (2e), 3-Phenetylfuran (2f)
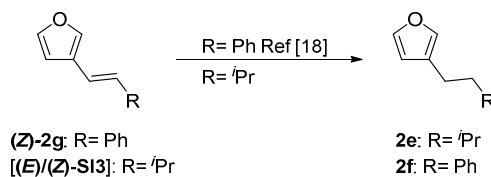
Furans **2g**, **2e** and **2f** were prepared starting from 3-furaldehyde following a Wittig protocol described in the literature.[18] For **(Z)-2g** the residue was purified by FC on silica gel (hexanes/Et$_2$O 30:1 to 15:1) achieving the separation of *E* and *Z* isomers. Spectroscopic data for **(Z)-2g** were in agreement with those reported in the literature.[18] In the case of [**(E)/(Z)-SI3**], the residue was not purified by FC and it was used without further purification in the next step with traces of solvent.
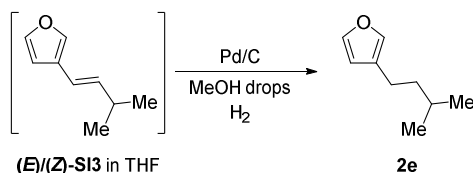
3-Isopentylfuran (2e). Hydrogenation of [**(E)/(Z)-SI3**] was prepared following a procedure described in the literature with slight modifications.[18] The residue was placed in a flask and ~4

drops of MeOH were added. H_2 bubbled through it 10 min at room temperature and Pd on activated carbon in 10%wt (2.5 mol%) was added. The reaction mixture was stirred for 1 day under H_2 atmosphere. The reaction was monitored by NMR and it was added more catalyst if necessary. When the reaction finished, the catalyst was removed by filtration through a pad of silica gel eluting with Et_2O. After careful removal of the solvent, the residue was purified by FC on silica gel (pentane to pentane/Et_2O 95:5) to afford **2e** as a colorless oil (401 mg, 2.9 mmol, 20%). R_f= 0.79 (hexanes/EtOAc 19:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 1H, $C_{heteroarom}$-H), 7.23-7.20 (m, 1H, $C_{heteroarom}$-H), 6.30-6.25 ($C_{heteroarom}$-H), 2.48-2.39 (m, 2H, $C_{heteroarom}$-CH_2), 1.73-1.53 (m, 1H, CH), 1.52-1.39 (m, 2H, CH**CH$_2$**), 0.93 (d, *J* = 6.6 Hz, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 ($C_{heteroarom}$-H), 138.7 ($C_{heteroarom}$-H), 125.6 ($C_{heteroarom}$), 111.2 ($C_{heteroarom}$-H), 39.3 (CH_2), 27.7 (CH), 22.8 (CH_2), 22.6 (CH_3). IR (neat): 2959 (C-H st), 1187 (CO-C st) cm^{-1}. MS (EI) m/z (%): 138 (12, M$^+$), 82 (100).

3-Phenethylfuran (2f). Hydrogenation of (*E*)-**2g** and (*Z*)-**2g** was prepared following a procedure described in the literature.[18] Spectroscopic data for **2f** were in agreement with those reported in the literature.[18]

O-based methylenfurans 2k-n and 2o
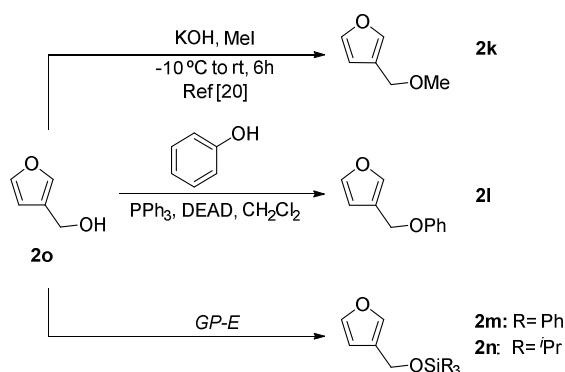
3-Hydroxymethylfuran **2o** was prepared from 3-furaldehyde following a procedure described in the literature.[19] Spectroscopic data for **2o** were in agreement with those reported in the literature.

19 Xu, P.; Chen, D.-S.; Xi, J.; Yao Z.-J. *Chem. Asian J.* **2015**, *10*, 976.

3-(Methoxymethyl)furan (2k). 3-(Methoxymethyl)furan **2k** was prepared following a procedure described in the literature.[20] NMR data were in agreement with those reported in the literature.
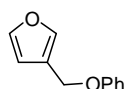
3-(Phenoxymethyl)furan (2l). To a solution of 3-hydroxymethylfuran **2o** (1 g, 10.2 mmol, 1 eq) in CH_2Cl_2 (10 mL, 1M) was added phenol (1.92 g, 20.4 mmol, 2 eq) and PPh_3 (5.3 g, 20.4 mmol, 2 eq) at 0 ºC. Diethyl azodicarboxylate (3.3 mL, 20.4 mmol, 2 eq) was added dropwise. The mixture was stirred for 16h at room temperature. After that, the mixture was concentrated and pentane was added, then the precipitate was filtered through Al_2O_3 and washed with pentane. The solvent was evaporated and the residue was purified by FC on silica gel (hexanes to hexanes/EtOAc 9:1) obtaining a colorless oil which solidified after standing (355 mg, 2.04 mmol, 20%). R_f= 0.23 (hexanes/EtOAc 19:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (bs, 1H, $C_{heteroarom}$-H), 7.47 (bs, 1H, $C_{heteroarom}$-H), 7.40-7.30 (m, 2H, C_{arom}-H), 7.06-6.98 (m, 3H, C_{arom}-H), 6.54(bs, 1H, $C_{heteroarom}$-H), 4.97 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7 (C_{arom}-O), 143.6 ($C_{heteroarom}$-H), 140.9 ($C_{heteroarom}$-H), 129.6 (C_{arom}-H), 121.5 ($C_{heteroarom}$), 121.1 (C_{arom}-H), 114.9 (C_{arom}-H), 110.3 ($C_{heteroarom}$-H), 61.8 (CH_2). IR (neat): 1235 (C-O-C st as), 1020 (CO-C st) cm^{-1}. MS (EI) m/z (%): 174 (27, M$^+$), 81 (100, [M$^+$-C_6H_5O]). M.p.: 30-32ºC (hexanes/EtOAc).

General Procedure E (GP-E) for the synthesis of *O*-Silylated methylenefurans 2m-n: Silane derivatives were prepared according to a literature procedure as follows.[21] To a stirring solution of 3-hydroxymethylfuran **2o** (14 mmol, 1 eq) in CH_2Cl_2 (21 mL, 0.7M) were added imidazole (21 mmol, 1.5 eq) and the corresponding chlorosilane (17 mmol, 1.2 eq) at 0ºC. The mixture was allowed to warm up to room temperature and stirred for 10 h. After completion, saturated aqueous $NaHCO_3$ was added (10 mL) and the aqueous solution was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and filtered. After the removal of the solvent under reduced pressure the crude was purified by FC on silica gel. Spectroscopic data for **2m**[21] were in agreement with those reported in the literature.

20   Li, N.-N.; Zhang, Y. L.; Mao, S.; Gao, Y.-R.; Guo, D.-D.; Wang, Y.-Q. *Org. Lett.* **2014**, *16*, 2732.
21   Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.
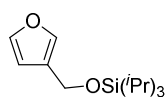
(Furan-3-ylmethoxy)triisopropylsilane (2n). Following *GP-E*, **2n** was isolated after FC on silica gel (hexanes to hexanes/CH$_2$Cl$_2$, 95:5) as a colorless oil (2.47 g, 9.7 mmol, 95%), using 3-hydroxymethylfuran **2o** (1 g, 10.2 mmol) in CH$_2$Cl$_2$ (15 mL, 0.7M), imidazole (1.04 g, 15.3 mmol) and triisopropylchlorosilane (2.7 mL, 12.2 mmol). R$_f$= 0.91 (5% CH$_2$Cl$_2$ in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (bs, 1H, C$_{heteroarom}$-H), 6.39 (d, *J* = 1.5 Hz, 1H, C$_{heteroarom}$-H), 4.70 (bs, 1H, C$_{heteroarom}$-H), 1.25-1.04 (m, 21H, 6×CH$_3$ + 3×CH). ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.1 (C$_{heteroarom}$-H), 139.2 (C$_{heteroarom}$-H), 126.2 (C$_{heteroarom}$), 109.5 (C$_{heteroarom}$-H), 58.0 (CH$_2$), 18.1 (CH$_3$), 12.2 (CH). IR (neat): 2944 (C-H st), 1095 (Si-O st), cm^{-1}. MS (EI) m/z (%): 254 (1, M$^+$), 211 (100, [M$^+$-C$_3$H$_7$]). HRMS: Calculated for [C$_{14}$H$_{27}$O$_2$Si]$^+$: 255.1775 [M+H]$^+$; found: 255.1780.

N-based methylenfurans 2p-s and 2t
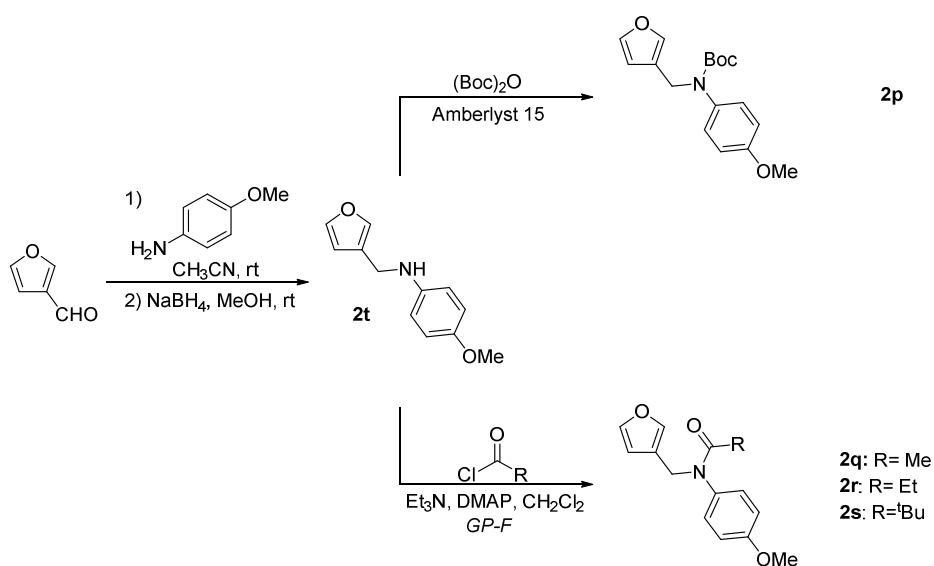
N-(Furan-3-ylmethyl)-4-methoxyaniline (2t). It was prepared as follows. Aniline (2.2 g, 17.9 mmol, 1.1 eq) was dissolved in dry acetonitrile (125 mL, 0.13M) and 3-furaldehyde (1.43 mL, 16.2 mmol, 1 eq) was added to the reaction mixture and stirred 16 h at room temperature. After evaporation, the greenish solid was redissolved in MeOH. NaBH$_4$ (2.7 g, 70 mmol, 4 eq) was added in small portions and stirred at room temperature for 5h. After that, the solvent was evaporated; 50 mL of water were added and extracted with CH$_2$Cl$_2$ (3×50 mL), dried over

Na$_2$SO$_4$, filtered and concentrated. The residue was filtered through a small pad of silica gel (petroleum ether/AcOEt 1:1) obtaining **2t** as a yellow oil (3.2 g, 15.7 mmol, 97%). R$_f$= 0.63 (hexanes/EtOAc 8:2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40-7.35 (m, 2H, C$_{heteroarom}$-H), 6.81 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.64 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.42-6.37 (m, 1H, C$_{heteroarom}$-H), 4.10 (s, 2H, CH$_2$), 3.74 (s, 3H, OCH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.5 (C$_{arom}$-O), 143.3 (C$_{heteroarom}$-H), 142.3 (C$_{arom}$), 140.0 (C$_{heteroarom}$-H), 123.6 (C$_{heteroarom}$), 114.9 (C$_{arom}$-H), 114.6 (C$_{arom}$-H), 110.3 (C$_{heteroarom}$-H), 55.8 (OCH$_3$), 40.4 (CH$_2$). IR (neat): 3396 (NH st), 1232 (C-O-C st as), 1038 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 203 (M$^+$, 100), 122 (97, [M$^+$-C$_5$H$_5$O]). HRMS: Calculated for [C$_{12}$H$_{14}$NO$_2$]$^+$: 204.1025 [M+H]$^+$; found: 204.1029.
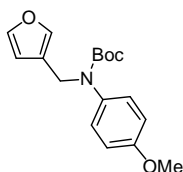
***tert*-Butyl (furan-3-ylmethyl)(4-methoxyphenyl)carbamate (2p).** To a mixture of (Boc)$_2$O (500 mg, 2.3 mmol, 1 eq) and Amberlyst-15 (75 mg, 15% w/w) was added amine **2t** (475 mg, 2.3 mmol, 1 eq) and the mixture was stirred at room temperature for 1 h. After that, CH$_2$Cl$_2$ was added and the catalyst was filtered. The filtrate was collected and concentrated under reduced pressure and the residue was isolated by FC on silica gel (petroleum ether/AcOEt 19:1 to 8:2) as a yellow oil (545 mg, 1.8 mmol, 78%). R$_f$= 0.6 (hexanes/AcOEt 9:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30-7.26 (m, 1H, C$_{heteroarom}$-H), 7.21-7.18 (m, 1H, C$_{heteroarom}$-H), 6.98 (d, J = 8.4 Hz, 2H, C$_{arom}$-H), 6.80-6.72 (m, 2H, C$_{arom}$-H), 6.31 (bs, 1H, C$_{heteroarom}$-H), 4.54 (s, 2H, CH$_2$), 3,69 (s, 3H, OCH$_3$), 1.40 (s, 9H, 3×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.6 (C$_{arom}$-O), 154.8 (C=O), 142.8 (C$_{heteroarom}$-H), 140.2 (C$_{heteroarom}$-H), 135.1 (C$_{arom}$), 128.1 (C$_{arom}$-H), 122.2 (C$_{heteroarom}$), 113.7 (C$_{arom}$-H), 110.5 (C$_{heteroarom}$-H), 79.9 (**C**(CH$_3$)$_3$), 55.0 (OCH$_3$), 44.9 (CH$_2$), 28.2 (3×CH$_3$). IR (neat): 1691 (C=O st) cm^{-1}. MS (EI) m/z (%): 303 (3, M$^+$). HRMS: Calculated for [C$_{17}$H$_{21}$NO$_4$Na]$^+$: 326.1368 [M+Na]$^+$; found: 326.1376. M.p.: 37-39 ℃ (CH$_2$Cl$_2$).

General Procedure F (GP-F) for the synthesis of furans 2q-s: *N*-(Furan-3-ylmethyl)-4-methoxyaniline **2t** (1.8 mmol, 1 eq) was dissolved in CH$_2$Cl$_2$ (0.3M) with DMAP (0.18 mmol, 10 mol%). Triethylamine (2.7 mmol, 1.5 eq) was added and the mixture was cooled to 0℃. The corresponding acyl chloride (2.2 mmol, 1.2 eq) was added slowly. The reaction was stirred for 10 min at 0℃ and 16h at room temperature. When the reaction has finished, CH$_2$Cl$_2$ was removed under vacuum and Et$_2$O and NH$_4$Cl aq. sat. solution was added in the same proportion. The

mixture was separated and organic layer was washed with brine, dried over Na_2SO_4 and filtered. Afforded residue was purified through a small plug of silica eluted with petroleum ether/AcOEt obtaining **2q-s**.
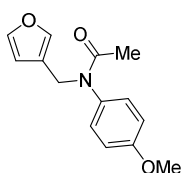
N-(Furan-3-ylmethyl)-N-(4-methoxyphenyl)acetamide (2q). Following *GP-F*, **2q** was isolated after eluting the crude through a small plug of silica obtaining a yellow oil (288 mg, 1.24 mmol, 95%), using *N*-(furan-3-ylmethyl)-4-methoxyaniline **2t** (270 mg, 1.33 mmol) in CH_2Cl_2 (4.4 mL, 0.3M), DMAP (16 mg, 0.12 mmol), Et_3N (0.28 mL, 2 mmol) and acetyl chloride (0.11 mL, 1.6 mmol) were added. R_f= 0.34 (petroleum ether/AcOEt 6:4). ^{1}H NMR (300 MHz, CDCl_3) δ 7.34-7.30 (m, 1H, $C_{heteroarom}$-H), 7.22-7.18 (m, 1H, $C_{heteroarom}$-H), 6.93 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.85 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.34-6.28 (m, 1H, $C_{heteroarom}$-H), 4.64 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.83 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 170.8 (C=O), 159.1 (C_{arom}-O), 143.1 ($C_{heteroarom}$-H), 141.2 ($C_{heteroarom}$-H), 135.6 (NC_{arom}), 129.3 (C_{arom}-H), 121.3 ($C_{heteroarom}$), 114.7 (C_{arom}-H), 111.3 ($C_{heteroarom}$-H), 55.5 (OCH_3), 43.6 (CH_2), 22.7 (CH_3). IR (neat): 2937 (C-H st) 1651 (C=O st), 1242 (C-O-C st as), 1020 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 245 (100, M^+). HRMS: Calculated for $[C_{14}H_{16}NO_3]^+$: 246.1130 $[M+H]^+$; found: 246.1138.
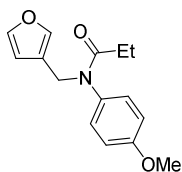
N-(Furan-3-ylmethyl)-N-(4-methoxyphenyl)propionamide (2r). Following *GP-F*, **2r** was isolated after eluting the crude through a small plug of silica obtaining a pale yellow oil (610 mg, 2.3 mmol, 95%), using *N*-(furan-3-ylmethyl)-4-methoxyaniline **2t** (500 mg, 2.46 mmol) in CH_2Cl_2 (8 mL, 0.3M), DMAP (30 mg, 0.25 mmol), Et_3N (0.51 mL, 3.7 mmol) and propionyl chloride (0.38 mL, 2.9 mmol) were added. R_f= 0.44 (petroleum ether/AcOEt 8:2). ^{1}H NMR (300 MHz, CDCl_3) δ 7.29 (t, J = 1.7 Hz, 1H, $C_{heteroarom}$-H), 7.19-7.16 (m, 1H, $C_{heteroarom}$-H), 6.90 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.82 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.29 (bs, 1H, $C_{heteroarom}$-H), 4.61 (s, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 2.00 (q, J = 7.5 Hz, 2H, **CH**$_2$CH_3), 1.01 (t, J = 7.5 Hz, 3H, CH_2**CH**$_3$). ^{13}C NMR (75 MHz, CDCl_3) δ 174.0 (C=O), 159.0 (C_{arom}-O), 142.9 ($C_{heteroarom}$-H), 141.1 ($C_{heteroarom}$-H), 135.0 (NC_{arom}), 129.4 (C_{arom}-H), 121.4 ($C_{heteroarom}$), 114.6 (C_{arom}-H), 111.2 ($C_{heteroarom}$-H), 55.4 (OCH_3), 43.7 (NCH_2), 27.7 (**CH**$_2$CH_3), 9.7 (CH_2**CH**$_3$). IR (neat): 1655 (C=O

st), 1245 (C-O-C st as), 1038 (C-O-C st sim) cm^{-1}. MS (EI) m/z (%): 259 (100, M$^+$), 203 ([M+H]$^+$-C$_3$H$_5$O). HRMS: Calculated for [C$_{15}$H$_{18}$NO$_3$]$^+$: 260.1287 [M+H]$^+$; found: 260.1297.
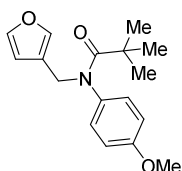
_N_-(Furan-3-ylmethyl)-_N_-(4-methoxyphenyl)pivalamide (2s). Following *GP-F*, **2s** was isolated after eluting the crude through a small plug of silica obtaining a pale yellow oil (485 mg, 1.69 mmol, 97%), using *N*-(furan-3-ylmethyl)-4-methoxyaniline **2t** (359 mg, 1.76 mmol) in CH$_2$Cl$_2$ (5.9 mL, 0.3M), DMAP (21.5 mg, 0.18 mmol), Et$_3$N (0.36 mL, 2.6 mmol) and pivaloyl chloride (0.26 mL, 2.1 mmol) were added. R$_f$= 0.72 (petroleum ether/AcOEt 8:2). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33-7.30 (m, 1H, C$_{heteroarom}$-H), 7.16 (bs, 1H, C$_{heteroarom}$-H), 6.92 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.81 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.32 (bs, 1H, C$_{heteroarom}$-H), 4.55 (s, 2H, NCH$_2$), 3.79 (s, 3H, OCH$_3$), 1.00 (s, 3H, 3×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 177.9 (C=O), 159.1 (C$_{arom}$-O), 142.8 (C$_{heteroarom}$-H), 141.4 (C$_{heteroarom}$-H), 135.8 (NC$_{arom}$), 131.0 (C$_{arom}$-H), 121.6 (C$_{heteroarom}$), 114.0 (C$_{arom}$-H), 111.5 (C$_{heteroarom}$-H), 55.5 (OCH$_3$), 47.4 (NCH$_2$), 41.0 (**C**(CH$_3$)$_3$), 29.6 (3×CH$_3$). IR (neat): 2951 (C-H st), 1634 (C=O st), 1243 (C-O-C st as), 1020 (C-O-C st sim) cm^{-1}. MS (EI) m/z (%): 287 (64, M$^+$), 203 (63, M$^+$-C$_5$H$_9$O). HRMS: Calculated for [C$_{17}$H$_{22}$NO$_3$]$^+$: 288.1600 [M+H]$^+$; found: 288.1601.

Cyclopentadiene (2w). Compound **2w** was prepared following the procedure reported in the literature.[22] Spectroscopic data were in agreement with those reported in the literature.

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[22] Musa, O. M. Ring-Opening Metathesis Polymerization of Norbornene and Oxanorbornene Moieties and Uses thereof. U.S. Patent 0065880, March 17, 2011.

Ethyl 3-(furan-3-yl)propanoate (2y)
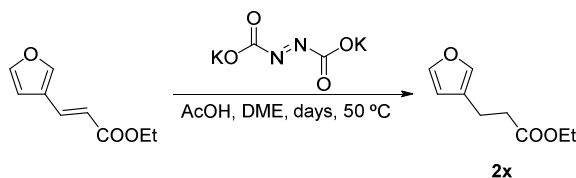
Ethyl (*E*)-3-(furan-3-yl)acrylate was isolated after a HWE reaction starting from 3-furaldehyde following a procedure described in the literature.[23] For **2x**, we were unable to generate it by following literature procedure.[23] Ethyl 3-(furan-3-yl)propanoate **2x** was prepared as follows. To a solution of acetic acid (0.1 mL, 1.8 mmol, 3 eq) in DME (7.4 mL, 0.08M), dipotassium azo-1,2-dicarboxylate salt[24] (0.35 g, 1.8 mmol, 3 eq) and ethyl (*E*)-3-(furan-3-yl)acrylate (100 mg, 0.6 mmol, 1 eq) in DME (6 mL, 0.1M) were added dropwise at 50 ºC. The reaction was monitored by NMR and more azodicarboxylate was added salt if necessary. Then, it was cooled and filtered through a small pad of Celite and the solvent was removed in vacuo. Spectroscopic data for ethyl 3-(furan-3-yl)propanoate **2x**[23] were in agreement with those reported in the literature.

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[23] (a) Davis, C. H.; Hurst, T. E.; Jacob, A. M.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 4414. (b) Weyerstahl, P.; Licha, K.; Marschall, H. *Liebigs Ann. Chem.* **1994**, 917.

[24] (a) Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H. *Org. Let.* **2010**, *12*, 1120. (b) Groves, J. T.; Ma, K. W. *J. Am. Chem. Soc*. **1977**, *99*, 4076.

2.3 <u>Synthesis of catalysts</u>

(3a), **(3b)**, **(3c)**, **(3d)** and **(3e)** catalysts are commercially available. Catalysts **(3f)**,[25] **(3h)**,[26] **(3l)**,[25] **(3m)**,[25] **(3n)**,[27] **(3o)**[28] and **(3p)**[29] has been previously synthesized and used in the literature.

2.3.1 Synthesis of precursors
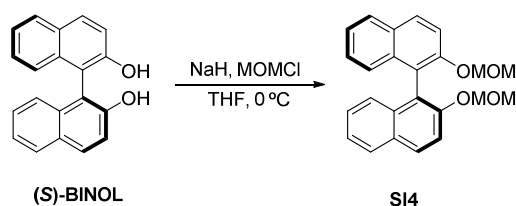
(S)-2,2´-bis(methoxymethoxy)-1,1´-binaphthalene (SI4). (*S*)-2,2´-Bis(methoxymethoxy)-1,1´-binaphthalene was prepared following the procedure described in the literature with slight modifications, instead of using MOMBr, it was used MOMCl.[30] NMR spectral data were in agreement with those reported in the literature.[30]

Silylated BINOL derivative (SI5a-b)
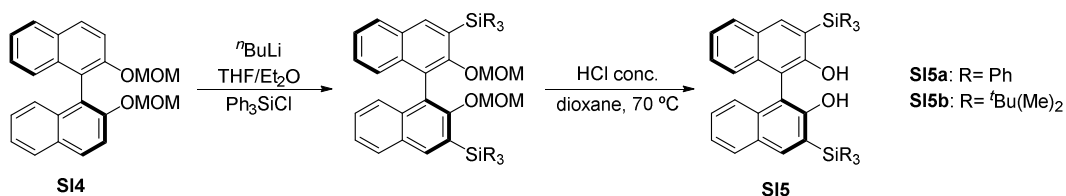
SI5a and **SI5b** were prepared from (*S*)-2,2´-bis(methoxymethoxy)-1,1´-binaphthalene with the corresponding silanol derivative in two steps following a procedure described in the literature.[31] Spectroscopic data for **SI5a**[31] and **SI5b**[32] were in agreement with those reported in the literature.

25   Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem. Eur. J.* **2010**, *16*, 13116.

26   Sai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 7091.

27   Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

28   Knipe, P. C.; Smith, M. D. *Org. Biomol. Chem.* **2014**, *12*, 5094.

29   Lalli, C.; van de Weghe, P. *Chem. Commun.* **2014**, *50*, 7495.

30   Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.

31   Storer, R. I.; Diane, E. C., Yike, N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

32   Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.

SI5a: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.98 (s, 2H, C$_{arom}$-H), 7.80-7.65 (m, 14H, C$_{arom}$-H), 7.51-7.28 (m, 24H, C$_{arom}$-H), 5.36 (s, 2H, OH). ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.5 (C$_{arom}$-OH), 142.1 (C$_{arom}$-H), 136.3 (C$_{arom}$-H), 134.7 (C$_{arom}$), 134.2 (C$_{arom}$), 129.5 (C$_{arom}$-H), 129.2 (C$_{arom}$), 129.0 (C$_{arom}$-H), 128.2 (C$_{arom}$-H), 127.8 (C$_{arom}$-H), 123.9 (C$_{arom}$-H), 123.8 (C$_{arom}$-H), 123.6 (C$_{arom}$), 110.6 (C$_{arom}$).

(*S*)-3,3´-Dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol (SI6)
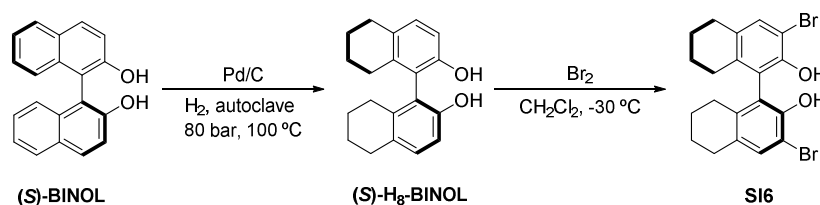
(*S*)-H$_8$-Binol was synthesized following the procedure described in the literature.[33] Spectroscopic data for (*S*)-H$_8$-binol were in agreement with those reported in the literature.[25,34]

SI6 was prepared following the reported procedure in the literature from (*S*)-H$_8$-binol by a bromination step.[25] Spectroscopic data for **SI6** were in agreement with those reported in the literature.[25]

(*S*)-3,3′-Bis(triphenylsilyl)-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′binaphthalene]2,2′-diol (SI7)
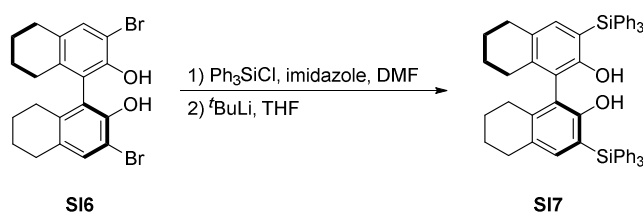
SI7 was synthesized following a procedure described in the literature with slight modifications as follows.[35] **SI6** (1g, 2.21 mmol, 1 eq) was dissolved in DMF (16 mL, 0.14M), imidazole (0.67 g,

33 Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220.

34 The enantiomeric excess of (*S*)-H$_8$-Binol was calculated by HPLC analysis on chiral stationary phase using *Chiralcel OD-H* column [*n*-hexane/ *i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ$_{minor}$ = 13.85 min, τ$_{major}$ = 16.77 min (99% ee).

35 Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405.

9.9 mmol, 4.5 eq) and corresponding silyl chloride (4.1 g, 13.3 mmol, 6 eq) were added at room temperature. The mixture was stirred at room temperature for 72 h until all starting material was consumed (reaction monitored by TLC using hexanes/CH_2Cl_2 2.5:1). The reaction was quenched with a saturated solution of Na_2CO_3 (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and combined organic extracts were washed with HCl (1M, 20 mL) and brine (20 mL). Organic layer was dried over Na_2SO_4 and filtered. After the removal of the solvent, the residue was filtered through a small plug of silica gel (hexanes/EtOAc 19:1) obtaining a crude wich pure enough to perform the next step. To a solution of bromosilyl ether (1 g, 1.03 mmol, 1 eq) in dry THF (25 mL, 0.04M) was dropwise added ^{t}BuLi (1.6M in pentane) (3.9 mL, 6.2 mmol, 6 eq) over 10 min at 0 ºC. The mixture was stirred at room temperature for 5 h. Then, the mixture was cooled to 0 ºC and a saturated solution of NH_4Cl (15 mL) was added dropwise to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×10 mL) and combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by FC on silica gel (hexanes/EtOAc 19:1 to 8:2) to obtain **SI7** (1.07 g, 1.32 mmol, 60% two steps). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61-7.55 (m, 12H, C$_{arom}$-H), 7.45-7.29 (m, 18H, C$_{arom}$-H), 6.93 (s, 2H, C$_{arom}$-H), 4.87 (s, 2H, 2×OH), 2.58 (bs, 4H, 2×CH$_2$), 2.45-2.24 (m, 4H, 2×CH$_2$), 1.77-1.61 (m, 8H, 4×CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.3 (C$_{arom}$-O), 140.2 (C$_{arom}$), 139.8 (C$_{arom}$-H), 136.4 (C$_{arom}$-H), 134.8 (C$_{arom}$), 130.2 (C$_{arom}$), 129.5 (C$_{arom}$-H), 127.8 (C$_{arom}$-H), 119.0 (C$_{arom}$), 117.3 (C$_{arom}$), 29.3 (CH$_2$), 27.6 (CH$_2$), 23.1 (CH$_2$).

1,1´-Spirobiindane-7,7´-derivatives

The *spiroanalog* of BINOL was prepared following the procedure available on the literature with some modifications.[36]
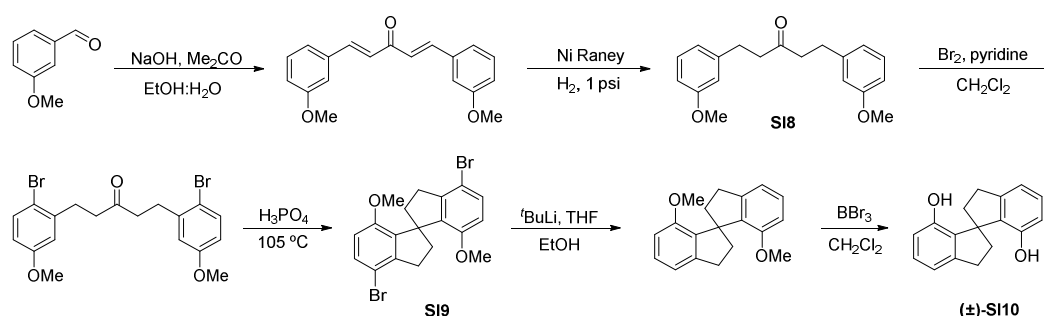
1,5-bis-*m*-anisyl-3-pentanone (SI8). A solution of *m*-anisaldehyde (367.2 mmol, 2.0 eq) and acetone (183.6 mmol, 1 eq) in 25 mL of EtOH was added dropwise to a solution of 37.5 g of NaOH in 300 mL of 50% aqueous ethanol, stirring in a water bath at room temperature. The mixture was stirred for 2 h with mechanic stirring. Then CH_2Cl_2 was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. A solution of 1,5-bis-*m*-anisyl-1,4-pentadien-3-one (53.5 mmol, 1 eq) in the minimum quantity of acetone was stirred with Ni Raney (2 eq) under an atmosphere of H_2 (1 atm, balloon) at room temperature, monitoring the reaction by TLC and adding more catalyst as necessary. After 16 h, the catalyst was filtered off, washed with acetone and the filtrate was evaporated under reduced pressure. The crude was obtained as a colorless oil wich was purificated by FC on silica (hexanes to hexanes/EtOAc 8:2) to obtain **SI8** (21.4 mmol, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.19 (m, 2H, C_{arom}-H), 6.80-6.76 (m, 6H, C_{arom}-H), 3.79 (s, 6H, OCH_3), 2.90 (t, J = 7.5 Hz, 4H, CH_2), 2.71 (t, J = 7.5 Hz, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0 (C=O), 159.7 (C_{arom}-O), 142.6 (C_{arom}), 129.4 (C_{arom}-H), 120.6 (C_{arom}-H), 114.1 (C_{arom}-H), 111.4 (C_{arom}-H), 55.1 (OCH_3), 44.4 (O=CCH_2), 29.7 (CH_2).

4,4´-dibromo-7,7´-dimethoxy-1,1´-spirobiindane (SI9). SI8 (9.8 mmol, 1 eq) was dissolved in the minimum quantity of CH_2Cl_2, pyridine (34.3 mmol, 3.5 eq) was added and the mixture was

36   Birman, V. B.; Rheingold, A. L.; Lam, K.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 125.

cooled to -10 °C. A solution of bromine in CH_2Cl_2 (24.5 mmol, 2.5 eq, 10% v/v) was added dropwise. After that, the reaction mixture was allowed to warm to room temperature and stirred until the starting material disappeared (1 day). The mixture was washed with aqueous $NaHSO_3$ to remove excess bromine, washed with diluted HCl and water and dried over Na_2SO_4, filtered and concentrate under vacuum. The product solidified on standing and it was used without further purification. The crude (5.5 mmol, 1 eq) was stirred with 22 g of H_3PO_4 (PPA can be used as well) at 105 °C for 5.5 h. Due to the complex workup, low scale reaction is recommended. The crude was cooled to 0°C and quenched with aqueous KOH solution and stirred for 10 minutes. The mixture was extracted with Et_2O (3×30 mL) and then with CH_2Cl_2 (3×30 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by FC on silica gel (hexanes/EtOAc 9:1) and **SI9** was obtained (6.4 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H, C_{arom}-H), 6.52 (d, J = 8.6 Hz, 2H, C_{arom}-H), 3.52 (s, 3H, OCH_3), 3.12-2.89 (m, 4H, CH_2), 2.37-2.27 (m, 2H, CH_2), 2.20-2.12 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C_{arom}-O), 144.8 (C_{arom}), 138.2 (C_{arom}), 130.3 (C_{arom}-H), 110.8 (C_{arom}-H), 110.5 (C_{arom}-Br), 61.9 (C_{spiro}), 55.4 (OCH_3), 37.9 (CH_2), 33.2 (CH_2).

rac-1,1´-Spirobiindane-7,7´–diol, (±)-SI10. In a dried flask a solution of **SI9** (1.4 mmol, 1 eq) in THF (0.12M) was placed under Argon atmosphere. The solution was cooled to -78 °C and treated with [t]BuLi 1.9M solution in pentane (5.6 mmol, 4 eq). After 1 h, the reaction mixture was quenched with EtOH and aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Combined organic layers were washed with water and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure The residue was used in the next step without further purification. In a dried flask a solution of 7,7´-dimethoxy-1,1´-spirobiindane (1.96 mmol, 1 eq) in CH_2Cl_2 (0.22M) was cooled to -78 °C, treated with BBr_3 in CH_2Cl_2 (4.5 mmol, 2.3 eq) and allowed to warm to room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water until washings had neutral pH. Organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by FC on silica gel (hexane/EtOAc, 19:1 to 8:2) to give product **(±)-SI10** (1.1 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J = 7.7 Hz, 2H, C_{arom}-H), 6.90 (d, J = 7.4 Hz, 2H, C_{arom}-H), 6.68 (d, J = 8.0 Hz, 2H, C_{arom}-H), 4.72 (s, 2H, OH), 3.09-2.98 (m, 4H, CH_2), 2.36-2.14 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C_{arom}-

OH), 145.8 (C$_{arom}$), 130.5 (C$_{arom}$), 129.8 (C$_{arom}$-H), 117.6 (C$_{arom}$-H), 114.3 (C$_{arom}$-H), 57.4 (C$_{spiro}$), 37.4 (CH$_2$), 31.2 (CH$_2$).

7,7´-Bis-(*L*-menthyloxy-carbonyloxy)-1,1´-spirobiindane (*R*)-SI11 and (*S*)-SI11
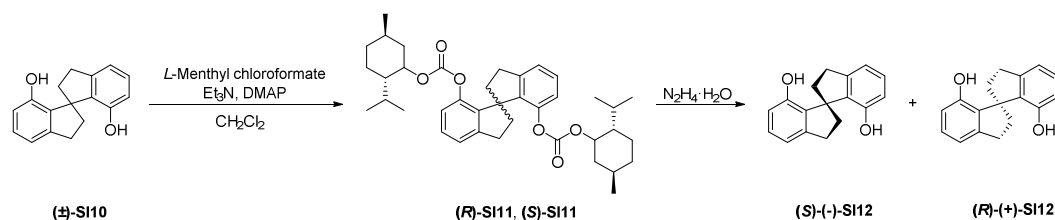
The resolution of *rac*-1,1´-spirobiindane-7,7´–diol (±)-SI10 was achieved using *L*-Menthyl chloroformate (1.9 mmol, 2.4 eq) which was added to a stirring solution of *rac*-1,1´-spirobiindane-7,7´–diol (±)-SI10 (0.8 mmol, 1 eq), Et$_3$N (2.95 mmol, 3.7 eq) and DMAP (0.08 mmol, 10 mol%) in CH$_2$Cl$_2$ (0.1M) under Ar atmosphere. After stirring for 9 h at room temperature the organic layer was washed with water, HCl and brine. The organic layer was dried with Na$_2$SO$_4$, evaporated and the residue was purified by FC on silica gel (hexane to hexane/EtOAc 95:5) to give (*R*)-SI11 (0.44 mmol, 40%) and (*S*)-SI11 (0.46 mmol, 42%). Mixed fractions were gotten as well.

(*R*)-SI11: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (t, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 7.09 (d, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 6.98 (d, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 4.33 (td, *J* = 10.8, 4.4 Hz, 2H, 2×C$_{cy}$H), 3.17-2.99 (m, 4H, 2×C$_{cy}$H$_2$), 2.46-2.33 (m, 2H, C$_{cy}$H$_2$), 2.32-2.19 (m, 2H, C$_{cy}$H$_2$), 1.95-1.20 (m, 14H, 2×C$_{cy}$H + 6×C$_{cy}$H$_2$), 1.07-0.82 (m, 16H, 2×C$_{cy}$H + 2×CH + 4×CH$_3$), 0.71 (d, *J* = 6.9 Hz, 6H, 2×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.6 (C=O), 147.6 (C$_{arom}$), 145.7 (C$_{arom}$), 138.9 (C$_{arom}$), 127.8 (C$_{arom}$-H), 121.9 (C$_{arom}$-H), 119.9 (C$_{arom}$-H), 78.5 (OCH), 59.1 (C$_{spiro}$), 46.5 (CH), 40.2 (C$_{cy}$H$_2$), 38.8 (C$_{cy}$H$_2$), 34.0 (C$_{cy}$H$_2$), 31.2 (C$_{cy}$H$_2$), 31.1 (CH), 25.4 (CH), 23.0 (C$_{cy}$H$_2$), 21.9 (CH$_3$), 20.7 (CH$_3$), 16.1 (CH$_3$).

(*S*)-SI11: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22 (t, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 7.12 (d, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 6.95 (d, *J* = 7.7 Hz, 2H, C$_{arom}$-H), 4.39 (td, *J* = 10.9, 4.4 Hz, 2H, 2×C$_{cy}$-H), 3.14-2.92 (m, 4H, 2×C$_{cy}$H$_2$), 2.37-1.17 (m, 18H, 4×C$_{cy}$H + 6×C$_{cy}$H$_2$ + 2×CH), 1.01-0.83 (m, 12H, 4×CH$_3$), 0.72 (d, *J* = 6.9 Hz, 6H, 2×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.0 (C=O), 147.4 (C$_{arom}$), 145.4 (C$_{arom}$), 139.0 (C$_{arom}$), 127.8 (C$_{arom}$-H), 122.0 (C$_{arom}$-H), 120.3 (C$_{arom}$-H), 78.3

(OCH), 58.5 (C_{spiro}), 46.6 (CH), 40.3 ($C_{cy}H_2$), 38.3 ($C_{cy}H_2$), 33.9 ($C_{cy}H_2$), 31.1 ($C_{cy}H_2$), 30.9 (CH), 25.4 (CH), 22.9 ($C_{cy}H_2$), 21.8 (CH_3), 20.6 (CH_3), 15.9 (CH_3).

(*S*)-(−)-1,1´-Spirobiindane-7,7´-diol, (*S*)-SI12. For the preparation of **(*S*)-SI12**, a solution of **(*S*)-SI11** (0.32 mmol, 1 eq) and hydrazine hydrate (4.4 mmol, 6 eq) in THF (0.15M) were added. The mixture was refluxed under Ar atmosphere for 2 h. The crude was diluted with CH_2Cl_2, washed with diluted HCl, water and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. FC on silica gel (hexanes/EtOAc 19:1 to 8:2) afforded **(*S*)-SI12** (0.18 mmol, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 2H, C_{arom}-H), 6.89 (d, *J* = 7.6 Hz, 2H, C_{arom}-H), 6.68 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 4.57 (s, 2H, OH), 3.07-3.01 (m, 4H, CH_2), 2.35-2.14 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C_{arom}-O), 145.8 (C_{arom}), 130.4 (C_{arom}), 129.9 (C_{arom}-H), 117.7 (C_{arom}-H), 114.3 (C_{arom}-H), 57.4 (C_{spiro}), 37.4 (CH_2), 31.2 (CH_2). $[\alpha]_D^{20}$: -43.9 (*c* = 1.0, CH_2Cl_2). Literature value $[\alpha]_D^{20}$: -32.7 (*c* = 1.0, $CHCl_3$).

The opposite enantiomer was obtained following the same procedure described.

(*S*)-6,6´-bis(triphenylsilyl)-2,2´,3,3´-tetrahydro-1,1´-spirobiindane-7,7´-diol, (*S*)-SI13
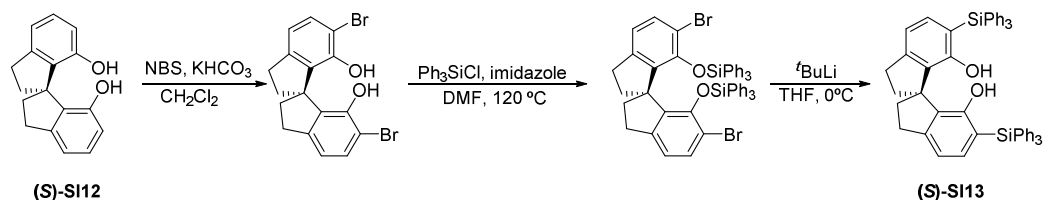
(*S*)-6,6´-bis(triphenylsilyl)-2,2´,3,3´-tetrahydro-1,1´-spirobiindane-7,7´-diol **(*S*)-SI13** was prepared through an *ortho*-bromination step of **(*S*)-SI12** following a patented procedure with slight modifications as follows.[37] To a solution of **(*S*)-SI12** (0.16 mmol, 1 eq) and $KHCO_3$ (0.32 mmol, 2 eq) in CH_2Cl_2 (1.5 mL, 0.11M), *N*-bromo succinimide (0.33 mmol, 2.05 eq) was added slowly at -20ºC. The reaction mixture was stirred for 20 h. The mixture was quenched with HCl (2M, 5 mL) and extracted with CH_2Cl_2 (3×5 mL). Combined organic layers were dried over Na_2SO_4 and filtered. After removal of the solvent, the crude was filtered through a small plug of

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37 Chipa, L.; Zambad, S. P.; Gupta, R.; Tuli, D.; Kasundra, A.; Munshi, S.; Siddiqui, M. A.; Bhattamisra, S. K.; Dutt, C.; Chauthaiwale, V. Pyrazole derivatives as thyroid receptor modulators and their preparation, pharmaceutical compositions and use in the treatment of diseases. International Patent WO 2008149379, July 02, 2008.

silica and it was used in the next step without further purification. NMR spectral data were in agreement with those reported in the literature.[38]

(*S*)-SI13. Silylation and rearrangement step were developed following a procedure reported in the literature.[39]. Spectroscopic data for **(*S*)-SI13** were in agreement with those reported in the literature.[39] ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63-7.60 (m, 12H, C$_{arom}$-H), 7.43-7.37 (m, 6H, C$_{arom}$-H), 7.32-7.27 (m, 12H, C$_{arom}$-H), 7.12 (d, *J* = 7.4 Hz, 2H, C$_{arom}$-H), 6.87 (d, *J* = 7.4 Hz, 2H, C$_{arom}$-H), 5.20 (s, 2H, 2×OH), 3.16-2.96 (m, 4H, 2×CH$_2$), 2.40-2.22 (m, 4H, 2×CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.5 (C$_{arom}$), 149.2 (C$_{arom}$), 139.0 (C$_{arom}$-H), 136.3 (C$_{arom}$-H), 134.5 (C$_{arom}$), 131.4 (C$_{arom}$), 129.6 (C$_{arom}$-H), 128.0 (C$_{arom}$-H), 117.9 (C$_{arom}$-H), 117.6 (C$_{arom}$), 58.2 (C$_{spiro}$), 37.3 (CH$_2$), 31.2 (CH$_2$).

38 Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard III, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500.

39 Xing, C.-H.; Liao Y.-X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q.-S. *Eur. J. Org. Chem.* **2012**, *6*, 1115.

2.3.2 Synthesis of catalysts

Catalysts 3g-j

3g:	Ar= Ph, X= O
3h:	Ar= Ph, X=S
3i:	[H$_8$], Ar= Ph, X= O
3j:	Ar= TBDM, X= O
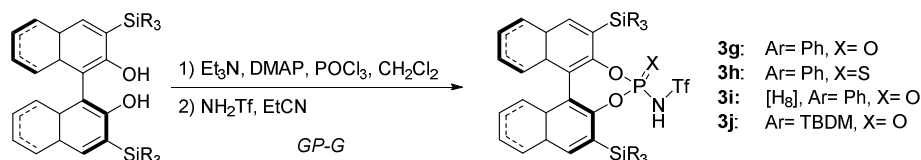
General Procedure G (GP-G) for the synthesis of catalysts 3g-j: Corresponding (*S*)-diol (0.5 mmol, 1 eq) was placed in a two-necked flask fitted with a reflux condenser under Argon atmosphere and was dissolved in dry CH$_2$Cl$_2$ (0.15M). Freshly distilled and dry Et$_3$N (3.5 mmol, 7 eq) and POCl$_3$ (0.75 mmol, 1.5 eq) respectively were added at 0ºC and the reaction mixture was stirred for 5 min. DMAP (1 mmol, 2 eq) was added into the reaction mixture at 0ºC and it was stirred at room temperature for 2 h. Freshly distilled EtCN (0.15M) was added followed by corresponding sulfonamide (1.5 mmol, 3 eq) and the reaction was heated to 95ºC for 14 h. The mixture was cooled to room temperature and quenched with water (10 mL), stirred for 30 minutes and diluted with CH$_2$Cl$_2$. The organic layer was separated from the mixture and the aqueous phase was extracted with CH$_2$Cl$_2$ (3×10 mL). The combined organic extracts were washed with NaHCO$_3$ sat. aq. (5 mL) and 5M HCl (3×5 mL). Combined organic extracts were dried with Na$_2$SO$_4$, filtered and solvent was removed under reduced pressure. The residue was purified by FC on silica gel (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH 95:5). After purification, residue must be cleaned with 5M HCl (5×5 mL) since no calcium ions are present during the synthetic steps, it is likely that *N*-triflylphosphoramides bound calcium cations from the silica gel used for the final column chromatography but they release it upon acidic washing.[40] EDX measurements had been done to confirm that these highly acidic Brønsted acids are free from any metal impurities.[41] **(3h)** was synthesized following a procedure in the literature.[26]

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40   Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *122*, 3911.

41   Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem. Eur. J.* **2010**, *16*, 13116.
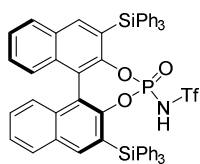
1,1,1-trifluoro-N-((11b*S*)-4-oxido-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1´,2´-*f*][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide (3g).

Following *GP-G*, **3g** was isolated as a white solid by FC on silica gel (314 mg, 0.31 mmol, 63%), starting from **SI5a** (400 mg, 0.5 mmol) in CH_2Cl_2 (2.6 mL) with Et_3N (0.49 mL, 3.5 mmol), $POCl_3$ (70 μL, 0.75 mmol), DMAP (122 mg, 1 mmol), EtCN (2.6 mL) and NH_2Tf (235 mg, 1.5 mmol). R_f= 0.33 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H, C_{arom}-H), 8.13 (s, 1H, C_{arom}-H), 7.93 (d, *J* = 8.1 Hz, 1H, C_{arom}-H), 7.85-7.78 (m, 7H, C_{arom}-H), 7.78-7.69 (m, 6H, C_{arom}-H), 7.58-7.24 (m, 24H, C_{arom}-H), 4.26 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (C_{arom}-H), 142.1 (C_{arom}-H), 136.9 (C_{arom}-H), 136.6 (C_{arom}-H), 134.3 (C_{arom}), 133.3 (C_{arom}), 133.2 (C_{arom}), 131.1 (C_{arom}), 131.0 (C_{arom}), 129.9 (C_{arom}-H), 129.5 (C_{arom}-H), 128.9 (C_{arom}-H), 128.8 (C_{arom}-H), 128.2 (C_{arom}-H), 127.9 (C_{arom}-H), 127.7 (C_{arom}-H), 126.8 (C_{arom}-H), 126.0 (C_{arom}-H), 125.9 (C_{arom}-H), 125.1 (C_{arom}), 121.7 (C_{arom}), 120.9 (C_{arom}). ^{19}F NMR (282 MHz, $CDCl_3$) δ -77.8. IR (CH_2Cl_2): 1430 (SO_2 st as), 1190 (SO_2 st sim), 1190 (P=O st)cm^{-1}. HRMS: Calculated for $[C_{57}H_{40}NO_5PSF_3Si_2]^-$: 994.1855 [M-H]$^-$; found: 994.1848. M.p.: 160-162°C (CH_2Cl_2). $[α]_D^{20}$: +175.4 (*c* = 1.0, CH_2Cl_2).
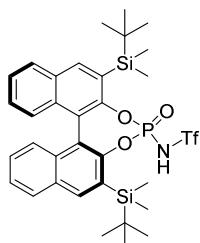
N-((11b*S*)-2,6-bis(*tert*-butyldimethylsilyl)-4-oxidodinaphtho[2,1-d:1´,2´-*f*][1,3,2]dioxaphosphepin-4-yl)-1,1,1-trifluoromethanesulfonamide (3h).

Following *GP-G*, **3j** was isolated as a white solid by FC on silica gel (314 mg, 0.31 mmol, 52%), starting from **SI5b** (125 mg, 0.24 mmol) in CH_2Cl_2 (0.8 mL) with Et_3N (0.23 mL, 1.7 mmol), $POCl_3$ (33 μL, 0.36 mmol), DMAP (58.6 mg, 1 mmol), EtCN (0.8 mL) and NH_2Tf (111 mg, 0.72 mmol). R_f= 0.27 (CH_2Cl_2/MeOH, 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.91 (dd, *J* = 8.3, 5.1 Hz, 2H, C_{arom}-H), 7.47-7.35 (m, 2H, C_{arom}-H), 7.25-7.17 (m, 2H, C_{arom}-H), 7.06-6.97 (m, 2H, C_{arom}-H), 2.49 (s, 1H, NH), 0.81 (s, 9H, 3×CH_3), 0.79 (s, 9H, 3×CH_3), 0.61 (s, 3H, CH_3), 0.49 (s, 3H, CH_3), 0.48 (s, 3H, CH_3), 0.39 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5 (C_{arom}), 151.4 (C_{arom}), 151.2 (C_{arom}), 151.1 (C_{arom}), 138.6 (C_{arom}-H), 133.8 (C_{arom}), 133.7 (C_{arom}), 130.8 (C_{arom}), 130.7 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}-H), 128.4 (C_{arom}-H), 127.1 (C_{arom}-H), 126.9 (C_{arom}-H), 126.8 (C_{arom}-H), 126.7 (C_{arom}-H), 125.4 (C_{arom}-H), 125.3 (C_{arom}-H), 121.6 (C_{arom}), 121.0 (C_{arom}), 26.9 (CH_3), 26.9 (CH_3), 17.8 (CH_3), 17.7 (CH_3), -3.3 (CH_3), -3.8 (CH_3), -4.4 (CH_3), -4.8 (CH_3). ^{19}F NMR (282

MHz, CDCl$_3$) δ -79.4. HRMS: Calculated for [C$_{33}$H$_{40}$NO$_5$SPF$_3$Si$_2$]$^-$: 706.1855 [M-H]$^-$; found: 706.1850. M.p.: 105-107ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +151.9 (*c* = 0.6, CH$_2$Cl$_2$).
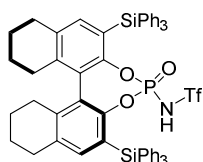
1,1,1-trifluoro-*N*-((11b*S*)-4-oxido-2,6-bis(triphenylsilyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1´,2´-f][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide (3i). Following *GP-G*, **3i** was isolated as a white solid by FC on silica gel (226 mg, 0.22 mmol, 55%), starting from **SI7** (330 mg, 0.41 mmol) in CH$_2$Cl$_2$ (1.6 mL) with Et$_3$N (0.4 mL, 2.9 mmol), POCl$_3$ (57 μL, 0.61 mmol), DMAP (100 mg, 0.82 mmol), EtCN (1.6 mL) and NH$_2$Tf (180 mg, 1.2 mmol). R$_f$= 0.4 (CH$_2$Cl$_2$:MeOH, 96:4). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.62 (dd, *J* = 7.7, 1.7 Hz, 6H, C$_{arom}$-H), 7.54 (dd, *J* = 7.7, 1.7 Hz, 6H, C$_{arom}$-H), 7.46-7.24 (m, 19H, C$_{arom}$-H), 7.06 (s, 1H, C$_{arom}$-H), 3.07 (bs, 1H, NH), 2.83-2.54 (m, 6H, 3×CH$_2$), 2.41-2.20 (m, 2H, 2×CH$_2$), 1.93-1.56 (m, 8H, 4×CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.6 (C$_{arom}$), 150.4 (C$_{arom}$), 150.1 (C$_{arom}$), 150.0 (C$_{arom}$), 141.7 (C$_{arom}$), 141.6 (C$_{arom}$), 140.9 (C$_{arom}$), 140.9 (C$_{arom}$), 140.3 (C$_{arom}$-H), 139.5 (C$_{arom}$-H), 136.9 (C$_{arom}$-H), 136.6 (C$_{arom}$-H), 135.7 (C$_{arom}$), 135.7 (C$_{arom}$), 135.5 (C$_{arom}$), 135.1 (C$_{arom}$), 133.6 (C$_{arom}$), 133.4 (C$_{arom}$), 132.1 (q, $^1J_{C-F}$ = 273.8 Hz, CF$_3$), 130.0 (C$_{arom}$-H), 129.5 (C$_{arom}$-H), 128.3 (C$_{arom}$-H), 127.7 (C$_{arom}$-H), 126.5 (C$_{arom}$), 126.5 (C$_{arom}$), 125.8 (C$_{arom}$), 122.9 (C$_{arom}$), 122.8 (C$_{arom}$), 121.7 (C$_{arom}$), 121.6 (C$_{arom}$), 29.3 (CH$_2$), 28.1 (CH$_2$), 28.1 (CH$_2$), 22.7 (CH$_2$), 22.7 (CH$_2$), 22.6 (CH$_2$), 22.6 (CH$_2$). ^{19}F NMR (282 MHz, CDCl$_3$) δ -77.9. IR (CH$_2$Cl$_2$): 1428 (SO$_2$ st as), 1195 (SO$_2$ st sim), 1109 (P=O st) cm^{-1}. HRMS: Calculated for [C$_{57}$H$_{48}$NO$_5$SPF$_3$Si$_2$]$^-$: 1002.2481 [M-H]$^-$; found: 1002.2486. M.p.: 158-160ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +87.5 (*c* = 1.0, CH$_2$Cl$_2$).

(S)-SI13 → **3k**

1) Et₃N, DMAP, POCl₃
CH₂Cl₂

2) NH₂Tf, EtCN
GP-G
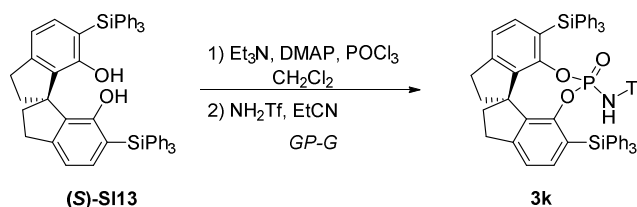
Following *GP-G*, **3k** was isolated after FC on silica gel (36 mg, 0.04 mmol, 24%), starting from (*S*)**-SI13** (120 mg, 0.15 mmol) in CH₂Cl₂ (0.85 mL) with Et₃N (0.15 mL, 1.1 mmol), POCl₃ (22 µL, 0.23 mmol), DMAP (38.1 mg, 0.31 mmol), EtCN (0.85 mL) and NH₂Tf (72.7 mg, 0.47 mmol). R_f= 0.33 (CH₂Cl₂:MeOH, 96:4). ^{1}H NMR (300 MHz, CDCl₃) δ 7.61-7.48 (m, 10H, C_{arom}-H), 7.44-7.20 (m, 20H, C_{arom}-H), 7.16 (d, J = 7.4 Hz, 1H, C_{arom}-H), 7.08 (d, J = 7.4 Hz, 1H, C_{arom}-H), 3.23-2.80 (m, 4H, 2×CH₂), 2.59 (s, 1H, NH), 2.40-2.14 (m, 3H, CH₂+C**H**$_a$H$_b$), 2.12-1.92 (m, 1H, CH$_a$**H**$_b$). ^{13}C NMR (75 MHz, CDCl₃) δ 164.8 (q, $^1JC_{-F}$ = 234.1 Hz, CF₃), 149.3 (C_{arom}-O), 139.4 (C_{arom}-H), 138.7 (C_{arom}-H), 136.9 (C_{arom}-H), 136.7 (C_{arom}-H), 135.0 (C_{arom}-H), 133.6 (C_{arom}), 133.2 (C_{arom}), 129.6 (C_{arom}-H), 129.3 (C_{arom}-H), 128.1 (C_{arom}-H), 127.9 (C_{arom}), 127.7 (C_{arom}-H), 127.5 (C_{arom}-H), 123.2 (C_{arom}-H), 123.1 (C_{arom}-H), 60.1 (C_{spiro}), 39.0 (CH2), 38.2 (CH₂), 30.1 (CH₂), 30.0 (CH₂). ^{19}F NMR (282 MHz, CDCl₃) δ -78.4. IR (CH₂Cl₂): 1278 (SO₂ st as), 1260 (SO₂ st sim), 1207 (C-F st) cm^{-1}. HRMS: Calculated for [C₅₄H₄₂NO₅SPF₃Si₂]⁻: 960.2012 [M-H]⁻; found: 960.2014. M.p.: 114-116ºC (CH₂Cl₂). [α]$_D^{20}$: -244.0 (*c* = 0.6, CH₂Cl₂).

2.4 **Preparation of DMDO**

DMDO was prepared following the procedure reported in the literature.[42] Concentration of DMDO solution was determined by classical iodometric titration.[43]

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42   Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X.; Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532.

43   Hayes, C. J.; Sherlock, A. E.; Selby, M. D. *Org. Biomol. Chem.* **2006**, *4*, 193.

2.5 <u>Synthesis of cycloadducts 4a-k</u>

4a: R^1-R^2 = COCH$_2$CH$_2$CH$_2$
4b: R^1 = Me; R^2 = Ts
4c: R^1 = Ph; R^2 = Ts
4d: R^1 = 4-BrC$_6$H$_4$; R^2 = Ts
4e: R^1 = 2,4,6-(Me)$_3$C$_6$H$_2$; R^2 = Ts
4f: R^1 = *p*-MeOC$_6$H$_4$; R^2 = Ts
4g: R^1 = *p*-MeOC$_6$H$_4$; R^2 = Ac
4h: R^1 = Ph; R^2 = Boc
4i: R^1 = 4-BrC$_6$H$_4$; R^2 = Boc
4k: R^1 = 3,4,5-(MeO)$_3$C$_6$H$_2$; R^2 = Boc
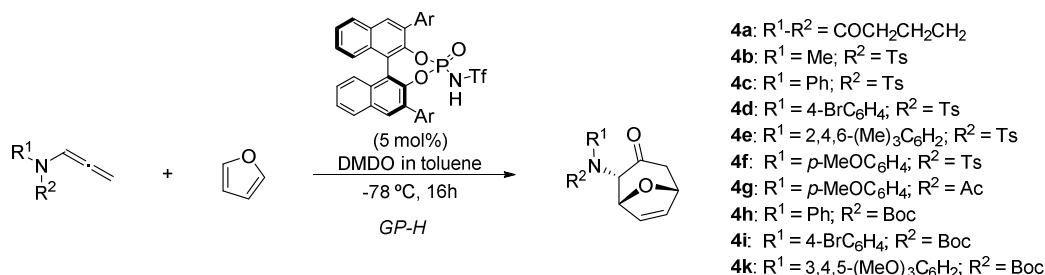
General Procedure H (GP-H) for the synthesis of 4a-k: A test tube equipped with a stirring bar was charged with the corresponding catalyst (5 mol%) and cooled to -78 ºC. Then, corresponding allene (0.1 mmol, 1 eq) was added followed by a precooled mixture of DMDO in toluene (0.2 mmol, 2 eq). Subsequently, furan (0.3 mmol, 3 eq) was added. The mixture was stirred for 16 h at -78 ºC. The crude reaction was purified by flash column chromatography on silica gel. TLCs were developed in *p*-anisaldehyde dip.

The racemic standards for HPLC separation were prepared using diphenyl phosphate or diphenyl-*N*-triflyl phosphoramide catalyst.
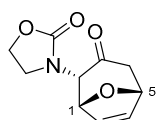
3-((1*R*,2*S*,5*R*)-3-Oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)oxazolidin-2-one (4a). Following *GP-H*, **4a** (22.2 mg, 44%) was isolated by FC (hexanes/EtOAc 1:1 to 2:8), as an oil after 16h, starting from catalyst **3g** (11.9 mg, 0.01 mmol), allene **1a** (30 mg, 0.24 mmol), DMDO solution in toluene (1.7 mL, 0.48 mmol) and furan (52 µL, 0.72 mmol). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.40 (dd, *J* = 6.1, 1.9 Hz, 1H, H-6), 6.27 (d, *J* = 6.2 Hz, 1H, H-7), 5.06 (m, 1H, H-5), 5.03 (dd, *J* = 4.7, 1.8 Hz, 1H, H-1), 4.51-4.23 (m, 2H, CH$_2$), 3.72-3.61 (m, 1H, C**H**$_a$H$_b$), 3.33-3.18 (m, 1H, CH$_a$**H**$_b$), 2.87 (dd, *J* = 15.9, 5.2 Hz, 1H, H-4a), 2.44 (d, *J* = 15.9 Hz, H-4b). ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.7 (C=O), 158.9 (O-C=O), 136.1 (C-6), 131.2 (C-7), 80.1 (C-5), 78.2 (C-1), 65.9 (C-2), 62.6 (OCH$_2$), 45.9 (C-4), 42.8 (CH$_2$). IR (CH$_2$Cl$_2$): 1745, 1716 cm^{-1}. MS (EI) m/z (%): 123 (20). HRMS: Calculated for [C$_{10}$H$_{12}$NO$_4$]$^+$: 210.0766 [M+H]$^+$; found: 210.0766. The ee was determined by HPLC using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 0.60 mL/min; τ$_{minor}$ =39.1 min, τ$_{major}$ = 45.9 min (20% ee).
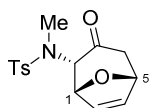
***N*,4-Dimethyl-*N*-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)benzenesulfonamide (4b).** Following *GP-H*, **4b** (14.0 mg, 34%) was isolated by FC (hexanes/EtOAc 2:8 to 1:1), as a solid after 16h, starting from catalyst **3g** (6.6 mg, 0.007 mmol), allene **1b** (30 mg, 0.13 mmol), DMDO solution in toluene (1.7 mL, 0.27 mmol) and furan (29 μL, 0.4 mmol). $R_f$= 0.51 (hexanes/EtOAc 1:1). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H, C$_{arom}$-H), 7.28 (d, *J* = 8.2 Hz, C$_{arom}$-H), 6.36-6.30 (m, 2H, H-6 + H-7), 5.05-4.95 (m, 2H, H-1 + H-5), 4.92 (d, *J* = 4.8 Hz, 1H, H-2), 2.76 (dd, *J* = 16.3, 5.3 Hz, 1H, H-4a), 2.66 (s, 3H, NCH$_3$), 2.41 (s, 3H, C$_{arom}$-CH$_3$), 2.34 (dd, *J* = 16.3, 0.9 Hz, 1H, H-4b). ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.8 (C=O), 143.5 (C$_{arom}$), 135.8 (C$_{arom}$), 135.3 (C-7), 131.9 (C-6), 129.5 (C$_{arom}$-H), 127.2 (C$_{arom}$-H), 81.3 (C-5), 77.5 (C-1), 69.1 (C-2), 45.8 (C-4), 32.6 (CH$_3$N), 21.5 (**C**H$_3$-C$_{arom}$). IR (CH$_2$Cl$_2$): 1724 (C=O st), 1332 (SO$_2$ st as), 1153 (SO$_2$ st sy) cm^{-1}. MS (EI) m/z (%): 307 (M$^+$, 1), 152 (100). HRMS: Calculated for [C$_{15}$H$_{18}$NO$_4$S]$^+$: 308.0957 [M+H]$^+$; found: 308.0951. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.00 mL/min; τ$_{minor}$ = 26.3 min, τ$_{major}$ = 39.5 min (48% ee). M.p: 91-93ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +18.0 (*c* = 1.0, CH$_2$Cl$_2$).
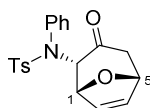
4-Methyl-*N*-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)-*N*-phenylbenzenesulfonamide (4c). Following *GP-H*, **4c** (10.4 mg, 27%) was isolated by FC (hexanes/EtOAc 9:1 to 6:4), as an oil after 16h, starting from catalyst **3g** (5.2 mg, 0.005 mmol), allene **1c** (30 mg, 0.1 mmol), DMDO solution in toluene (0.75 mL, 0.21 mmol) and furan (22 μL, 0.3 mmol). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-H), 7.40-7.13 (m, 7H, C$_{arom}$-H), 5.93 (dd, *J* = 6.1, 1.7 Hz, 1H, H-6), 5.45 (d, *J* = 4.4 Hz, 1H, H-2), 5.03 (dd, *J* = 4.4, 1.7 Hz, 1H, H-1), 4.91 (m, 1H, H-5), 4.61 (dd, *J* = 6.1, 1.7 Hz, 1H, H-7), 2.84 (dd, *J* = 15.7, 5.1 Hz, 1H, H-4a), 2.41 (s, 3H, CH$_3$), 2.33 (d, *J* = 15.6 Hz, 1H, H-4b). ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.0 (C=O), 143.4 (C$_{arom}$), 137.0 (C$_{arom}$), 136.8 (C$_{arom}$), 133.9 (C$_{arom}$-H), 132.9 (C$_{arom}$-H), 131.6 (C-6), 129.3 (C-7), 129.1 (C$_{arom}$-H), 129.0 (C$_{arom}$-H), 128.2 (C$_{arom}$-H), 81.4 (C-5), 78.0 (C-2), 72.2 (C-1), 45.6 (C-4), 21.6 (CH$_3$). IR (CH$_2$Cl$_2$): 1730 (C=O st), 1339 (SO$_2$ st as), 1156 (SO$_2$ st sy) cm^{-1}. MS (EI) m/z (%): 214 (100), 289 (77). HRMS: Calculated for [C$_{20}$H$_{20}$NO$_4$S]$^+$: 370.1113 [M+H]$^+$; found: 370.1121. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ =26.6 min, τ$_{minor}$ = 30.1 min (74% ee). [α]$_D^{20}$: +197.9 (*c* = 0.4, CH$_2$Cl$_2$).
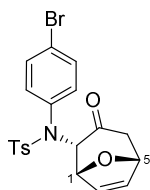
N-(4-bromophenyl)-4-methyl-*N*-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)benzenesulfonamide (4d). Following *GP-H*, **4d** (8.5 mg, 23%) was isolated by FC (hexanes/EtOAc 19:1 to 7:3), as a solid after 16h, starting from catalyst **3g** (4.1 mg, 0.004 mmol), allene **1d** (30 mg, 0.08 mmol), DMDO solution in toluene (0.7 mL, 0.16 mmol) and furan (18 µL, 0.25 mmol). R_f= 0.34 (hexanes/EtOAc 7:3). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-H), 7.41 (d, *J* = 8.7 Hz, 2H, C$_{arom}$-H), 7.24 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 7.07 (d, *J* = 8.7 Hz, 2H, C$_{arom}$-H), 6.0 (dd, *J* = 6.1 Hz, 1.8 Hz, 1H, H-6), 5.45 (d, *J* = 4.3 Hz, 1H, H-2), 5.02 (dd, *J* = 4.3, 1.7 Hz, 1H, H-1), 4.96-4.90 (m, 1H, H-5), 4.78 (dd, *J* = 6.1, 1.7 Hz, 1H, H-7), 2.85 (dd, *J* = 15.7, 5.1 Hz, 1H, H-4a), 2.42 (s, 3H, CH$_3$), 2.33 (d, *J* = 15.7 Hz, 1H, H-4b). ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.9 (C=O), 143.7 (C$_{arom}$SO$_2$), 136.4 (C$_{arom}$), 136.1 (C$_{arom}$), 134.5 (C$_{arom}$-H), 134.4 (C-6), 132.4 (C$_{arom}$-H), 131.5 (C-7), 129.2 (C$_{arom}$-H), 128.1 (C$_{arom}$-H), 123.7 (C$_{arom}$-Br), 81.3 (C-5), 78.0 (C-2), 72.2 (C-1), 45.6 (C-4), 21.6 (CH$_3$). IR (CH$_2$Cl$_2$): 1726 (C=O st), 1339 (SO$_2$ st as), 1159 (SO$_2$ st sy) cm^{-1}. HRMS: Calculated for [C$_{20}$H$_{19}$NO$_4$SBr]$^+$: 448.0218 [M+H]$^+$; found: 448.0222. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} =39.5 min, τ_{minor} = 48.3 min (39% ee). M.p.: 184-186 ºC (CH$_2$Cl$_2$, decomp). [α]$_D$^{20}: +98.1 (*c* = 0.5, CH$_2$Cl$_2$).
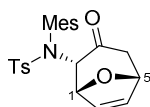
N-Mesityl-4-methyl-*N*-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)benzenesulfonamide (4e). Following *GP-H*, **4e** (6.8 mg, 18%) was isolated by FC (hexanes/EtOAc 19:1 to 7:3), as solid after 16h, starting from **3f** (3.4 mg, 0.005 mmol), allene **1e** (30 mg, 0.09 mmol), DMDO solution in toluene (0.63 mL, 0.18 mmol) and furan (20 µL, 0.28 mmol). R_f= 0.38 (hexanes/EtOAc 7:3). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-H), 7.21 (d, *J* = 8.1 Hz, 2H, C$_{arom}$-H), 6.92 (d, *J* = 2.1 Hz, 1H, C$_{arom}$-H), 6.77 (d, *J* = 2.2 Hz, 1H, C$_{arom}$-H), 6.11 (dd, *J* = 6.1, 1.7 Hz, 1H, H-6), 5.22 (d, *J* = 4.5 Hz, 1H, H-2), 5.09 (dd, *J* = 6.1, 1.7 Hz, 1H, H-7), 4.94 (app d, *J* = 5.4 Hz, 1H, H-5), 4.81 (dd, *J* = 4.5, 1.8 Hz, 1H, H-1), 2.90 (dd, *J* = 15.4, 5.0 Hz, 1H, H-4a), 2.44-2.34 (m, 4H, H-4b+CH$_3$), 2.30 (s, 3H, CH$_3$), 2.27 (s, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.2 (C=O), 143.1 (C$_{arom}$), 140.9 (C$_{arom}$), 140.4 (C$_{arom}$), 139.0 (C$_{arom}$), 137.7 (C$_{arom}$), 134.6 (C-6), 132.7 (C$_{arom}$), 131.5 (C-7), 130.0 (C$_{arom}$-H), 129.9 (C$_{arom}$-H), 128.9 (C$_{arom}$-H), 128.6 (C$_{arom}$-H), 79.9 (C-5), 78.2 (C-2), 72.9 (C-1), 45.2 (C-4), 21.5 (CH$_3$), 20.9 (CH$_3$), 20.1 (CH$_3$), 19.1 (CH$_3$). IR (ATR): 1734 (C=O st), 1336 (SO$_2$ st as), 1159 (SO$_2$ st sy) cm^{-1}. HRMS:

Calculated for $[C_{23}H_{25}NO_4SNa]^+$: 434.1402 $[M+Na]^+$; found: 434.1407. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} =13.1 min, τ_{minor} = 17.3 min (50% ee). M.p.: 165-167 ℃ (hexanes/EtOAc). $[\alpha]_D^{20}$: +116.6 (*c* = 1.0, CH_2Cl_2).
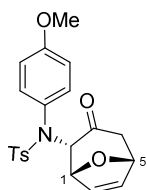
N-(4-methoxyphenyl)-4-methyl-N-((1R,2S,5R)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)benzenesulfonamide (4f). Following *GP-H*, **4f** (5.0 mg, 50%) was isolated by FC (hexanes/EtOAc 9:1 to 6:4), as a solid after 16h reaction time, starting from catalyst **3g** (4.7 mg, 0.005 mmol), allene **1f** (30 mg, 0.09 mmol), DMDO solution in toluene (1.2 mL, 0.2 mmol) and furan (21 µL, 0.28 mmol).

R_f= 0.33 (hexanes/EtOAc 6:4). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-H), 7.21 (d, *J* = 8.1 Hz, 2H, C$_{arom}$-H), 7.07 (d, *J* = 9.0 Hz, 2H, C$_{arom}$-H), 6.76 (d, *J* = 9.0 Hz, 2H, C$_{arom}$-H), 5.95 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.43 (d, *J* = 4.4 Hz, 1H, H-2), 5.02 (dd, *J* = 4.4, 1.7 Hz, 1H, H-1), 4.91 (m, 1H, H-5), 4.73 (dd, *J* = 6.1, 1.7 Hz, 1H, H-7), 3.79 (s, 3H, OCH$_3$), 2.83 (dd, *J* = 15.6, 5.0 Hz, 1H, H-4a), 2.41 (s, 3H, C$_{arom}$CH$_3$), 2.32 (d, *J* = 15.8 Hz, 1H, H-4b). ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.1 (C=O), 159.9 (**C**$_{arom}$OCH$_3$), 143.3 (C$_{arom}$SO$_2$), 136.8 (**C**$_{arom}$CH$_3$), 133.9 (C-7), 133.8 (C$_{arom}$-H), 131.7 (C$_{arom}$-H), 129.2 (C$_{arom}$-N), 129.0 (C$_{arom}$-H), 128.1 (C$_{arom}$-H), 114.1 (C-6), 81.4 (C-1), 78.0 (C-5), 72.2 (C-2), 55.3 (OCH$_3$), 45.5 (C-4), 21.5 (CH$_3$). IR (CH$_2$Cl$_2$): 1730 (C=O st), 1339 (SO$_2$ st as), 1253(C-O-C st as), 1156 (SO$_2$ st sy) cm^{-1}. MS (EI) m/z: 332 (100), 244 (2). HRMS: Calculated for $[C_{21}H_{22}NO_5S]^+$: 400.1219 $[M+H]^+$; found: 400.1216. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} =56.5 min, τ_{minor} = 78.2 min (60% ee). M.p.: 176-178 ℃ (CH$_2$Cl$_2$, decomp). $[\alpha]_D^{20}$: +57.4 (*c* = 1.0, CH$_2$Cl$_2$).
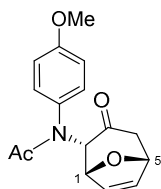
N-(4-Methoxyphenyl)-N-((1R,2S,5R)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)acetamide (4g). Following *GP-H*, **4g** (21.7 mg, 50%) was isolated by FC (hexanes/EtOAc 9:1 to 6:4), as a solid after 16h reaction time, starting from catalyst **3g** (7.5 mg, 0.007 mmol), allene **1g** (30 mg, 0.15 mmol), DMDO solution in toluene (0.8 mL, 0.3 mmol) and furan (33 µL, 0.45 mmol). R_f= 0.24

(hexanes/EtOAc 4:6). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.18 (bs, 2H, C$_{arom}$-H), 6.90 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 6.0 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.70 (d, *J* = 4.3 Hz, 1H, H-2), 5.00-4.91 (m, 2H, H-1 + H-5), 4.69 (dd, *J* = 6.1, 1.7 Hz, 1H, H-7), 3.84 (s, 3H, OCH$_3$), 2.90 (dd, *J* = 15.5, 5.0 Hz, 1H, H-4a), 2.37 (d, *J* = 15.5 Hz, 1H, H-4b), 1.87 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz,

CDCl$_3$) δ 201.4 (C-3), 171.9 (C=O), 159.9 (OC=O), 133.8 (C$_{arom}$), 133.6 (C-6), 132.2 (C-7), 114.9 (C$_{arom}$-H), 80.7 (C-1), 78.4 (C-5), 69.6 (C-2), 55.6 (OCH$_3$), 45.3 (C-4), 22.7 (CH$_3$). IR (CH$_2$Cl$_2$): 2962 (C-H st), 1659 (C=O st), 1242 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{16}$H$_{18}$NO$_4$]$^+$: 288.1236 [M+H]$^+$; found: 288.1243. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 33.7 min, τ$_{minor}$ = 46.4 min (22% ee). M.p.: 134-136ºC (CH$_2$Cl$_2$).
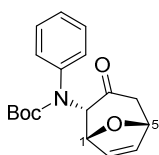
***tert*-Butyl-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(phenyl)carbamate (4h).** Following *GP-H*, **4h** (15.3 mg, 37%) was isolated by FC (hexanes/EtOAc 19:1 to 8:2), as an oil after 16h, starting from catalyst **3g** (6.4 mg, 0.06 mmol), allene **1h** (30 mg, 0.13 mmol), DMDO solution in toluene (0.9 mL, 0.26 mmol) and furan (28 µL, 0.39 mmol). R$_f$= 0.46 (hexanes/EtOAc 7:3). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38-7.27 (m, 3H, C$_{arom}$-H), 7.25-7.15 (m, 2H, C$_{arom}$-H), 5.98 (dd, *J* =6.1, 1.8 Hz, 1H, H-6), 5.26 (bs, 1H, H-2), 5.00 (dd, *J* = 4.4, 1.7 Hz, 1H, H-1), 4.93 (m, 1H, H-5), 4.67 (d, *J* = 6.1 Hz, 1H, H-7), 2.85 (dd, *J* = 15.6, 5.1 Hz, 1H, H-4a), 2.38 (d, *J* = 15.6 Hz, 1H, H-4b), 1.36 (s, 9H, 3×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.7 (C=O), 155.2 (O-C=O), 140.4 (C$_{arom}$), 133.2 (C$_{arom}$-H), 132.2 (C$_{arom}$-H), 130.2 (C-6), 128.9 (C-7), 127.9 (C$_{arom}$-H), 80.6 (C-1), 78.2 (C-5), 77.2 (**C**(CH$_3$)$_3$), 71.1 (C-2), 45.2 (C-4), 28.1 (CH$_3$). IR (ATR): 1726 (C=O st) cm^{-1}. MS (EI) m/z (%): 259 (22), 215 (39). HRMS: Calculated for [C$_{18}$H$_{21}$NO$_4$Na]$^+$: 338.1368 [M+Na]$^+$; found: 338.1367. The ee was determined by HPLC using a *Chiralcel OZ-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{major}$ =10.3 min, τ$_{minor}$ = 22.5 min (64% ee).
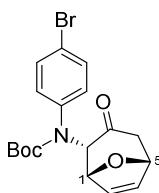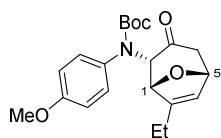

***tert*-Butyl (4-bromophenyl)-((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate (4i).** Following *GP-H*, **4i** (8.1 mg, 21%) was isolated by FC (hexanes/EtOAc 19:1 to 8:2), as a solid after 16h, starting from catalyst **3g** (4.8 mg, 0.005 mmol), allene **1i** (30 mg, 0.1 mmol), DMDO solution in toluene (0.7 mL, 0.2 mmol) and furan (21 µL, 0.3 mmol). R$_f$= 0.38 (hexanes/EtOAc 8:2). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.45 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 7.09 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 6.03 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.24 (bs, 1H, H-2), 4.98 (dd, *J* = 4.4, 1.8 Hz, 1H, H-1), 4.95 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 4.83 (d, *J* = 5.6 Hz, 1H, H-7), 2.85 (dd, *J* = 15.6, 5.2 Hz, 1H, H-4a), 2.39 (d, *J* = 15.6 Hz, 1H, H-4b), 1.36 (s, 9H, 3×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.6 (C=O), 154.8 (O-C=O), 139.5 (C$_{arom}$-N), 133.7 (C-6), 132.1 (C-5), 132.0 (C$_{arom}$-H), 121.7

(C_{arom}-Br), 81.2 (**C**(CH$_3$)$_3$), 80.5 (C-1), 78.2 (C-5), 71.0 (C-2), 45.2 (C-4), 28.1 (CH$_3$). IR (ATR): 1730 (C=O st), 1701 (C=O st) cm^{-1}. MS (EI) m/z (%): 184 (100), 155 (54). HRMS: Calculated for [C$_{18}$H$_{20}$NO$_4$BrNa]$^+$: 416.0473 [M+Na]$^+$; found: 416.0478. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (93:7)]; flow rate 1.00 mL/min; τ_{major} =11.0 min, τ_{minor} = 14.3 min (71% ee). M.p.: 106-108 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +121.8 (*c* = 0.7, CH$_2$Cl$_2$).
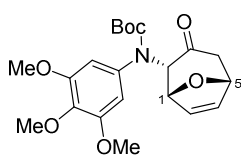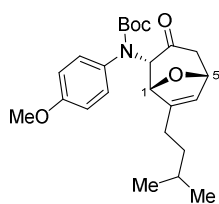
tert-**Butyl ((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(3,4,5-trimethoxyphenyl) carbamate (4k).** Following *GP-H*, **4k** (14.2 mg, 38%) was isolated by FC (hexanes/EtOAc 8:2 to 1:1) as an oil after 16h, starting from catalyst **3g** (4.6 mg, 0.005 mmol), allene **1k** (30 mg, 0.09 mmol), DMDO solution in toluene (1.0 mL, 0.19 mmol) and furan (20.3 µL, 0.28 mmol). dr: >20:1. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.46 (s, 2H, C_{arom}-H), 6.04 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.32-5.04 (m, 1H, H-2), 5.01 (dd, *J* = 4.5, 1.7 Hz, 1H, H-1), 4.99-4.93 (m, 1H, H-5), 4.84 (bs, 1H, H-7), 3.85 (s, 3H, OCH$_3$), 3.81 (s, 6H, 2×OCH$_3$), 2.85 (dd, *J* = 15.5, 5.0 Hz, 1H, H-4a), 2.39 (d, *J* = 15.5 Hz, 1H, H-4b), 1.40 (bs, 9H, C(CH$_3$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.0 (C=O), 155.3 (OC=O), 153.2 (C_{arom}), 138.0 (C_{arom}), 133.4 (C-6), 132.5 (C-7), 107.7 (C_{arom}-H), 80.8 (C-1 + **C**(CH$_3$)$_3$), 78.5 (C-5), 77.4 (C-2), 61.2 (OCH$_3$), 56.4 (OCH$_3$), 45.4 (C-4), 28.4 (C(CH$_3$)$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1701 (C=O st) cm^{-1}. HRMS: Calculated for [C$_{21}$H$_{27}$NO$_7$Na]$^+$: 428.1685 [M+Na]$^+$; found: 428.1681. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 19.7 min, τ_{minor} = 33.0 min (73% ee).

2.6 <u>Synthesis of cycloadducts 4j, 5a-s and 6a-y</u>
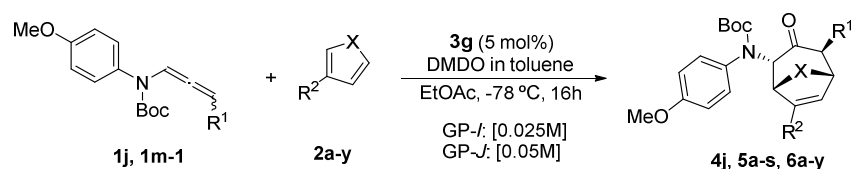
General Procedure I (GP-I): A test tube with a stirring bar was charged with **3g** catalyst (0.003 mmol, 5 mol%) and it was cooled to -78 °C. Then, corresponding allene (0.05 mmol, 0.33 eq) was added followed by a precooled mixture of DMDO in toluene (0.11 mmol, 2.1 eq) and EtOAc (0.2M). Subsequently, corresponding diene (0.05 mmol, 1 eq) was added. After 1 h, another addition of allene (0.05 mmol, 0.33 eq) was made with the corresponding mixture of DMDO solution (0.11 mmol, 2.1 eq) and EtOAc (0.2M). After 1 h, a third addition was repeated. The mixture was stirred for 16 h at -78 °C. After that, the reaction was quenched with NaHCO$_3$ (sat. aqueous, 2 mL) and extracted with Et$_2$O (3×5 mL). Combined organic layers were dried over Na$_2$SO$_4$ and after the removal of the solvent under reduced pressure the crude was purified by FC on silica gel (petroleum ether/EtOAc). For **14c** and **15b-d**: 5 equivalents of allene, 12.5 eq of DMDO in toluene were portionwise added in 5 aditions (30 minutes each) under [0.015M].

General Procedure J (GP-J): A test tube equipped with a stirring bar was charged with **3g** catalyst (0.005 mmol, 5 mol%) and it was cooled to -78 °C. Then, corresponding allene[44] (0.11 mmol, 1 eq) was added followed by a precooled mixture of DMDO in toluene (0.27 mmol, 2.5 eq) and EtOAc (0.05M). Subsequently, corresponding furan (0.22 mmol, 2 eq) was added.[45] The mixture was stirred for 16 h at -78 °C. After that, the reaction was quenched with NaHCO$_3$ (sat. aqueous, 2 mL) and extracted with Et$_2$O (3×5 mL). Combined organic layers were dried over Na$_2$SO$_4$ and after the removal of the solvent under reduced pressure the crude was purified by FC on silica gel (petroleum ether/EtOAc).

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[44] For oily allenes: it was dissolved in the corresponding quantity of EtOAc and precooled before the addition. Then, DMDO solution and furan were added sequentially.

[45] When furan is used 13 equivalents are needed.

The racemic standards for HPLC analysis were prepared using diphenyl phosphoric acid or its *N*-triflyl phosphoramide analog. In some cases it was needed the use of (**R**)-**3g**+(**S**)-**3g** to get the racemic standards. TLCs were developed in *p*-anisaldehyde dip.
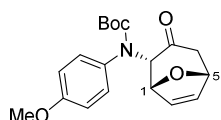
***tert*-Butyl (4-methoxyphenyl)((1*R*,2*S*,5*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate 4j.** Following *GP-J*, **4j** (29.6 mg, 78%) was isolated by FC (hexanes/EtOAc 9:1 to 6:4) as a solid after 16h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.2 mL, 0.27 mmol), EtOAc (1 mL) and furan (0.1 mL, 1.43 mmol, 13 eq). R_f= 0.40 (hexanes/EtOAc 7:3). dr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC) δ 7.11 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.89 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.12 (dd, J = 6.1, 1.9 Hz, 1H, H-6), 5.07 (dd, J = 4.4, 1.7 Hz, 1H, H-1), 5.04 (d, J = 4.4 Hz, 1H, H-2), 4.92 (d, J = 5.1 Hz, H-5), 4.77 (d, J = 6.1 Hz, 1H, H-7), 3.78 (s, 3H, OCH$_3$), 2.82 (dd, J = 15.7, 5.1 Hz, 1H, H-4a), 2.28 (d, J = 15.7 Hz, 1H, H-4b), 1.32 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 201.1 (C=O), 158.2 (C_{arom}), 154.1 (OC=O), 133.5 (C-6), 132.7 (C_{arom}), 131.0 (C-7), 130.5 (C_{arom}-H), 113.5 (C_{arom}-H), 79.4 (C-1), 79.1 (**C**(CH$_3$)$_3$), 77.3 (C-5), 70.7 (C-2), 54.3 (OCH$_3$), 44.4 (C-4), 27.4 (C(CH$_3$)$_3$). IR (CH$_2$Cl$_2$): 2972 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1038 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 246 (100). HRMS: Calculated for [C$_{19}$H$_{24}$NO$_5$H]$^+$: 346.1654 [M+H]$^+$; found: 346.1657. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.00 mL/min; τ_{major} = 34.3 min, τ_{major} = 44.9 min (82% ee). [α]$_D^{20}$: +147.5 (c = 1.0, CH$_2$Cl$_2$). M.p.: 144-146ºC (CH$_2$Cl$_2$).
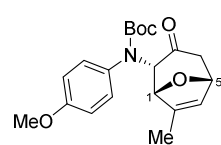
***tert*-Butyl (4-methoxyphenyl)((1*R*,2*S*,5*R*)-7-methyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5a.** Following *GP-I*, **5a** (16 mg, 78%) was isolated by FC (hexanes/EtOAc 2:8 to 1:1), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.56 mL, 0.36 mmol), EtOAc (0.72 mL, 0.025M) and 3-methylfuran **2a** (5.2 µL, 0.05 mmol). R_f= 0.62 (hexanes/EtOAc 7:3). rr: 14:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC) δ 7.17 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.91 (d, J = 8.9 Hz, C_{arom}-H), 5.96-5.93 (m, 1H, H-6), 4.83 (d, J = 5.7 Hz, 1H, H-5), 4.74 (d, J = 5.0 Hz, 1H, H-1), 4.44 (d, J = 5.0 Hz, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.79 (dd, J = 17.1, 5.7 Hz, 1H, H-4a), 2.42 (d, J = 17.1 Hz,

1H, H-4b), 1.52 (s, 3H, CH$_3$), 1.30 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 200.2 (C=O), 157.8 (C$_{arom}$), 153.2 (OC=O), 142.3 (C-7), 135.6 (C$_{arom}$), 129.0 (C-6), 128.7 (C$_{arom}$-H), 113.9 (C$_{arom}$-H), 81.1 (C-1), 79.6 (**C**(CH$_3$)$_3$), 76.9 (C-5), 71.7 (C-2), 55.0 (OCH$_3$), 44.0 (C-4), 27.4 (C(CH$_3$)$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 260 (100), 222 (12), 178 (22), 137 (8). HRMS: Calculated for [C$_{20}$H$_{25}$NO$_5$Na]$^+$: 382.1630 [M+Na]$^+$; found: 382.1624. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{minor}$ = 14.5 min, τ$_{major}$ = 16.4 min (83% ee). [α]$_D^{20}$: -115.8 (*c* = 1.0, CH$_2$Cl$_2$).

***tert*-Butyl   ((1*R*,2*S*,5*R*)-7-ethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 5b.** Following *GP-I*, **5b** (14.1 mg, 66%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as an oil after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.6 mL, 0.36 mmol), EtOAc (0.69 mL) and furan **2c** (20.4 µL, 0.06 mmol). R$_f$= 0.52 (petroleum ether/EtOAc 7:3). rr 10:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.13 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.90 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 5.93-5.91 (m, 1H, H-6), 4.84 (d, *J* = 5.9 Hz, 1H, H-5), 4.77 (d, *J* = 5.1 Hz, 1H, H-1), 4.34 (d, *J* = 5.1 Hz, 1H, H-2), 3.76 (s, 3H, OCH$_3$), 2.77 (dd, *J* = 17.4, 5.9 Hz, 1H, H-4a), 2.41 (d, *J* = 17.4 Hz, 1H, H-4b), 1.87-1.74 (m, 2H, C**H**$_2$CH$_3$), 1.27 (s, 9H, C(CH$_3$)$_3$), 0.97 (t, *J* = 7.3 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 201.1 (C=O), 158.6 (C$_{arom}$), 154.1 (OC=O), 149.8 (C-7), 136.7 (C$_{arom}$), 131.5 (C$_{arom}$), 129.4 (C$_{arom}$-H), 127.5 (C-6), 114.8 (C$_{arom}$-H), 80.8 (C-1), 80.4 (**C**(CH$_3$)$_3$), 77.7 (C-5), 72.5 (C-2), 56.0 (OCH$_3$), 44.8 (C-4), 28.3 (C(CH$_3$)$_3$), 21.5 (**CH**$_2$CH$_3$), 12.3 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2969 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{21}$H$_{27}$NO$_5$Na]$^+$: 396.1787 [M+Na]$^+$; found: 396.1780. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{minor}$ = 12.2 min, τ$_{major}$ = 13.7 min (71% ee). [α]$_D^{20}$: +69.6 (*c* = 1.0, CH$_2$Cl$_2$).
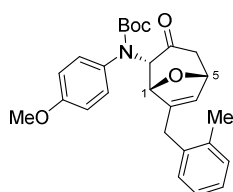
***tert*-Butyl (4-methoxyphenyl)((1*R*,2*S*,5*R*)-7-(2-methylbenzyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5c.** Following *GP-I*, **5c** (11.5 mg, 45%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.56 mL, 0.36 mmol), EtOAc (0.72 mL) and furan **2d** (8.5 µL, 0.06 mmol). R_f= 0.38 (petroleum ether/EtOAc 7:3). rr: 10:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.18 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 7.15-7.10 (m, 3H, C$_{arom}$-H), 7.07-7.04 (m, 1H, C$_{arom}$-H), 6.92 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 5.75 (app s, 1H, H-6), 4.84 (d, *J* = 5.9 Hz, 1H, H-5), 4.80 (d, *J* = 4.9 Hz, 1H, H-1), 4.48 (d, *J* = 4.9 Hz, 1H, H-2), 3.76 (s, 3H, OCH$_3$), 3.13 (d, *J* = 16.6 Hz, 1H, C**H**$_a$H$_b$), 3.03 (d, *J* = 16.6 Hz, 1H, CH$_a$**H**$_b$), 2.81 (dd, *J* = 17.1, 5.9 Hz, 1H, H-4a), 2.43 (d, *J* = 17.1 Hz, 1H, H-4b), 2.19 (s, 3H, CH$_3$), 1.34 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 200.0 (C=O), 157.7 (C$_{arom}$), 153.3 (OC=O), 145.7 (C-7), 136.6 (C$_{arom}$), 135.7 (C$_{arom}$), 135.4 (C$_{arom}$), 129.9 (C-6), 129.6 (C$_{arom}$-H), 128.6 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 125.8 (C$_{arom}$-H), 125.3 (C$_{arom}$-H), 113.9 (C$_{arom}$-H), 80.2 (C-1), 79.6 (O**C**(CH$_3$)$_3$), 76.8 (C-5), 72.0 (C-2), 55.0 (OCH$_3$), 43.9 (C-4), 31.1 (CH$_2$), 27.5 (C(**C**H$_3$)$_3$), 18.3 (CH$_3$). IR (CH$_2$Cl$_2$): 2972 (C-H st), 1698 (C-H st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{27}$H$_{31}$NO$_5$Na]$^+$: 472.2100 [M+Na]$^+$; found: 472.2099. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 12.8 min, τ_{major} = 17.4 min (85% ee). M.p.: 115-117 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: -66.6 (*c* = 1.1, CH$_2$Cl$_2$).

***tert*-Butyl ((1*R*,2*S*,5*R*)-7-isopentyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 5d.** Following *GP-J*, **5d** (17.8 mg, 40%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as an oil after 16 h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.25 mL, 0.27 mmol), EtOAc (0.95 mL) and furan **2e** (29.8 µL, 0.22 mmol). R_f= 0.5 (petroleum ether/EtOAc 7:3). rr: 15:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.15 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.91 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 5.94-5.92 (m, 1H, H-6), 4.84 (d, *J* = 5.8 Hz, 1H, H-5), 4.80 (d, *J* = 5.0 Hz, 1H, H-1), 4.48 (d, *J* = 5.0 Hz, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.80 (dd, *J* = 17.1, 5.8 Hz, 1H, H-4a), 2.41 (d, *J* = 17.1 Hz, 1H, H-4b), 1.69 (bs, 2H, CH$_2$), 1.51-1.41 (m, 1H, C**H**(CH$_3$)$_2$), 1.29 (s, 11H, CH$_2$ +

C(CH$_3$)$_3$), 0.85 (d, J = 6.0 Hz, 6H, 2×CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 200.3 (C=O), 157.7 (C$_{arom}$), 153.2 (OC=O), 147.5 (C-7), 135.4 (C$_{arom}$), 128.7 (C$_{arom}$-H), 127.3 (C-6), 113.8 (C$_{arom}$-H), 80.1 (C-1), 79.4 (OC(CH$_3$)$_3$), 76.8 (C-5), 71.7 (C-2), 54.9 (OCH$_3$), 44.0 (C-4), 36.1 (CHCH$_2$), 27.4 (C(CH$_3$)$_3$), 26.8 (CH), 25.1 (C7CH$_2$), 21.8 (CH$_3$), 21.5 (CH$_3$). IR (CH$_2$Cl$_2$): 2959 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{24}$H$_{33}$NO$_5$Na]$^+$: 438.2256 [M+Na]$^+$; found: 438.2257. The ee was determined by HPLC using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 6.7 min, τ_{major} = 7.9 min (76% ee). [α]$_D^{20}$: -41.5 (c = 0.9, CH$_2$Cl$_2$).
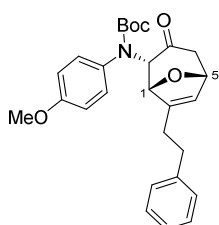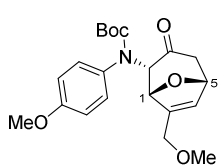
tert-**Butyl** **(4-methoxyphenyl)((1R,2S,5R)-3-oxo-7-phenethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5e.** Following *GP-I*, **5e** (7.8 mg, 30%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.35 mL, 0.36 mmol), EtOAc (0.93 mL) and furan **2f** (7.8 µL, 0.06 mmol). R$_f$= 0.5 (petroleum ether/EtOAc 7:3). rr 18:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.29-7.23 (m, 2H, C$_{arom}$-H), 7.20-7.10 (m, 5H, C$_{arom}$-H), 6.87 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.03-6.00 (m, 1H, H-6), 4.86 (d, J = 5.8 Hz, 1H, H-5), 4.82 (d, J = 5.0 Hz, 1H, H-1), 4.48 (d, J = 5.0 Hz, 1H, H-2), 3.71 (s, 3H, OCH$_3$), 2.81 (dd, J = 17.1, 5.8 Hz, 1H, H-4a), 2.76-2.71 (m, 2H, C**H**$_2$CH$_2$Ph), 2.43 (d, J = 17.1 Hz, 1H, H-4b), 2.07-1.94 (m, 2H, CH$_2$C**H**$_2$Ph), 1.27 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 200.3 (C=O), 157.7 (C$_{arom}$), 153.3 (OC=O), 146.8 (C-7), 140.8 (C$_{arom}$), 135.4 (C$_{arom}$), 128.7 (C$_{arom}$-H), 128.0 (C-6), 127.6 (C$_{arom}$-H), 127.5 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 80.1 (C-1), 79.5 (OC(CH$_3$)$_3$), 76.8 (C-5), 71.8 (C-2), 54.8 (OCH$_3$), 44.0 (C-4), 33.1 (**C**H$_2$CH$_2$Ph), 28.7 (CH$_2$**C**H$_2$Ph), 27.4 (C(CH$_3$)$_3$). IR (CH$_2$Cl$_2$): 2934 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{27}$H$_{31}$NO$_5$Na]$^+$: 472.2100 [M+Na]$^+$; found: 472.2100. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 19.3 min, τ_{minor}= 21.4 min (62% ee). M.p.: 108-110 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: -110.7 (c = 0.2, CH$_2$Cl$_2$).
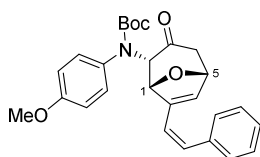
tert-Butyl (4-methoxyphenyl)((1R,2S,5R)-3-oxo-7-((Z)-styryl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5f. Following *GP-I*, **5f** (3.1 mg, 12%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.56 mL, 0.36 mmol), EtOAc (0.72 mL) and furan **2g** (8.2 µL, 0.06 mmol). R_f= 0.52 (petroleum ether/EtOAc 7:3). rr 20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38-7.31 (m, 4H, C_{arom}-H), 7.30-7.25 (m, 1H, C_{arom}-H), 6.90 (d, J = 8.8 Hz, 2H, C_{arom}-H), 6.79 (d, J = 8.8 Hz, 2H, C_{arom}-H), 6.38 (d, J = 12.2 Hz, 1H, HC=C**H**Ph), 6.23-6.20 (m, 1H, H-6), 5.93 (d, J = 12.2 Hz, 1H, **H**C=CHPh), 4.97-4.93 (m, 1H, H-5), 4.90 (d, J = 5.2 Hz, 1H, H-1), 4.22 (bs, 1H, H-2), 3.74 (s, 3H, OCH$_3$), 2.82 (dd, J = 17.5, 5.9 Hz, 1H, H-4a), 2.45 (d, J = 17.5 Hz, 1H, H-4b), 1.30 (s, 9H, 3×CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 200.7 (C=O), 158.5 (C_{arom}), 156.7 (OC=O), 142.5 (C-7), 137.5 (C_{arom}), 136.5 (C_{arom}), 132.6 (C-6), 131.3 (HC=**C**HPh), 129.4 (C_{arom}-H), 129.0 (C_{arom}-H), 128.7 (C_{arom}-H), 127.9 (C_{arom}-H), 122.9 (H**C**=CHPh), 114.8 (C_{arom}-H), 114.6 (C_{arom}-H), 81.0 (**C**(CH$_3$)$_3$), 79.9 (C-1), 78.1 (C-5), 72.2 (C-2), 55.9 (OCH$_3$), 44.4 (C-4), 28.4 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1705 (C=O st), 1242 (C-O-C st as) cm^{-1}. HRMS: Calculated for [C$_{27}$H$_{29}$NO$_5$Na]$^+$: 470.1943 [M+Na]$^+$; found: 470.1951. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 0.70 mL/min; τ_{minor} = 16.9 min, τ_{major}= 18.3 min (85% ee).
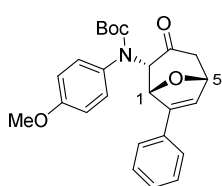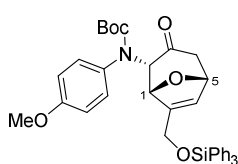
tert-Butyl (4-methoxyphenyl)((1R,2S,5R)-3-oxo-7-phenyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5f. Following *GP-I*, **5f** (8.2 mg, 34%) was isolated by FC (hexanes/EtOAc 2:8 to 1:1), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.56 mL, 0.36 mmol), EtOAc (0.72 mL) and 3-phenylfuran **2h** (8.2 mg, 0.06 mmol). R_f= 0.27 (hexanes/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100°C) δ 7.56 (d, J = 7.2 Hz, 2H, C_{arom}-H), 7.35 (t, J = 7.6 Hz, 2H, C_{arom}-H), 7.28-7.22 (m, 1H, C_{arom}-H), 7.18 (d, J = 8.4 Hz, 2H, C_{arom}-H), 6.89 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.79 (bs, 1H, H-6), 5.56 (d, J = 5.4 Hz, 1H, H-1), 5.09 (dd, J = 6.0, 2.4 Hz, 1H, H-5), 4.31 (d, J = 5.4 Hz, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.92 (dd, J = 18.0, 6.2 Hz, 1H, H-4a), 2.58 (d, J = 18.0 Hz, 1H, H-4b), 0.92 (s, 9H, 3×CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ

199.9 (C=O), 157.1 (C_{arom}-O), 152.3 (O-C=O), 144.9 (C-7), 136.8 (C_{arom}-N), 132.9 (C_{arom}), 127.8 (C-6), 127.7 (C_{arom}-H), 127.5 (C_{arom}-H), 127.1 (C_{arom}-H), 125.6 (C_{arom}-H), 113.7 (C_{arom}-H), 79.4 (**C**(CH₃)₃), 78.3 (C-1), 77.4 (C-5), 71.8 (C-2), 54.9 (OCH₃), 43.5 (C-4), 26.9 (C(**CH₃**)₃). IR (CH₂Cl₂): 2972 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1034 (C-O-C st sy) cm⁻¹. HRMS: Calculated for [C₂₅H₂₇NO₅Na]⁺: 444.1787 [M+Na]⁺; found: 444.1786. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 27.9 min, τ_{minor} = 33.1 min (76% ee). M.p: 122-124°C (CH₂Cl₂). [α]$_D^{20}$: -93.6 (*c* = 1.0, CH₂Cl₂).
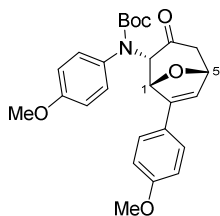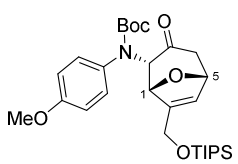

tert-**Butyl (4-Methoxyphenyl)((1*R*,2*S*,5*R*)-7-(4-methoxyphenyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5h.** Following *GP-I*, **5h** (4 mg, 17%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as an oil after 16 h, starting from catalyst **3g** (2.5 mg, 0.002 mmol), allene **1j** (40 mg, 0.15 mmol), DMDO solution in toluene (1.3 mL, 0.32 mmol),
EtOAc (1.0 mL) and furan **2i** (8.9 mg, 0.05 mmol). R$_f$= 0.24 (petroleum ether/EtOAc 7:3). rr >20:1. ¹H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.47 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.17 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.88 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.61 (d, *J* =2.4 Hz, 1H, H-6), 5.51 (d, *J* = 5.4 Hz, 1H, H-1), 5.05 (dd, *J* = 6.0, 2.4 Hz, 1H, H-5), 4.31 (d, *J* = 5.4 Hz, 1H, H-2), 3.77 (s, 6H, 2×OCH₃), 2.90 (dd, *J* = 17.9, 6.0 Hz, 1H, H-4a), 2.55 (d, *J* = 17.9 Hz, 1H, H-4b), 0.95 (s, 9H, C(CH₃)₃). ¹³C NMR (125 MHz, DMSO-d_6, 100 °C) δ 200.0 (C=O), 158.8 (C_{arom}), 157.1 (C_{arom}), 155.6 (OC=O), 144.5 (C-7), 127.6 (C_{arom}-H), 127.0 (C_{arom}-H), 125.8 (C_{arom}), 125.5 (C-6), 113.7 (C_{arom}-H), 113.5 (C_{arom}-H), 79.1 (**C**(CH₃)₃), 78.4 (C-5), 77.4 (C-1), 71.8 (C-2), 54.9 (OCH₃), 54.9 (OCH₃), 43.6 (C-4), 26.9 (C(**CH₃**)₃). IR (CH₂Cl₂): 2972 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm⁻¹. HRMS: Calculated for [C₂₆H₂₉NO₆Na]⁺: 474.1893 [M+Na]⁺; found: 474.1890. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 60.8 min, τ_{major} = 96.2 min (63% ee).
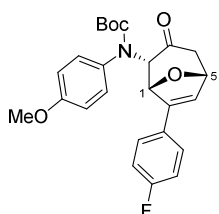
tert-Butyl ((1R,2S,5R)-7-(4-fluorophenyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 5i. Following *GP-I*, **5i** (8.4 mg, 34%) was isolated by FC (hexanes/EtOAc 2:8 to 1:1), as a solid after 16h reaction time, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.63 mL, 0.36 mmol), EtOAc (0.65 mL) and furan **2j** (9.2 mg, 0.06 mmol). R_f= 0.29 (hexanes/EtOAc 7:3). rr: >20:1. ^{1}H-NMR (500 MHz, DMSO-d_6, 100ºC) δ 7.61-7.54 (m, 2H, C_{arom}-H), 7.20-7.09 (m, 4H, C_{arom}-H), 6.87 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.75 (d, *J* = 2.4 Hz, 1H, H-6), 5.56 (d, *J* = 5.4 Hz, 1H, H-1), 5.08 (dd, *J* = 6.0, 2.4 Hz, 1H, H-5), 4.33 (d, *J* = 5.4 Hz, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.92 (dd, *J* = 17.9, 6.2 Hz, 1H, H-4a), 2.57 (d, *J* = 18.0 Hz, 1H, H-4b), 0.96 (s, 9H, 3×CH$_3$). ^{13}C-NMR (125 MHz, DMSO-d_6, 100 ºC) δ 199.9 (C=O), 161.3 (d, $^1J_{C-F}$ = 245.5 Hz, C_{arom}-F), 157.2 ($\mathbf{C}_{arom}$OCH$_3$), 152.3 (OC=O), 144.0 (C-7), 136.7 (C_{arom}), 129.6 (d, $^3J_{C-F}$ = 7.6 Hz, C_{arom}-H), 127.8 (C_{arom}), 127.8 (C-6), 127.7 (C_{arom}-H), 127.6 (C_{arom}-H), 114.5 (d, $^2J_{C-F}$ = 21.9 Hz, C_{arom}-H), 113.7 (C_{arom}-H), 79.7 ($\mathbf{C}$(CH$_3$)$_3$), 78.4 (C-1), 77.5 (C-5), 71.8 (C-2), 54.9 (OCH$_3$), 43.5 (C-4), 26.9 (CH$_3$). IR (CH$_2$Cl$_2$): 2972 (C-H st), 1709 (C=O st), 1245 (C-O-C st as), 1159 (C-F st), 1038 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{25}$H$_{26}$NO$_5$FNa]$^+$: 462.1693 [M+Na]$^+$; found: 462.1690. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 28.0 min, τ_{major} = 30.4 min (57% ee).

tert-Butyl ((1R,2S,5R)-7-(methoxymethyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate 5j. Following *GP-J*, **5j** (24.3 mg, 57%) was isolated by FC (petroleum ether/EtOAc 8:2 to 1:1), as an oil after 16 h, starting from catalyst **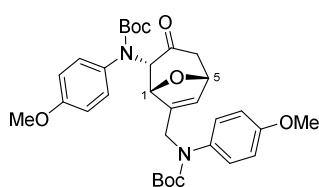3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.2 mL, 0.27 mmol), EtOAc (1.0 mL) and furan **2k** (20.5 µL, 0.22 mmol). R_f= 0.45 (petroleum ether/EtOAc 1:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC) δ 7.14 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.93 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.21-6.19 (m, 1H, H-6), 4.93-4.88 (m, 2H, H-5+H-1), 4.42 (d, *J* = 5.0 Hz, 1H, H-2), 3.78 (s, 3H, C_{arom}OCH$_3$), 3.67 (d, *J* = 13.7 Hz, 1H, C$\mathbf{H}_a$H$_b$), 3.56 (d, *J* = 13.7 Hz, CH$_a\mathbf{H}_b$), 3.21 (s, 3H, OCH$_3$), 2.83 (dd, *J* = 17.3, 5.9 Hz, H-4a), 2.44 (d, *J* = 17.3 Hz, 1H, H-4b), 1.30 (s, 9H, 3×CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 199.9 (C=O), 157.8

($\mathbf{C}_{arom}OCH_3$), 153.2 (C-7), 144.0 (OC=O), 135.5 ($C_{arom}N$), 130.3 (C-6), 128.6 (C_{arom}-H), 113.9 (C_{arom}-H), 79.6 ($\mathbf{C}(CH_3)_3$), 78.3 (C-1), 76.7 (C-5), 71.5 (C-2), 67.7 ($\mathbf{CH_2}OCH_3$), 57.0 ($CH_2O\mathbf{CH_3}$), 55.0 ($C_{arom}O\mathbf{CH_3}$), 43.6 (C-4), 27.4 ($C(\mathbf{CH_3})_3$). IR (CH_2Cl_2): 2972 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 290 (100), 258 (20), 178 (62). HRMS: Calculated for $[C_{21}H_{27}NO_6Na]^+$: 412.1736 $[M+Na]^+$; found: 412.1740. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 18.4 min, τ_{major} = 22.2 min (82% ee). $[\alpha]_D^{20}$: -146.3 (*c* = 1.0, CH_2Cl_2).
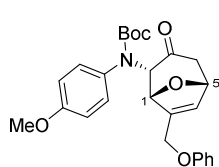
***tert*-Butyl (4-methoxyphenyl)((1*R*,2*S*,5*R*)-3-oxo-7-(phenoxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5k.** Following *GP-I*, **5k** (14 mg, 54%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (4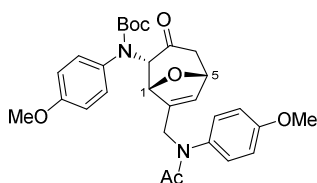5 mg, 0.17 mmol), DMDO solution in toluene (1.42 mL, 0.35 mmol), EtOAc (0.86 mL) and furan **2l** (9.9 mg, 0.06 mmol). R_f= 0.39 (petroleum ether/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.31-7.25 (m, 2H, C_{arom}-H), 7.16 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.97-6.92 (m, 1H, C_{arom}-H), 6.89-6.83 (m, 4H, C_{arom}-H), 6.37-6.35 (m, 1H, H-6), 5.07 (d, *J* = 4.9 Hz, 1H, H-1), 4.96 (d, *J* = 5.9 Hz, 1H, H-5), 4.56 (d, *J* = 4.9 Hz, 1H, H-2), 4.27-4.11 (m, 2H, CH_aH_bOPh), 3.73 (s, 3H, OCH_3), 2.87 (dd, *J* = 17.1, 5.9 Hz, 1H, H-4a), 2.47 (app s, 1H, H-4b), 1.27 (s, 9H, 3×CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 200.9 (C=O), 158.8 ($C_{arom}O$), 158.7 ($C_{arom}O$), 154.3 (OC=O), 143.9 (C-7), 136.2 (C_{arom}), 132.1 (C-6), 129.8 (C_{arom}-H), 129.8 (C_{arom}-H), 121.3 (C_{arom}-H), 115.3 (C_{arom}-H), 114.9 (C_{arom}-H), 80.7 ($\mathbf{C}(CH_3)_3$), 79.6 (C-1), 77.9 (C-5), 72.6 (C-2), 64.8 (CH_2OPh), 55.8 (OCH_3), 44.7 (C-4), 28.3 ($C(\mathbf{CH_3})_3$). IR (CH_2Cl_2): 2976 (C-H st), 1698 (C=O st), 1243 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for $[C_{26}H_{29}NO_6Na]^+$: 474.1893 $[M+Na]^+$; found: 474.1901. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 26.3 min, τ_{major} = 28.8 min (89% ee). M.p.: 80-82 °C (CH_2Cl_2). $[\alpha]_D^{20}$: -119.3 (*c* = 1.0, CH_2Cl_2).

***tert*-Butyl** **(4-methoxyphenyl)((1*R*,2*S*,5*R*)-3-oxo-7-(((triphenylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5l.** Following *GP-I*, **5l** (25.4 mg, 68%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.35 mL, 0.36 mmol), EtOAc (0.93 mL) and furan **2m** (20.3 mg, 0.06 mmol). R_f= 0.37 (petroleum ether/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC) δ 7.54 (m, 6H, C_{arom}-H), 7.48 (m, 3H, C_{arom}-H), 7.43 (m, 6H, C_{arom}-H), 7.05 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.76 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.24-6.22 (m, 1H, H-6), 4.99 (d, J = 5.0 Hz, 1H, H-1), 4.91 (d, J = 5.9 Hz, 1H, H-5), 4.43 (d, J = 4.8 Hz, 1H, H-2), 4.15 (d, J = 14.1 Hz, 1H, **CH$_a$H$_b$**), 4.02 (d, J = 14.1 Hz, 1H, CH$_a$**H$_b$**), 3.69 (s, 3H, OCH$_3$), 2.83 (dd, J = 17.2, 5.9 Hz, 1H, H-4a), 2.44 (d, J = 17.2 Hz, 1H, H-4b), 1.19 (s, 9H, 3×CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 50 ºC) δ 200.5 (C=O), 157.8 (C_{arom}-O), 153.4 (OC=O), 146.1 (C-7), 135.2 (C_{arom}), 134.6 (C_{arom}-H), 133.3 (C_{arom}-H), 130.2 (C-6), 130.1 (C_{arom}-H), 129.0 (C_{arom}-H), 127.9 (C_{arom}-H), 113.9 (C_{arom}-H), 79.8 (**C**(CH$_3$)$_3$), 78.4 (C-1), 77.0 (C-5), 71.7 (C-2), 60.1 (OCH$_2$), 55.0 (OCH$_3$), 43.9 (C-4), 27.5 (C(**CH**$_3$)$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1026 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 259 (30), 199 (100). HRMS: Calculated for [C$_{38}$H$_{39}$NO$_6$Si]$^+$: 656.2444 [M+H]$^+$; found: 656.2440. The ee was determined by HPLC using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.00 mL/min; τ_{minor} = 17.5 min, τ_{major} = 20.7 min (90% ee). M.p.: 61-63 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +121.9 (*c* = 1.0, CH$_2$Cl$_2$).

***tert*-Butyl** **(4-methoxyphenyl)((1*R*,2*S*,5*R*)-3-oxo-7-(((triisopropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5m.** Following *GP-I*, **5m** (21.3 mg, 70%) was isolated by FC (petroleum ether/EtOAc 9:1 to 4:6), as 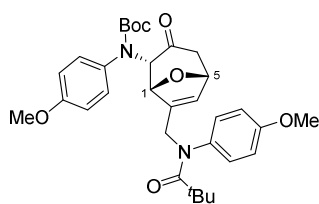an oil after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.5 mL, 0.36 mmol), EtOAc (0.78 mL) and furan **2n** (15.3 µL, 0.06 mmol). R_f= 0.53 (petroleum ether/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.89 (d, J = 8.9 Hz, 2H, C_{arom}-H), 6.20-6.18 (m, 1H, H-6), 4.97 (d, J = 4.8 Hz, 1H, H-1), 4.91 (d, J = 5.8 Hz, 1H, H-5), 4.56 (d, J = 4.8 Hz, 1H, H-2), 4.03 (d, J = 14.6 Hz, 1H, **CH$_a$H$_b$**), 3.77 (s, 3H, OCH$_3$), 3.71 (bs, 1H, CH$_a$**H$_b$**), 2.84 (dd, J = 17.0, 5.8 Hz, 1H, H-4a), 2.43

(d, J = 17.0 Hz, 1H, H-4b), 1.29 (s, 9H, OC(CH$_3$)$_3$), 1.03 (s, 21H, 6×CH$_3$ + 3×CH). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 200.1 (C=O), 157.8 (C$_{arom}$-O), 153.4 (OC=O), 147.0 (C-7), 135.0 (C$_{arom}$), 129.0 (C-6), 128.9 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 79.6 (**C**(CH$_3$)$_3$), 78.5 (C-1), 76.7 (C-5), 71.5 (C-2), 59.3 (OCH$_2$), 54.8 (OCH$_3$), 43.9 (C-4), 27.3 (C(**C**H$_3$)$_3$), 17.2 (SiCH), 11.1 (SiCH(**C**H$_3$)$_2$). IR (CH$_2$Cl$_2$): 2926 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 356 (49), 199 (100). HRMS: Calculated for [C$_{29}$H$_{45}$NO$_6$SiNa]$^+$: 554.2916 [M+Na]$^+$; found: 554.2914. The ee was determined by HPLC using a *Chiralcel OZ-3* column [n-hexane/i-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 9.7 min, τ_{minor} = 132 min (91% ee). [α]$_D$^{20}: -95.5 (c = 1.0, CH$_2$Cl$_2$).

***tert*-Butyl ((1*R*,2*S*,5*R*)-7-(((*tert*-butoxycarbonyl)amino)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 5n.** Following *GP-J*, **5n** (31.9 mg, 50%) was isolated by FC (petroleum ether/EtOAc 8:2 to 1:1), as a solid after 16 h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.1 mL, 0.27 mmol), EtOAc (0.66 mL) and furan **2o** (66.7 mg, 0.22 mmol). rr >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.11 (d, J = 8.8 Hz, 2H, C$_{arom}$-H), 7.05 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.89 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 6.84 (d, J = 8.8 Hz, 2H, C$_{arom}$-H), 6.06 (app s, 1H, H-6), 4.83 (d, J = 5.9 Hz, 1H, H-5), 4.80 (d, J = 5.0 Hz, 1H, H-1), 4.32 (d, J = 5.0 Hz, 1H, H-2), 4.28 (d, J = 16.3 Hz, 1H, C**H**$_a$H$_b$), 3.78 (s, 3H, OCH$_3$), 3.77-3.70 (m, 4H, OCH$_3$ + CH$_a$**H**$_b$), 2.79 (dd, J = 17.4, 5.9 Hz, 1H, H-4a), 2.41 (d, J = 17.4 Hz, H-4b), 1.38 (s, 9H, C(CH$_3$)$_3$), 1.28 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 199.7 (C=O), 157.6 (C$_{arom}$), 156.9 (C$_{arom}$), 153.6 (OC=O), 153.1 (OC=O), 143.7 (C-7), 135.9 (C$_{arom}$), 134.8 (C$_{arom}$), 131.3 (C-6), 128.5 (C$_{arom}$-H), 127.5 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 113.5 (C$_{arom}$-H), 79.5 (**C**(CH$_3$)$_3$), 79.0 (C-1), 78.8 (**C**(CH$_3$)$_3$), 76.5 (C-5), 72.0 (C-2), 54.9 (OCH$_3$), 54.9 (OCH$_3$), 47.2 (CH$_2$N), 43.6 (C-4), 27.5 (C(**C**H$_3$)$_3$), 27.4 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2930 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{32}$H$_{41}$N$_2$O$_8$]$^+$: 581.2863 [M+H]$^+$; found: 581.2863. The ee was determined by HPLC using a *Chiralpak IA* column [n-hexane/i-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 20.8 min, τ_{minor} = 29.3 min (60% ee). M.p.: 54-56 ºC (CH$_2$Cl$_2$).
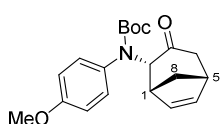
tert-Butyl (4-methoxyphenyl)(((1*R*,2*S*,5*R*)-7-((*N*-(4-methoxyphenyl)acetamido)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5o. Following *GP-I*, **5o** (23.2 mg, 78%) was isolated by FC (petroleum ether/EtOAc 8:2 to 4:6), as a solid after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.5 mL, 0.36 mmol), EtOAc (0.78 mL) and furan **2p** (14 mg, 0.06 mmol). R_f= 0.2 (petroleum ether/EtOAc 1:1). rr >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.12 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.97 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.86 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.03-5.98 (m, 1H, H-6), 4.83-4.78 (m, 2H, H-1 + H-5), 4.61 (d, *J* = 15.0 Hz, 1H, C**H**$_a$H$_b$), 4.22 (d, *J* = 5.0 Hz, 1H, H-2), 3.81 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.75 (bs, 1H, CH$_a$**H**$_b$), 2.78 (dd, *J* = 17.6, 5.9 Hz, 1H, H-4a), 2.40 (d, *J* = 17.6 Hz, H-4b), 1.78 (s, 3H, CH$_3$), 1.28 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 199.6 (C=O), 168.8 (NC=O), 158.1 (C_{arom}), 157.5 (C_{arom}), 153.0 (OC=O), 143.0 (C-7), 136.2 (C_{arom}), 135.2 (C_{arom}), 131.8 (C-6), 128.7 (C_{arom}-H), 128.4 (C_{arom}-H), 114.2 (C_{arom}-H), 113.7 (C_{arom}-H), 79.5 (**C**(CH$_3$)$_3$), 78.6 (C-1), 76.4 (C-5), 72.0 (C-2), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 46.1 (CH$_2$N), 43.4 (C-4), 27.4 (C(**C**H$_3$)$_3$), 21.6 (CH$_3$). IR (CH$_2$Cl$_2$): 2934 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 245 (73), 203 (62), 81 (100). HRMS: Calculated for [C$_{29}$H$_{35}$N$_2$O$_7$]$^+$: 523.2444 [M+H]$^+$; found: 523.2443. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.00 mL/min; τ_{major} = 11.2 min, τ_{minor} = 17.3 min (69% ee). M.p.: 153-155 ºC (CH$_2$Cl$_2$).
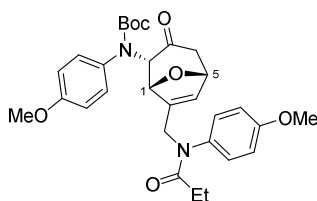
tert-Butyl (4-methoxyphenyl)(((1*R*,2*S*,5*R*)-7-((*N*-(4-methoxyphenyl)propionamido)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5p. Following *GP-J*, **5p** (44.8 mg, 76%) was isolated by FC (petroleum ether/EtOAc 8:2 to 1:1), as an oil after 16 h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.2 mL, 0.27 mmol), EtOAc (0.78 mL) and furan **2q** (57 mg, 0.22 mmol). R_f= 0.34 (petroleum ether/EtOAc 1:1). rr >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.11 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.97 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.86 (d, *J* = 8.4 Hz,

2H, C$_{arom}$-H), 6.01 (app s, 1H, H-6), 4.81 (d, *J* = 5.9 Hz, 1H, H-5), 4.79 (d, *J* = 5.2 Hz, 1H, H-1), 4.63 (d, *J* = 14.8 Hz, 1H, C**H**$_a$H$_b$), 4.22 (d, *J* = 5.2 Hz, 1H, H-2), 3.80 (s, 3H, OCH$_3$), 3.78-3.71 (m, 4H, OCH$_3$ + CH$_a$**H**$_b$), 2.78 (dd, *J* = 17.5, 5.9 Hz, 1H, H-4a), 2.40 (d, *J* = 17.5 Hz, H-4b), 2.10-1.96 (m, 2H, C**H**$_2$CH$_3$), 1.28 (s, 9H, C(CH$_3$)$_3$), 0.96 (t, *J* = 7.4 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 ºC) δ 199.6 (C=O), 172.2 (NC=O), 158.1 (C$_{arom}$), 157.5 (C$_{arom}$), 153.0 (OC=O), 143.0 (C-7), 136.3 (C$_{arom}$), 134.7 (C$_{arom}$), 131.8 (C-6), 128.8 (C$_{arom}$-H), 128.4 (C$_{arom}$-H), 79.5 (**C**(CH$_3$)$_3$), 78.6 (C-1), 76.4 (C-5), 72.1 (C-2), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 46.3 (CH$_2$N), 43.4 (C-4), 27.5 (C(**C**H$_3$)$_3$), 26.4 (**C**H$_2$CH$_3$), 8.9 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{30}$H$_{37}$N$_2$O$_7$]$^+$: 537.2601 [M+H]$^+$; found: 537.2610. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{major}$ = 39.5 min, τ$_{minor}$ = 45.8 min (71% ee). [α]$_D^{20}$: -31.1 (*c* = 1.5, CH$_2$Cl$_2$).

tert-**Butyl** **(4-methoxyphenyl)((1*R*,2*S*,5*R*)-7-((N-(4-methoxyphenyl)pivalamido)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 5q.** Following *GP-I*, **5q** (24.3 mg, 75%) was isolated by FC (petroleum ether/EtOAc 8:2 to 1:1), as an oil after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1j** (45 mg, 0.17 mmol), DMDO solution in toluene (1.56 mL, 0.36 mmol), EtOAc (0.72 mL) and furan **2r** (16.4 mg, 0.06 mmol). rr >20:1.

^{1}H NMR (500 MHz, DMSO-*d$_6$*, 100 ºC) δ 7.19 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 7.10 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 6.95 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 6.85 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 5.96 (app s, 1H, H-6), 4.82 (d, *J* = 5.9 Hz, 1H, H-5), 4.77 (d, *J* = 5.1 Hz, 1H, H-1), 4.66 (d, *J* = 14.5 Hz, 1H, C**H**$_a$H$_b$), 4.22 (d, *J* = 5.0 Hz, 1H, H-2), 3.81 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.58 (d, *J* = 14.5 Hz, 1H, CH$_a$**H**$_b$), 2.78 (dd, *J* = 17.5, 5.9 Hz, 1H, H-4a), 2.40 (d, *J* = 17.5 Hz, H-4b), 1.27 (s, 9H, C(CH$_3$)$_3$), 0.99 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 ºC) δ 199.7 (C=O), 176.1 (NC=O), 158.3 (C$_{arom}$), 157.5 (C$_{arom}$), 153.0 (OC=O), 143.1 (C-7), 136.3 (C$_{arom}$), 135.3 (C$_{arom}$), 131.9 (C-6), 130.3 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 79.4 (O**C**(CH$_3$)$_3$), 78.7 (C-1), 76.4 (C-5), 72.1 (C-2), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 49.6 (CH$_2$N), 43.5 (C-4), 39.3 (**C**(CH$_3$)$_3$), 28.8 (C(**C**H$_3$)$_3$), 27.5 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2962 (C-H st), 1698 (C=O st), 1242(C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 287 (40). HRMS: Calculated for [C$_{32}$H$_{41}$N$_2$O$_7$]$^+$: 565.2914

[M+H]$^+$; found: 565.2921. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.00 mL/min; τ_{major} = 31.0 min, τ_{minor} = 33.6 min (54% ee).
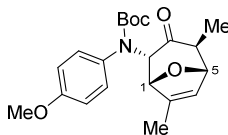
tert-**Butyl (4-methoxyphenyl)((1R,2S,5R)-3-oxobicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5r.** Following *GP-J*, **5r** (16.7 mg, 44%) was isolated by FC (*n*-hexane/EtOAc, 9:1 to 7:3), as a solid after 16h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (1.5 mL, 0.27 mmol), EtOAc (0.7 mL) and cyclopentadiene **2w** (0.12 mL, 1.43 mmol, 13 eq). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.10 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 6.80 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 5.72 (m, 1H, H-6), 5.19 (bs, 1H, H-2), 4.46 (dd, *J* = 6.0, 2.6 Hz, 1H, H-7), 3.80 (s, 3H, OCH$_3$), 2.95 (m, 1H, H-1), 2.81 (m, 1H, H-5), 2.54 (dd, *J* = 15.9, 3.4 Hz, 1H, H-4a), 2.36 (d, *J* = 15.9 Hz, 1H, H-4b), 2.16 (m, 1H, H-8a), 2.00 (d, *J* = 11.1 Hz, 1H, H-8b), 1.32 (s, 9H, 3×CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.4 (C=O), 158.8 (**C**$_{arom}$OCH$_3$), 156.2 (OC=O), 135.5 (C-6), 134.3 (C-7), 133.2 (C$_{arom}$-N), 131.7 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 80.2 (**C**(CH$_3$)$_3$), 71.3 (C-2), 55.5 (OCH$_3$), 44.9 (C-4), 44.9 (C-8), 44.7 (C-1), 39.5 (C-5), 28.4 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2970 (C-H st), 1701 (C=O st), 1240 (C-O-C st as), 1035 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 343 (2, M$^+$), 243 (38), 149 (100). HRMS: Calculated for [C$_{20}$H$_{25}$NO$_4$Na]$^+$: 366.1681 [M+Na]$^+$; found: 366.1684. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.00 mL/min; τ_{minor} = 11.5 min, τ_{major} = 15.0 min (27% ee). M.p.: 132-134 °C (CH$_2$Cl$_2$).
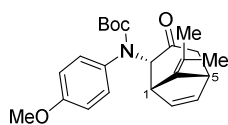
tert-**Butyl (4-methoxyphenyl)((1S,5R)-3-oxo-8-(propan-2-ylidene)bicyclo[3.2.1]oct-6-en-2-yl)carbamate, 5s.** Following *GP-J*, **5s** (9.5 mg, 22%) was isolated by FC (hexanes/EtOAc 2:8 to 1:1), as a solid after 16 h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1j** (30 mg, 0.11 mmol), DMDO solution in toluene (0.84 mL, 0.27 mmol), EtOAc (1.4 mL) and 6,6-dimethylfulvene **2x** (40 µL, 0.33 mmol, 3 eq). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-H), 6.85-6.78 (m, 2H, C$_{arom}$-H), 5.83 (dd, *J* = 6.3, 2.9 Hz, 1H, H-6), 5.04 (bs, 1H, H-2), 4.64-4.52 (m, 1H, H-7), 3.81 (s, 3H, OCH$_3$), 3.53 (bs, 1H, H-1), 3.42-3.37 (m, 1H, H-5), 2.51-2.39 (m, 2H, H-4a + H-4b), 1.78 (s, 3H, CH$_3$), 1.70 (s, 3H, CH$_3$), 1.33 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.2 (C=O), 158.8 (C$_{arom}$), 156.0 (OC=O), 141.4 (C-8), 135.5 (C-6),

134.4 (C-7), 133.5 (C_{arom}), 131.7 (C_{arom}-H), 118.0 ($C(CH_3)_2$), 113.8 (C_{arom}-H), 80.1 ($C(CH_3)_3$), 72.1 (C-2), 55.5 (OCH_3), 46.6 (C-1), 45.6 (C-4), 41.3 (C-5), 28.4 ($C(CH_3)_3$), 19.7 (CH_3), 19.4 (CH_3). IR (CH_2Cl_2): 2980 (C-H st), 1724 (C=O st), 1242 (C-O-C st as), 1049 (C-O-C st sy) cm^{-1}. MS (ESI) m/z (%): 284 (100). HRMS: Calculated for $[C_{23}H_{29}NO_4Na]^+$: 406.1994 $[M+Na]^+$; found: 406.2000. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.00 mL/min; τ_1 = 32.9 min, τ_2 = 48.9 min (0% ee). M.p: 139-141ºC (CH_2Cl_2).
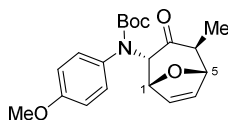
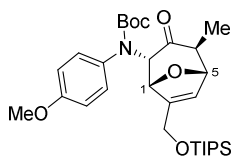***tert*-Butyl (4-methoxyphenyl) ((1*R*,2*S*,4*S*,5*S*)-4-methyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 6a.** Following *GP-J*, **6a** (26.4 mg, 67%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16h, starting from catalyst **3g** (5.5 mg, 0.005 mmol), allene **1l** (30 mg, 0.11 mmol, 1 eq), DMDO solution in toluene (1.2 mL, 0.27 mmol), EtOAc (1.0 mL) and furan **2a** (0.1 mL, 1.43 mmol, 13 eq). R_f= 0.42 (petroleum ether/EtOAc 7:3). dr: >20:1.
^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.10 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.89 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.13 (dd, *J* = 6.0, 1.7 Hz, 1H, H-6), 5.18 (d, *J* = 4.3 Hz, 1H, H-2), 5.03 (dd, *J* = 4.3, 1.7 Hz, 1H, H-1), 4.75 (d, *J* = 6.0 Hz, 1H, H-7), 4.61-4.570 (m, 1H, H-5), 3.78 (s, 3H, OCH_3), 2.41-2.35 (m, 1H, H-4), 1.33 (s, 9H, $C(CH_3)_3$), 1.30 (q, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 204.9 (C=O), 158.2 (C_{arom}), 154.1 (OC=O), 133.6 (C-6), 132.5 (C_{arom}), 131.2 (C-7), 130.6 (C_{arom}-H), 113.5 (C_{arom}-H), 82.2 (C-5), 79.7 (C-1), 79.1 ($C(CH_3)_3$), 68.1 (C-2), 54.9 (OCH_3), 48.5 (C-4), 27.4 ($C(CH_3)_3$), 14.9 (CH_3). IR (CH_2Cl_2): 2972 (C-H st), 1691 (C=O st), 1245 (C-O-C st as), 1045 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 359 (1, M$^+$). HRMS: Calculated for $[C_{20}H_{26}NO_5]^+$: 360.1811 $[M+H]^+$; found: 360.1811. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 11.9 min, τ_{minor} = 14.5 min (35% ee). M.p.: 101-103 ºC (CH_2Cl_2).

***tert*-Butyl ((1*R*,2*S*,4*S*,5*S*)-4,7-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6b.** Following *GP-I*, **6b** (17.3 mg, 86%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (2.7 mg, 0.003 mmol), allene **1l** (45 mg, 0.16 mmol), DMDO solution in toluene (1.36 mL, 0.34 mmol), EtOAc (0.81 mL) and 3-

methylfuran **2b** (4.9 µL, 0.05 mmol). R_f= 0.42 (petroleum ether/EtOAc 7:3). rr: 15:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, J = 8.7 Hz, 2H, C$_{arom}$-H), 6.91 (d, J = 8.7 Hz, 2H, C$_{arom}$-H), 5.97-5.94 (m, 1H, H-6), 4.73 (d, J = 4.9 Hz, 1H, H-1), 4.54 (bs, 1H, H-2), 4.51-4.46 (m, 1H, H-5), 3.77 (s, 3H, OCH$_3$), 2.46 (q, J = 7.5 Hz, 1H, H-4), 1.45 (bs, 3H, CH$_3$), 1.30 (s, 9H, C(CH$_3$)$_3$), 1.27 (d, J = 7.5 Hz, 3H, C-4CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 204.5 (C=O), 157.8 (C$_{arom}$), 153.2 (OC=O), 142.4 (C-7), 135.5 (C$_{arom}$), 128.9 (C-6), 128.9 (C$_{arom}$-H), 113.9 (C$_{arom}$-H), 82.4 (C-5), 81.4 (C-1), 79.5 (**C**(CH$_3$)$_3$), 69.8 (C-2), 55.0 (OCH$_3$), 48.1 (C-4), 27.4 (C(**C**H$_3$)$_3$), 16.5 (CH$_3$). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1720 (C=O st), 1245 (C-O-C st as), 1043 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{21}$H$_{27}$NO$_5$Na]$^+$: 396.1787 [M+Na]$^+$; found: 396.1785. The ee was determined by HPLC using a *Chiralpak IA* column [n-hexane/i-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 10.5 min, τ_{minor} = 11.2 min (81% ee). M.p.: 122-124 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +35.7 (c = 0.8, CH$_2$Cl$_2$).
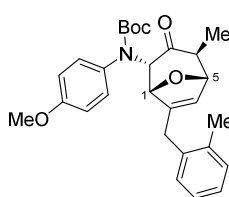
***tert*-Butyl (4-methoxyphenyl) ((1*R*,2*S*,4*S*,5*S*)-4-methyl-7-(2-methylbenzyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 6c.** Following *GP-I*, **6c** (13.3 mg, 53%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** 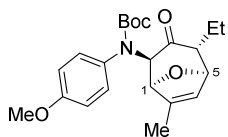(2.7 mg, 0.003 mmol), allene **1l** (45 mg, 0.16 mmol), DMDO solution in toluene (1.35 mL, 0.34 mmol), EtOAc (0.81 mL) and furan **2d** (8 µL, 0.05 mmol). R_f= 0.40 (petroleum ether/EtOAc 8:2). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.18 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 7.16-7.09 (m, 3H, C$_{arom}$-H), 7.05-7.01 (m, 1H, C$_{arom}$-H), 6.92 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 5.78-5.72 (m, 1H, H-6), 4.79 (d, J = 4.9 Hz, 1H, H-1), 4.60 (d, J = 4.9 Hz, 1H, H-2), 4.52-4.48 (m, 1H, H-5), 3.75 (s, 3H, OCH$_3$), 3.06 (d, J = 16.6 Hz, 1H, C**H**$_a$H$_b$), 2.97-2.89 (m, 1H, CH$_a$**H**$_b$), 2.48-2.44 (m, 1H, H-4), 2.17 (s, 3H, CH$_3$), 1.34 (s, 9H C(CH$_3$)$_3$), 1.28 (d, J = 7.3 Hz, 3H, C-4CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 204.3 (C=O), 157.8 (C$_{arom}$), 153.4 (OC=O), 145.9 (C$_{arom}$), 129.8 (C-6), 129.6 (C$_{arom}$-H), 128.8 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 125.8 (C$_{arom}$-H), 125.3 (C$_{arom}$), 114.0 (C$_{arom}$-H), 82.4 (C-5), 80.6 (C-1), 79.6 (**C**(CH$_3$)$_3$), 70.1 (C-2), 55.0 (OCH$_3$), 48.0 (C-4), 31.1 (CH$_2$), 27.5 (C(**C**H$_3$)$_3$), 18.3 (CH$_3$), 16.5 (C-4**C**H$_3$). IR (CH$_2$Cl$_2$): 2980 (C-H st), 1716 (C=O st), 1242 (C-O-C st as), 1035 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{28}$H$_{33}$NO$_5$Na]$^+$: 486.2256 [M+Na]$^+$; found: 486.2262. The ee was determined by

HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{minor} = 6.7 min, τ_{major} = 8.0 min (73% ee). $[\alpha]_D^{20}$: +121.3 (*c* = 0.6, CH$_2$Cl$_2$).
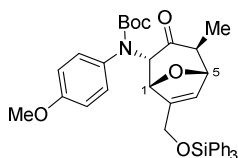
***tert*-Butyl (4-methoxyphenyl) ((1*R*,2*S*,4*S*,5*S*)-4-methyl-3-oxo-7-(((triphenylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 6d.** Following *GP-I*, **6d** (15 mg, 64%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (1.8 mg, 0.002 mmol), allene **1l** (30 mg, 0.11 mmol), DMDO solution in toluene (0.93 mL, 0.23 mmol), EtOAc (0.51 mL) and furan **2m** (12.8 mg, 0.04 mmol). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.56-7.51 (m, 6H, C$_{arom}$-H), 7.51-7.46 (m, 3H, C$_{arom}$-H), 7.46-7.39 (m, 6H, C$_{arom}$-H), 7.04 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.75 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.24-6.21 (m, 1H, H-6), 4.96 (d, *J* = 4.9 Hz, 1H, H-1), 4.59-4.51 (m, 2H, H-2 + H-5), 4.08 (d, *J* = 13.8 Hz, 1H, C**H**$_a$H$_b$), 3.92 (bs, 1H, CH$_a$**H**$_b$), 3.67 (s, 3H, OCH$_3$), 2.48-2.44 (m, 1H, H-4), 1.28 (d, *J* = 7.4 Hz, 3H, CH$_3$), 1.20 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 75 °C) δ 204.3 (C=O), 157.8 (C$_{arom}$), 153.3 (OC=O), 146.1 (C-7), 134.4 (C$_{arom}$-H), 134.2 (C$_{arom}$), 133.3 (C$_{arom}$-H), 130.0 (C-6), 129.8 (C$_{arom}$-H), 128.9 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 82.3 (C-5), 79.6 (C-1), 78.8 (**C**(CH$_3$)$_3$), 69.7 (C-2), 59.9 (CH$_2$O), 54.9 (OCH$_3$), 47.9 (C-4), 27.4 (C(**C**H$_3$)$_3$), 16.7 (CH$_3$). IR (ATR): 2934 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1059 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 356 (36), 199 (100). HRMS: Calculated for [C$_{39}$H$_{41}$NO$_6$SiNa]$^+$: 670.2601 [M+Na]$^+$; found: 670.2603. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.00 mL/min; τ_{major} = 39.4 min, τ_{minor} = 47.4 min (90% ee). M.p.: 125-127 °C (CH$_2$Cl$_2$). $[\alpha]_D^{20}$: +55.2 (*c* = 1.0, CH$_2$Cl$_2$).

***tert*-Butyl (4-methoxyphenyl) ((1*R*,2*S*,4*S*,5*S*)-4-methyl-3-oxo-7-(((triisopropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl) carbamate, 6e.** Following *GP-I*, **6e** (14.8 mg, 75%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (1.8 mg, 0.002 mmol), allene **1l** (30 mg, 0.11 mmol), DMDO solution in toluene (0.93 mL, 0.23 mmol), EtOAc (0.51 mL) and furan **2n** (9.7 μL, 0.04 mmol). R$_f$= 0.47 (petroleum ether/Et$_2$O 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.15 (d, *J* = 7.9 Hz, 2H, C$_{arom}$-H), 6.89 (d, *J* = 7.9 Hz, 2H, C$_{arom}$-H), 6.20-6.17 (m, 1H, H-6), 4.95 (d, *J* =

4.8 Hz, 1H, H-1), 4.69 (app s, 1H, H-2), 4.58-4.55 (m, 1H, H-5), 3.95 (d, J = 14.6 Hz, 1H, C**H**$_a$H$_b$), 3.77 (s, 3H, OCH$_3$), 3.60 (app s, 1H, CH$_a$**H**$_b$), 2.44-2.49 (m, 1H, H-4), 1.29 (s, 12H, C(CH$_3$)$_3$ + C-4CH$_3$), 1.03 (m, 21H, Si(C**H**(CH$_3$)$_2$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 75 ℃) δ 204.6 (C=O), 157.9 (C$_{arom}$), 153.5 (OC=O), 147.3 (C-7), 134.7 (C$_{arom}$), 129.4 (C$_{arom}$-H), 129.0 (C-6), 113.8 (C$_{arom}$-H), 82.2 (C-5), 79.6 (C-1), 79.0 (**C**(CH$_3$)$_3$), 69.5 (C-2), 59.3 (CH$_2$O), 54.9 (OCH$_3$), 48.2 (C-4), 27.4 (C(**C**H$_3$)$_3$), 17.4 (Si(CH(**C**H$_3$)$_2$)$_3$), 11.1 (CH$_3$). IR (CH$_2$Cl$_2$): 2944 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1063 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{30}$H$_{47}$NO$_6$SiNa]$^+$: 568.3070 [M+Na]$^+$; found: 568.3078. The ee was determined by HPLC using a *Chiralcel OZ-3* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 0.70 mL/min; τ$_{minor}$ = 16.9 min, τ$_{major}$ = 212 min (85% ee). M.p.: 118-120 ℃ (CH$_2$Cl$_2$). [α]$_D^{20}$: +54.3 (c = 1.3, CH$_2$Cl$_2$).
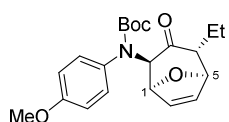
***tert*-Butyl ((1S,2*R*,4*R*,5*R*)-4-ethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6f.** Following *GP-J*, **6f** (25 mg, 64%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst *ent*-**3g** (5.2 mg, 0.005 mmol), allene **1m** (30 mg, 0.1 mmol, 1 eq), DMDO solution in toluene (0.98 mL, 0.26 mmol), EtOAc (1.1 mL) and furan **2a** (98 µL, 1.35 mmol, 13 eq). R$_f$= 0.33 (petroleum ether/EtOAc 8:2). dr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ℃) δ 7.11 (d, J = 8.5 Hz, 2H, C$_{arom}$-H), 6.89 (d, J = 8.5 Hz, 2H, C$_{arom}$-H), 6.13-6.09 (m, 1H, H-6), 5.14 (d, J = 4.3 Hz, 1H, H-2), 5.03 (d, J = 4.3 Hz, 1H, H-1), 4.72-4.70 (m, 1H, H-5), 4.68 (d, J = 6.3 Hz, 1H, H-7), 3.78 (s, 3H, OCH$_3$), 2.22-2.16 (m, 1H, H-4), 1.84-1.73 (m, 2H, CH$_2$), 1.33 (s, 9H, C(CH$_3$)$_3$), 0.98 (t, J = 7.5 Hz, 3H, CH$_2$CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ℃) δ 204.0 (C=O), 158.2 (C$_{arom}$), 154.1 (OC=O), 133.5 (C-7), 132.4 (C$_{arom}$), 131.3 (C-6), 130.7 (C$_{arom}$-H), 113.5 (C$_{arom}$-H), 80.5 (C-5), 79.8 (C-1), 79.1 (**C**(CH$_3$)$_3$), 68.7 (C-2), 55.8 (C-4), 54.9 (OCH$_3$), 27.4 (C(**C**H$_3$)$_3$), 22.8 (CH$_2$), 11.2 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2969 (C-H st), 1724 (C=O st), 1242 (C-O-C st as), 1049 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 373 (1, M$^+$), 317 (21), 244 (100). HRMS: Calculated for [C$_{21}$H$_{27}$NO$_5$Na]$^+$: 396.1787 [M+Na]$^+$; found: 396.1792. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{minor}$ = 11.4 min, τ$_{major}$ = 13.9 min (35% ee). M.p.: 89-91 ℃ (CH$_2$Cl$_2$).

tert-**Butyl** **((1S,2R,4R,5R)-4-ethyl-7-methyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate,** **6g.** 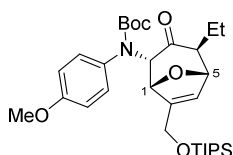Following *GP-I*, **6g** (15.3 mg, 76%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst *ent*-**3g** (2.6 mg, 0.003 mmol), allene **1m** (45 mg, 0.16 mmol), DMDO solution in toluene (1.4 mL, 0.33 mmol), EtOAc (0.66 mL) and 3-methylfuran **2b** (4.7 µL, 0.05 mmol). R_f= 0.50 (petroleum ether/EtOAc 8:2). rr: 10:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.17 (d, J = 8.4 Hz, 2H, C_{arom}-H), 6.91 (d, J = 8.4 Hz, 2H, C_{arom}-H), 5.96-5.90 (m, 1H, H-6), 4.74 (d, J = 4.7 Hz, 1H, H-1), 4.66-4.59 (m, 2H, H-2 + H5), 3.77 (s, 3H, OCH$_3$), 2.29-2.23 (m, 1H, H-4), 1.75 (p, J = 7.4 Hz, 2H, C**H**$_2$CH$_3$), 1.31 (m, 12H, C(CH$_3$)$_3$ + CH$_3$), 0.98 (t, J = 7.4 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.7 (C=O), 157.9 (C_{arom}), 153.4 (OC=O), 142.5 (C-7), 135.2 (C_{arom}), 129.2 (C-6), 129.1 (C_{arom}-H), 113.9 (C_{arom}-H), 81.7 (C-1), 80.4 (C-5), 79.4 (**C**(CH$_3$)$_3$), 70.6 (C-2), 55.3 (C-4), 55.0 (OCH$_3$), 27.4 (C(**C**H$_3$)$_3$), 23.9 (CH$_2$), 12.8 (CH$_3$), 11.1 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2972 (C-H st), 1724 (C=O st), 1245 (C-O-C st as), 1040 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 258 (93), 134 (100). HRMS: Calculated for $[C_{22}H_{29}NO_5Na]^+$: 410.1943 $[M+Na]^+$; found: 410.1947. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{minor} = 10.7 min, τ_{major} = 12.4 min (92% ee). $[\alpha]_D^{20}$: -107.8 (c = 1.0, CH$_2$Cl$_2$).
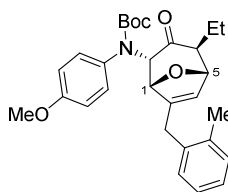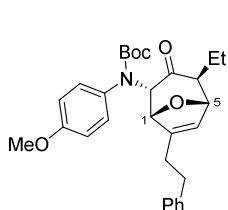
tert-**Butyl** **((1R,2S,4S,5S)-4-ethyl-7-(2-methylbenzyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate,** **6h.** Following *GP-I*, **6h** (14.9 mg, 60%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (2.6 mg, 0.003 mmol), allene **1m** (45 mg, 0.16 mmol), DMDO solution in toluene (1.38 mL, 0.33 mmol), EtOAc (0.69 mL) and furan **2d** (7.8 µL, 0.05 mmol). R_f= 0.61 (petroleum ether/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.19 (d, J = 8.8 Hz, 2H, C_{arom}-H), 7.14-7.07 (m, 3H, C_{arom}-H), 7.01-6.97 (m, 1H, C_{arom}-H), 6.92 (d, J = 8.8 Hz, 2H, C_{arom}-H), 5.72-5.65 (m, 1H, H-6), 4.82 (d, J = 4.7 Hz, 1H, H-1), 4.67 (d, J = 4.7 Hz, 1H, H-2), 4.64-4.61 (m, 1H, H-5), 3.75 (s, 3H, OCH$_3$), 2.94 (d, J = 16.9 Hz, 1H, C**H**$_a$H$_b$), 2.76 (d, J = 16.9 Hz, 1H, CH$_a$**H**$_b$), 2.30-2.25 (m, 1H, H-4), 2.14 (s, 3H, CH$_3$), 1.80-1.70 (m, 2H, C**H**$_2$CH$_3$), 1.34 (s, 9H, C(CH$_3$)$_3$), 0.97 (t, J = 7.5 Hz, 3H, CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100

ºC) δ 203.5 (C=O), 157.9 (C$_{arom}$), 153.5 (OC=O), 146.0 (C-7), 136.7 (C$_{arom}$), 135.4 (C$_{arom}$), 129.9 (C-6), 129.5 (C$_{arom}$-H), 129.1 (C$_{arom}$-H), 128.4 (C$_{arom}$-H), 125.8 (C$_{arom}$-H), 125.3 (C$_{arom}$-H), 114.0 (C$_{arom}$-H), 80.9 (C-1), 80.4 (C-5), 79.5 (**C**(CH$_3$)$_3$), 70.8 (C-2), 55.2 (C-4), 55.0 (OCH$_3$), 30.9 (CH$_2$), 27.5 (C(**C**H$_3$)$_3$), 24.0 (**C**H$_2$CH$_3$), 18.2 (CH$_3$), 11.1 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2972 (C-H st), 1724 (C=O st), 1242 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{29}$H$_{35}$NO$_5$Na]$^+$: 500.2413 [M+Na]$^+$; found: 500.2416. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ$_{minor}$ = 8.2 min, τ$_{major}$ = 13.3 min (87% ee).

tert-Butyl ((1*R*,2*S*,4*S*,5*S*)-4-ethyl-3-oxo-7-(((triisopropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6i. Following *GP-I*, **6i** (23.9 mg, 82%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (2.6 mg, 0.003 mmol), allene **1m** (45 mg, 0.16 mmol), DMDO solution in toluene (1.23 mL, 0.33 mmol) with EtOAc (0.85 mL) and furan **2n** (14 µL, 0.05 mmol). R$_f$= 0.42 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d$_6$*, 100 ºC) δ 7.16 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.89 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.19-6.17 (m, 1H, H-6), 4.95 (d, *J* = 4.6 Hz, 1H, H-1), 4.77 (app s, 1H, H-2), 4.71-4.69 (m, 1H, H-5), 3.83 (d, *J* = 13.7 Hz, 1H, C**H**$_a$H$_b$), 3.77 (s, 3H, OCH$_3$), 3.40 (app s, 1H, CH$_a$**H**$_b$), 2.29 (t, *J* = 7.2 Hz, 1H, H-4), 1.78 (p, *J* = 7.4 Hz, 2H, C**H**$_2$CH$_3$), 1.30 (s, 9H, C(CH$_3$)$_3$), 1.01 (m, 24H, Si(C**H**(CH$_3$)$_2$)$_3$ + CH$_2$C**H**$_3$). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 ºC) δ 203.5 (C=O), 157.9 (C$_{arom}$), 153.5 (OC=O), 147.3 (C-7), 134.4 (C$_{arom}$), 129.4 (C$_{arom}$-H), 129.1 (C-6), 113.7 (C$_{arom}$-H), 80.2 (C-5), 79.4 (C-1), 79.3 (**C**(CH$_3$)$_3$), 70.2 (C-2), 59.1 (CH$_2$O), 55.3 (C-4), 54.7 (OCH$_3$), 27.4 (C(**C**H$_3$)$_3$), 23.9 (**C**H$_2$CH$_3$), 17.2 (Si(CH(**C**H$_3$)$_2$)$_3$), 11.1 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2962 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1066 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{31}$H$_{49}$NO$_6$SiNa]$^+$: 582.3227 [M+Na]$^+$; found: 582.3229. The ee was determined by HPLC using a *Chiralcel OZ-3* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 0.70 mL/min; τ$_{minor}$ = 11.2 min, τ$_{major}$ = 14.8 min (93% ee). [α]$_D^{20}$: +79.4 (*c* = 1.7, CH$_2$Cl$_2$).

***tert*-Butyl ((1*R*,2*S*,4*S*,5*S*)-4-ethyl-3-oxo-7-phenethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6j.** Following *GP-I*, **6j** (18.1 mg, 73%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (2.6 mg, 0.003 mmol), allene **1m** (45 mg, 0.16 mmol), DMDO solution in toluene (1.38 mL, 0.33 mmol), EtOAc (0.69 mL) and furan **2f** (7.2 µL, 0.05 mmol). R_f= 0.38 (petroleum ether/EtOAc 8:2). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.28-7.22 (m, 2H, C$_{arom}$-H), 7.19-7.12 (m, 3H, C$_{arom}$-H), 7.09 (d, *J* = 7.3 Hz, 2H, C$_{arom}$-H), 6.86 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.02-5.98 (m, 1H, H-6), 4.82 (d, *J* = 4.6 Hz, 1H, H-1), 4.69 (bs, 1H, H-2), 4.66-4.63 (m, 1H, H-5), 3.68 (s, 3H, OCH$_3$), 2.69-2.53 (m, 2H, CH$_2$Ph), 2.32-2.26 (m, 1H, H-4), 1.82-1.73 (m, 4H, C-7CH$_2$ +**CH$_2$**CH$_3$), 1.29 (s, 9H, C(CH$_3$)$_3$), 0.99 (t, *J* = 7.4 Hz, 3H, CH$_2$**CH$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.6 (C=O), 157.9 (C$_{arom}$), 153.5 (OC=O), 147.1 (C-7), 140.8 (C$_{arom}$), 135.0 (C$_{arom}$), 129.1 (C$_{arom}$-H), 128.1 (C-6), 127.6 (C$_{arom}$-H), 127.5 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 80.8 (C-1), 80.3 (C-5), 79.4 (**C**(CH$_3$)$_3$), 70.5 (C-2), 55.3 (C-4), 54.8 (OCH$_3$), 33.2 (CH$_2$Ph), 28.4 (C-7CH$_2$), 27.4 (C(CH$_3$)$_3$), 23.9 (**CH$_2$**CH$_3$), 11.1 (CH$_2$**CH$_3$**). IR (CH$_2$Cl$_2$): 2980 (C-H st), 1701 (C=O st), 1242 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{29}$H$_{35}$NO$_5$Na]$^+$: 500.2413 [M+Na]$^+$; found: 500.2406. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 17.3 min, τ_{minor} = 20.1 min (77% ee). [α]$_D^{20}$: +24.1 (*c* = 0.5, CH$_2$Cl$_2$).
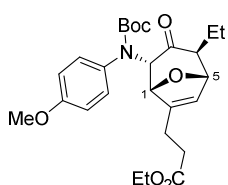
Ethyl 3-((1*S*,2*S*,4*S*,5*R*)-4-((tert-butoxycarbonyl)(4-methoxyphenyl)amino)-2-ethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-6-yl)propanoate, 6k. Following *GP-I*, **6k** (18.5 mg, 70%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (2.8 mg, 0.003 mmol), allene **1m** (48.5 mg, 0.17 mmol), DMDO solution in toluene (1.32 mL, 0.35 mmol), EtOAc (0.9 mL) and furan **2y** (9.4 mg, 0.06 mmol). R_f= 0.42 (petroleum ether/EtOAc 7:3). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, *J* = 9.0 Hz, 2H, C$_{arom}$-H), 6.90 (d, *J* = 9.0 Hz, 2H, C$_{arom}$-H), 5.99-5.95 (m, 1H, H-6), 4.83 (d, *J* = 4.9 Hz, 1H, H-1), 4.66-4.63 (m, 1H, H-5), 4.53 (bs, 1H, H-2), 4.06 (q, *J* = 7.1 Hz, 2H, COC**H$_2$**CH$_3$), 3.77 (s, 3H, OCH$_3$), 2.43-2.24 (m, 3H, H-4 + CH$_2$COOEt), 1.87 (bs, 2H, C-7CH$_2$), 1.78-1.70 (m, 2H, C-4CH$_2$), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.19 (t, *J* = 7.1 Hz, 3H, CO$_2$CH$_2$**CH$_3$**),

0.97 (t, J = 7.4 Hz, 3H, C-4CH$_2$**CH$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.4 (C=O), 171.3 (EtO**C**=O), 157.9 (C$_{arom}$), 153.3 (O**C**=O), 146.1 (C-7), 135.3 (C$_{arom}$), 128.8 (C$_{arom}$-H), 128.0 (C-6), 113.9 (C$_{arom}$-H), 80.5 (C-1), 80.3 (C-5), 79.4 (**C**(CH$_3$)$_3$), 70.6 (C-2), 59.2 (CO$_2$**C**H$_2$CH$_3$), 55.0 (C-4), 54.9 (O**C**H$_3$), 32.0 (C-7**C**H$_2$), 27.4 (C(**C**H$_3$)$_3$), 24.0 (C-4**C**H$_2$), 22.7 (**C**H$_2$CO$_2$Et), 13.5 (C-4CH$_2$**C**H$_3$), 11.1 (C-4**C**H$_2$CH$_3$). IR (CH$_2$Cl$_2$): 2980 (C-H st), 1701 (C=O st), 1245 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{26}$H$_{35}$NO$_7$Na]$^+$: 496.2311 [M+Na]$^+$; found: 496.2296. The ee was determined by HPLC using a *Chiralpak IA* column [n-hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.1 min, τ_{minor} = 15.7 min (85% ee). [α]$_D^{20}$: +50.6 (c = 0.8, CH$_2$Cl$_2$).
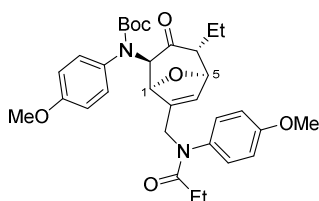
tert-**Butyl ((1S,2R,4R,5R)-4-ethyl-7-((N-(4-methoxyphenyl)propionamido)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6l.** Following *GP-J*, **6l** (35.3 mg, 60%) was isolated by FC (petroleum ether/EtOAc 8:2 to 1:1), as an oil after 16 h, starting from catalyst ***ent*-3g** (5.2 mg, 0.005 mmol), allene **1m** (30 mg, 0.10 mmol), DMDO solution in toluene (1.13 mL, 0.26 mmol), EtOAc (0.94 mL) and furan **2r** (53.7 mg, 0.2 mmol). R$_f$= 0.23 (petroleum ether/EtOAc 6:4). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.15 (d, J = 8.8 Hz, 2H, C$_{arom}$-H), 7.08 (d, J = 8.6 Hz, 2H, C$_{arom}$-H), 696 (d, J = 8.6 Hz, 2H, C$_{arom}$-H), 6.84 (d, J = 8.8 Hz, 2H, C$_{arom}$-H), 6.02-5.99 (m, 1H, H-6), 4.77 (d, J = 4.9 Hz, 1H, H-1), 4.63-4.60 (m, 1H, H-5), 4.46 (bs, 1H, C**H$_a$**H$_b$), 4.32 (bs, 1H, H-2), 3.81 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.59 (bs, 1H, CH$_a$**H$_b$**), 2.28-2.22 (m, 1H, H-4), 2.07-1.95 (m, 2H, COC**H$_2$**CH$_3$), 1.72 (p, J = 7.4 Hz, 2H, C-4C**H$_2$**CH$_3$), 1.29 (s, 9H, C(CH$_3$)$_3$), 0.99-0.92 (m, 6H, COCH$_2$**CH$_3$** + C-4CH$_2$**CH$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.0 (C=O), 172.2 (**C**OEt), 158.1 (C$_{arom}$), 157.6 (C$_{arom}$), 153.1 (O**C**=O), 143.3 (C-7), 135.9 (C$_{arom}$), 134.7 (C$_{arom}$), 131.6 (C-6), 128.8 (C$_{arom}$-H), 128.7 (C$_{arom}$-H), 114.2 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 80.0 (C-5), 79.4 (**C**(CH$_3$)$_3$), 79.2 (C-1), 71.0 (C-2), 55.0 (O**C**H$_3$), 54.9 (O**C**H$_3$), 54.5 (C-4), 46.1 (C-7**C**H$_2$), 27.4 (C(**C**H$_3$)$_3$), 26.4 (CO**C**H$_2$CH$_3$), 24.2 (C-4**C**H$_2$), 11.0 (CH$_2$**C**H$_3$), 8.9 (CH$_2$**C**H$_3$). IR (CH$_2$Cl$_2$): 2980 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 259 (90), 203 (100). HRMS: Calculated for [C$_{32}$H$_{41}$N$_2$O$_7$]$^+$: 565.2914 [M+H]$^+$; found: 565.2908. The ee was determined by HPLC using a

Chiralpak IA column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 7.2 min, τ_{major} = 13.9 min (68% ee). $[\alpha]_D^{20}$: -26.2 (*c* = 1.2, CH_2Cl_2).
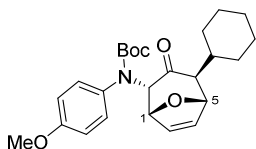
tert-Butyl ((1R,2S,4S,5S)-4-cyclohexyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 6m. Following *GP-J*, **6m** (16.5 mg, 44%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (4.3 mg, 0.004 mmol), allene **1n** (30 mg, 0.09 mmol, 1 eq), DMDO solution in toluene (0.9 mL, 0.22 mmol), EtOAc (0.84 mL) and furan **2a** (82 μL, 1.13 mmol, 13 eq). R_f= 0.61 (petroleum ether/EtOAc 8:2). dr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.12 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.89 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.11-6.05 (m, 1H, H-6), 5.09 (d, *J* = 4.3 Hz, 1H, H-2), 5.01 (d, *J* = 4.3 Hz, 1H, H-1), 4.88-4.84 (m, 1H, H-5), 4.58 (d, *J* = 6.0 Hz, 1H, H-7), 3.78 (s, 3H, OCH_3), 2.06-2.02 (m, 1H, H-4), 1.97-1.91 (m, 1H, C_{cy}H), 1.91-1.84 (m, 1H, C_{cy}H), 1.78-1.69 (m, 3H, 3×C_{cy}H), 1.69-1.60 (m, 2H, 2×C_{cy}H), 1.34 (s, 9H, $C(CH_3)_3$), 1.25-1.15 (m, 2H, 2×C_{cy}H), 1.12-1.01 (m, 2H, 2×C_{cy}H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 203.4 (C=O), 158.3 (C_{arom}), 154.1 (OC=O), 133.5 (C-6), 132.1 (C_{arom}), 131.5 (C-7), 130.9 (C_{arom}-H), 113.5 (C_{arom}-H), 79.8 (C-1), 79.1 (**C**$(CH_3)_3$), 78.9 (C-5), 70.0 (C-2), 60.0 (C-4), 54.9 (OCH_3), 37.2 (C_{cy}H), 30.9 ($C_{cy}H_2$), 30.2 ($C_{cy}H_2$), 27.5 (C(**C**$H_3)_3$), 25.3 ($C_{cy}H_2$), 25.2 ($C_{cy}H_2$), 25.2 ($C_{cy}H_2$). IR (CH_2Cl_2): 2962 (C-H st), 1701 (C=O st), 1257 (C-O-C st as), 1020 (C-O-C st sy) cm^{-1}. HRMS: Calculated for $[C_{25}H_{33}NO_5Na]^+$: 450.2256 $[M+Na]^+$; found: 450.2253. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 11.6 min, τ_{minor} = 22.6 min (80% ee). $[\alpha]_D^{20}$: +147.4 (*c* = 0.4, CH_2Cl_2).
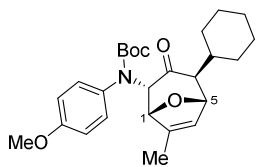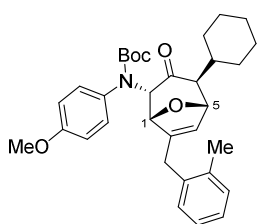
tert-Butyl ((1R,2S,4S,5S)-4-cyclohexyl-7-methyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 6n. Following *GP-I*, **6n** (10.3 mg, 40%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as a solid after 16 h, starting from catalyst **3g** (2.9 mg, 0.003 mmol), allene **1n** (60 mg, 0.17 mmol), DMDO solution in toluene (1.62 mL, 0.38 mmol), EtOAc (0.45 mL) and 3-methylfuran **2b** (5.3 μL, 0.06 mmol). R_f= 0.42 (petroleum ether/EtOAc 8:2). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.18 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.91-5.87 (m, 1H, H-6), 4.77-4.73

(m, 2H, H-1 + H-5), 4.72 (bs, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.15 (d, *J* = 6.9 Hz, 1H, H-4), 1.93-1.82 (m, 1H, C$_{cy}$H), 1.82-1.75 (m, 1H, C$_{cy}$H), 1.75-1.66 (m, 3H, 3×C$_{cy}$H), 1.66-1.59 (m, 1H, C$_{cy}$H), 1.31 (s, 9H, C(CH$_3$)$_3$), 1.26-1.08 (m, 8H, CH$_3$ + 5× C$_{cy}$H). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 °C) δ 203.3 (C=O), 158.0 (C$_{arom}$), 153.6 (OC=O), 142.6 (C-7), 134.8 (C$_{arom}$), 129.6 (C-6), 129.5 (C$_{arom}$-H), 113.9 (C$_{arom}$-H), 81.9 (C-1), 79.4 (**C**(CH$_3$)$_3$), 78.7 (C-5), 71.8 (C-2), 59.9 (C-4), 55.0 (OCH$_3$), 38.6 (C$_{cy}$H), 30.6 (C$_{cy}$H$_2$), 30.0 (C$_{cy}$H$_2$), 27.4 (C(**C**H$_3$)$_3$), 25.4 (C$_{cy}$H$_2$), 25.4 (C$_{cy}$H$_2$), 25.3 (C$_{cy}$H$_2$), 12.5 (CH$_3$). IR (CH$_2$Cl$_2$): 2922 (C-H st), 1698 (C=O st), 1260 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{26}$H$_{35}$NO$_5$Na]$^+$: 464.2413 [M+Na]$^+$; found: 464.2411. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 9.1 min, τ$_{minor}$ = 23.6 min (94% ee). M.p.: 97-99 °C (CH$_2$Cl$_2$). [α]$_D^{20}$: +211.8 (*c* = 0.2, CH$_2$Cl$_2$).

***tert*-Butyl ((1*R*,2*S*,4*S*,5*S*)-4-cyclohexyl-7-(2-methylbenzyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 6o.** Following *GP-I*, **6o** (17.8 mg, 76%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (2.2 mg, 0.002 mmol), allene **1n** (45 mg, 0.13 mmol), DMDO solution in toluene (1.1 mL, 0.28 mmol), EtOAc (0.70 mL) and furan **2d** (6.6 µL, 0.04 mmol). R$_f$= 0.33 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d$_6$*, 100 °C) δ 7.22 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 7.12-7.05 (m, 3H, C$_{arom}$-H), 6.95-6.90 (m, 3H, C$_{arom}$-H), 5.62-5.58 (m, 1H, H-6), 4.86 (d, *J* = 4.6 Hz, 1H, H-1), 4.78-4.74 (m, 2H, H-2 + H-5), 3.74 (s, 3H, OCH$_3$), 2.76 (d, *J* = 16.8 Hz, 1H, C**H**$_a$H$_b$), 2.55-2.51 (m, 1H, CH$_a$**H**$_b$), 2.16 (d, *J* = 6.9 Hz, 1H, H-4), 2.10 (s, 3H, CH$_3$), 1.93-1.82 (m, 1H, C$_{cy}$H), 1.81-1.66 (m, 4H, 4×C$_{cy}$H), 1.66-1.58 (m, 1H, C$_{cy}$H), 1.34 (s, 9H, C(CH$_3$)$_3$), 1.25-1.06 (m, 5H, C$_{cy}$H). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 °C) δ 203.1 (C=O), 158.0 (C$_{arom}$), 153.7 (OC=O), 146.2 (C-7), 136.7 (C$_{arom}$), 135.4 (C$_{arom}$), 134.9 (C$_{arom}$), 130.3 (C-6), 129.6 (C$_{arom}$-H), 129.5 (C$_{arom}$-H), 128.4 (C$_{arom}$-H), 125.7 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 114.0 (C$_{arom}$-H), 81.2 (C-1), 79.4 (**C**(CH$_3$)$_3$), 78.7 (C-5), 72.0 (C-2), 59.7 (C-4), 55.0 (OCH$_3$), 38.6 (C$_{cy}$H), 30.7 (CH$_2$), 30.5 (C$_{cy}$H$_2$), 29.9 (C$_{cy}$H$_2$), 27.5 (C(**C**H$_3$)$_3$), 25.4 (C$_{cy}$H$_2$), 25.4 (C$_{cy}$H$_2$), 25.3 (C$_{cy}$H$_2$), 18.2 (CH$_3$). IR (CH$_2$Cl$_2$): 2926 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{33}$H$_{41}$NO$_5$Na]$^+$: 554.2882 [M+Na]$^+$; found: 554.2879. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-

hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{minor} = 11.8 min, τ_{major} = 12.8 min (97% ee). $[\alpha]_D^{20}$: +82.9 (*c* = 1.0, CH$_2$Cl$_2$).
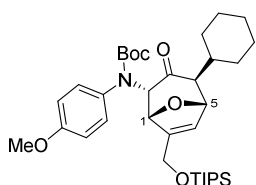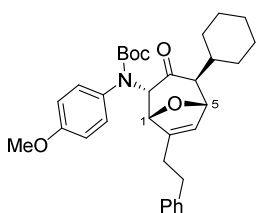
tert-Butyl **((1*R*,2*S*,4*S*,5*S*)-4-cyclohexyl-3-oxo-7-(((triisopropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 6p.** Following *GP-I*, **6p** (23.6 mg, 87%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (2.2 mg, 0.002 mmol), allene **1n** (45 mg, 0.13 mmol), DMDO solution in toluene (1.1 mL, 0.28 mmol), EtOAc (0.70 mL) and furan **2n** (11.7 µL, 0.04 mmol). R$_f$= 0.45 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d₆*, 100 ºC) δ 7.17 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.88 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.16-6.13 (m, 1H, H-6), 4.96 (d, *J* = 4.5 Hz, 1H, H-1), 4.90-4.81 (m, 2H, H-2 + H-5), 3.76 (s, 3H, OCH$_3$), 3.65 (d, *J* = 14.8 Hz, 1H, C**H**$_a$H$_b$), 3.12 (bs, 1H, CH$_a$**H**$_b$), 2.17 (d, *J* = 7.2 Hz, 1H, H-4), 1.94-1.86 (m, 1H, C$_{cy}$H), 1.86-1.79 (m, 1H, C$_{cy}$H), 1.77-1.67 (m, 3H, 3×C$_{cy}$H), 1.66-1.59 (m, 1H, C$_{cy}$H), 1.30 (s, 9H, C(CH$_3$)$_3$), 1.26-1.09 (m, 5H, 5× C$_{cy}$H), 0.99 (s, 21H, 3×C**H**(CH$_3$)$_2$). ^{13}C NMR (125 MHz, DMSO-*d₆*, 100 ºC) δ 203.1 (C=O), 158.1 (C$_{arom}$), 153.7 (OC=O), 147.5 (C-7), 133.9 (C$_{arom}$), 129.9 (C$_{arom}$-H), 129.5 (C-6), 113.7 (C$_{arom}$-H), 79.5 (C-1), 79.4 (**C**(CH$_3$)$_3$), 78.5 (C-5), 71.3 (C-2), 59.9 (C-4), 58.8 (CH$_2$), 54.7 (OCH$_3$), 38.4 (C$_{cy}$H), 30.6 (C$_{cy}$H$_2$), 30.0 (C$_{cy}$H$_2$), 27.4 (C(**C**H$_3$)$_3$), 25.4 (C$_{cy}$H$_2$), 25.3 (C$_{cy}$H$_2$), 25.3 (C$_{cy}$H$_2$), 17.2 (Si(**C**H(CH$_3$)$_2$)$_3$), 11.0 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2926 (C-H st), 1698 (C=O st) cm^{-1}. HRMS: Calculated for [C$_{35}$H$_{55}$NO$_6$SiNa]$^+$: 636.3696 [M+Na]$^+$; found: 636.3704. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 3.9 min, τ_{minor} = 7.7 min (99% ee). $[\alpha]_D^{20}$: +83.8 (*c* = 1.5, CH$_2$Cl$_2$).
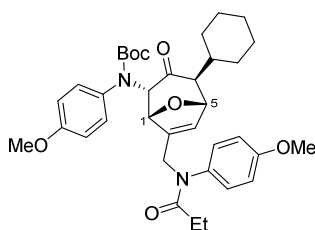
tert-Butyl **((1*R*,2*S*,4*R*,5*S*)-4-cyclohexyl-3-oxo-7-phenethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl) carbamate, 6q.** Following *GP-I*, **6q** (17.6 mg, 70%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (2.2 mg, 0.002 mmol), allene **1n** (45 mg, 0.13 mmol), DMDO solution in toluene (1.1 mL, 0.28 mmol), EtOAc (0.72 mL) and furan **2f** (6.7 µL, 0.04 mmol). R$_f$= 0.51 (petroleum ether/EtOAc 8:2). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d₆*, 100 ºC) δ 7.26-7.21 (m,

2H, C$_{arom}$-H), 7.18-7.13 (m, 3H, C$_{arom}$-H), 7.05 (d, J = 7.5 Hz, 2H, C$_{arom}$-H), 6.84 (d, J = 8.9 Hz, 2H, C$_{arom}$-H), 5.98-5.95 (m, 1H, H-6), 4.83 (d, J = 4.5 Hz, 1H, H-1), 4.80-4.75 (m, 2H, H-2 + H-5), 3.65 (s, 3H, OCH$_3$), 2.64-2.52 (m, 1H, C$_{cy}$H), 2.17 (d, J = 7.0 Hz, 1H, H-4), 1.93-1.85 (m, 1H, C$_{cy}$-H), 1.84-1.77 (m, 1H, CH$_a$H$_b$), 1.75-1.67 (m, 3H, 3×C$_{cy}$H), 1.67-1.60 (m, CH$_a$H$_b$), 1.60-1.51 (m, 2H, CH$_2$), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.27-1.07 (m, 6H, 6×C$_{cy}$H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 203.3 (C=O), 158.0 (C$_{arom}$), 153.6 (OC=O), 147.2 (C-7), 140.7 (C$_{arom}$), 134.6 (C$_{arom}$), 129.6 (C$_{arom}$-H), 128.5 (C-6), 127.5 (C$_{arom}$-H), 127.4 (C$_{arom}$-H), 125.1 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 81.0 (C-1), 79.3 (**C**(CH$_3$)$_3$), 78.7 (C-5), 71.8 (C-2), 59.9 (C-4), 54.8 (OCH$_3$), 38.6 (CH), 33.2 (CH$_2$), 30.6 (CH$_2$), 30.0 (CH$_2$), 28.0 (CH$_2$), 27.4 (C(**C**H$_3$)$_3$), 25.4 (CH$_2$), 25.4 (CH$_2$), 25.3 (CH$_2$). IR (CH$_2$Cl$_2$): 2926 (C-H st), 1698 (C=O st), 1245 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{33}$H$_{41}$NO$_5$Na]$^+$: 554.2882 [M+Na]$^+$; found: 554.2877. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 7.9 min, τ$_{minor}$ = 14.7 min (96% ee). [α]$_D^{20}$: +72.0 (c = 1.0, CH$_2$Cl$_2$).

***tert*-Butyl ((1*R*,2*S*,4*R*,5*S*)-4-cyclohexyl-7-((*N*-(4-methoxyphenyl)propionamido)methyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6r.** Following *GP-J*, **6r** (27.7 mg, 51%) was isolated by FC (petroleum ether/EtOAc 7:3 to 4:6), as a solid after 16 h, starting from catalyst **3g** (4.3 mg, 0.004 mmol), allene **1n** (30 mg, 0.09 mmol), DMDO solution in toluene (0.82 mL, 0.22 mmol), EtOAc (0.93 mL) and furan **2r** (45.1 mg, 0.17 mmol). R$_f$= 0.5 (petroleum ether/EtOAc 1:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.14 (d, J = 8.6 Hz, 2H, C$_{arom}$-H), 7.04 (d, J = 8.6 Hz, 2H, C$_{arom}$-H), 6.96 (d, J = 8.6 Hz, 2H, C$_{arom}$-H), 6.82 (d, J = 8.5 Hz, 2H, C$_{arom}$-H), 5.99 (app s, 1H, H-6), 4.79-4.73 (m, 2H, H-1 + H-5), 4.37 (bs, 1H, H-2), 4.24 (bs, 1H, CH$_a$H$_b$), 3.81 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$), 3.39 (bs, 1H, CH$_a$**H**$_b$), 2.18-2.14 (m, 1H, H-4), 2.03-1.95 (m, 2H, C**H**$_2$CH$_3$), 1.89-1.80 (m, 1H, C$_{cy}$H), 1.75-1.57 (m, 5H, 5×C$_{cy}$H), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.24-1.08 (m, 4H, 4×C$_{cy}$H), 1.07 (d, J = 6.1 Hz, 1H, C$_{cy}$H), 0.93 (t, J = 7.4 Hz, 3H, CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 202.6 (C=O), 172.1 (COEt), 158.1 (C$_{arom}$), 157.7 (C$_{arom}$), 153.2 (OC=O), 143.5 (C-7), 134.8 (C$_{arom}$), 131.8 (C-6), 129.0 (C$_{arom}$-H), 128.7 (C$_{arom}$-H), 114.2 (C$_{arom}$-H), 113.8 (C$_{arom}$-H), 79.5 (C-1), 79.4 (**C**(CH$_3$)$_3$), 78.6 (C-2), 72.2 (C-5), 59.0 (C-4), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 45.9 (CH$_2$N), 30.4

(C$_{cy}$H$_2$), 29.9 (C$_{cy}$H$_2$), 27.5 (C(CH$_3$)$_3$), 26.3 (**CH$_2$**CH$_3$), 25.5 (C$_{cy}$H$_2$), 25.4 (C$_{cy}$H$_2$), 25.2 (C$_{cy}$H$_2$), 8.9 (CH$_2$**CH$_3$**). IR (CH$_2$Cl$_2$): 2976 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1034 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{36}$H$_{47}$N$_2$O$_7$]$^+$: 619.3383 [M+H]$^+$; found: 619.3384. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 12.2 min, τ$_{minor}$ = 15.2 min (96% ee). M.p.: 83-85 ºC (CH$_2$Cl$_2$). [α]$_D^{20}$: +58.2 (*c* = 1.5, CH$_2$Cl$_2$).
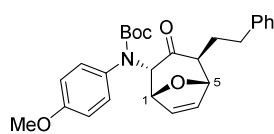
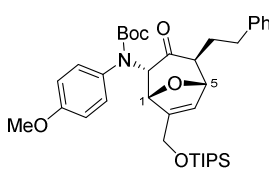***tert*-Butyl (4-methoxyphenyl) ((1*R*,2*S*,4*S*,5*S*)-3-oxo-4-phenethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 6s.** Following *GP-J*, **6s** (7.4 mg, 30%) was isolated by FC (petroleum ether/EtOAc 9:1 to 7:3), as an oil after 16 h, starting from catalyst **3g** (2.7 mg, 0.003 mmol), allene **1o** (20 mg, 0.05 mmol, 1 eq), DMDO solution in toluene (0.6 mL, 0.14 mmol), EtOAc (0.5 mL) and furan **2a** (52 µL, 0.71 mmol, 13 eq). R$_f$= 0.63 (petroleum ether/EtOAc 7:3). dr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d$_6$*, 100 ºC) δ 7.32-7.27 (m, 2H, C$_{arom}$-H), 7.25-7.22 (m, 2H, C$_{arom}$-H), 7.21-7.17 (m, 1H, C$_{arom}$-H), 7.12 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.89 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-H), 6.10 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.19 (d, *J* = 4.4 Hz, 1H, H-2), 5.06-5.03 (m, 1H, H-1), 4.76-4.74 (m, 1H, H-5), 4.70 (d, *J* = 6.1 Hz, 1H, H-7), 3.78 (s, 3H, OCH$_3$), 2.69 (t, *J* = 7.9 Hz, 2H, CH$_2$Ph), 2.34-2.29 (m, 1H, H-4), 2.13-1.98 (m, 2H, C-4CH$_2$), 1.33 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-*d$_6$*, 100 ºC) δ 204.0 (C=O), 158.2 (C$_{arom}$), 154.1 (OC=O), 140.7 (C$_{arom}$), 133.4 (C$_{arom}$), 132.4 (C-6), 131.4 (C-7), 130.7 (C$_{arom}$-H), 127.8 (C$_{arom}$-H), 127.7 (C$_{arom}$-H), 125.4 (C$_{arom}$-H), 113.5 (C$_{arom}$-H), 80.6 (C-5), 79.8 (C-1), 79.1 (**C**(CH$_3$)$_3$), 68.8 (C-2), 54.9 (OCH$_3$), 53.6 (C-4), 32.3 (CH$_2$Ph), 31.2 (C-4**CH$_2$**), 27.5 (C(**CH$_3$**)$_3$). IR (CH$_2$Cl$_2$): 2986 (C-H st), 1701 (C=O st), 1240 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{27}$H$_{31}$NO$_5$Na]$^+$: 472.2100 [M+Na]$^+$; found: 472.2099. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{minor}$ = 11.5 min, τ$_{major}$ = 14.1 min (13% ee).
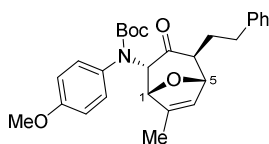
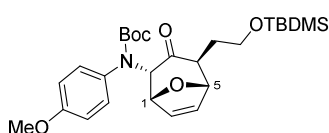**tert-Butyl (4-methoxyphenyl)((1R,2S,4S,5S)-7-methyl-3-oxo-4-phenethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 6t.** Following *GP-J*, **6t** (15.3 mg, 60%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (2.7 mg, 0.003 mmol), allene **1o** (20 mg, 0.05 mmol), DMDO solution in toluene (0.58 mL, 0.14 mmol), EtOAc (0.52 mL) and 3-methylfuran **2b** (10 μL, 0.11 mmol). R_f= 0.29 (petroleum ether/EtOAc 7:3). rr: 10:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.31-7.25 (m, 2H, C_{arom}-H), 7.25-7.21 (m, 2H, C_{arom}-H), 7.20-7.15 (m, 2H, C_{arom}-H), 6.91 (d, J = 8.6 Hz, 2H, C_{arom}-H), 5.94-5.90 (m, 1H, H-6), 4.75 (d, J = 4.8 Hz, 1H, H-1), 4.70-4.67 (m, 2H, H-5), 4.63 (bs, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 2.78-2.68 (m, 2H, CH$_2$Ph), 2.40-2.36 (m, 1H, H-4), 2.06-1.99 (m, 2H, C-4CH$_2$), 1.33 (s, 3H, CH$_3$), 1.29 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 203.7 (C=O), 157.9 (C_{arom}), 153.3 (OC=O), 142.6 (C-7), 141.0 (C_{arom}), 135.2 (C_{arom}), 129.1 (C_{arom}-H), 128.9 (C-6), 127.8 (C_{arom}-H), 127.7 (C_{arom}-H), 125.3 (C_{arom}-H), 113.9 (C_{arom}-H), 81.6 (C-1), 80.5 (C-5), 79.5 (**C**(CH$_3$)$_3$), 70.4 (C-2), 55.0 (OCH$_3$), 53.1 (C-4), 32.4 (CH$_2$Ph), 32.2 (C-4**C**H$_2$), 27.5 (CH$_3$), 27.4 (C(**C**H$_3$)$_3$). IR (CH$_2$Cl$_2$): 2980 (C-H st), 1698 (C=O st), 1257 (C-O-C st as), 1032 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{28}$H$_{33}$NO$_5$Na]$^+$: 486.2256 [M+Na]$^+$; found: 486.2255. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{minor} = 16.5 min, τ_{major} = 19.5 min (84% ee). [α]$_D^{20}$: +34.6 (c = 1.0, CH$_2$Cl$_2$).

tert-Butyl (4-methoxyphenyl)((1R,2S,4S,5S)-3-oxo-4-phenethyl-7-((triisopropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)carbamate, 6u. Following *GP-I*, **6u** (16.3 mg, 62%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (2.04 mg, 0.002 mmol), allene **1o** (75 mg, 0.2 mmol, 5 eq), DMDO solution in toluene (2.05 mL, 0.51 mmol, 12.5 eq), EtOAc (0.70 mL) and furan **2n** (11 μL, 0.04 mmol, 1 eq). Allene, DMDO and EtOAc were added in 5 portions (30 minutes per portion). R_f= 0.32 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.32-7.26 (m, 2H, C_{arom}-H), 7.23 (d, J = 7.5 Hz, 2H, C_{arom}-H), 7.21-7.13 (m, 3H, C_{arom}-H), 6.89 (d, J = 8.5 Hz, 2H, C_{arom}-H), 6.18-6.15 (m, 1H, H-6), 4.97 (d, J = 4.7 Hz, 1H, H-1), 4.82-4.73 (m, 2H, H-1 + H-5), 3.87 (d, J = 14.8 Hz, 1H, C**H**$_a$H$_b$), 3.77 (s, 3H, OCH$_3$), 3.47 (bs, 1H, CH$_a$**H**$_b$), 2.73 (t, J =

7.9 Hz, 2H, CH$_2$Ph), 2.44-2.38 (m, 1H, H-4), 2.09-2.01 (m, 2H, C-4CH$_2$), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.02 (s, 21H, 3×C**H**(C**H**$_3$)$_2$). ^{13}C NMR (125 MHz, DMSO-*d*$_6$, 100 °C) δ 203.5 (C=O), 157.9 (C$_{arom}$), 153.5 (OC=O), 147.4 (C-7), 140.9 (C$_{arom}$), 134.5 (C$_{arom}$), 129.3 (C$_{arom}$-H), 128.9 (C-6), 127.7 (C$_{arom}$-H), 125.3 (C$_{arom}$-H), 113.7 (C$_{arom}$-H), 80.3 (C-5), 79.5 (**C**(CH$_3$)$_3$), 79.2 (C-1), 70.1 (C-2), 59.1 (C-7**C**H$_2$), 54.7 (OCH$_3$), 53.2 (C-4), 32.3 (CH$_2$Ph), 32.1 (C-4**C**H$_2$), 27.4 (C(**C**H$_3$)$_3$), 17.2 (Si(CH(**C**H$_3$)$_2$)$_3$), 11.1 (Si**C**(CH$_3$)$_3$). IR (CH$_2$Cl$_2$): 2937 (C-H st), 1716 (C=O st), 1257 (C-O-C st as), 1030 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{37}$H$_{53}$NO$_6$SiNa]$^+$: 658.3540 [M+Na]$^+$; found: 658.3531. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 6.4 min, τ_{minor} = 7.9 min (82% ee). [α]$_D^{20}$: +37.3 (*c* = 0.48, CH$_2$Cl$_2$).

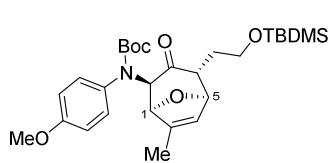*tert*-**Butyl   ((1*R*,2*S*,4*S*,5*S*)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6v**. Following *GP-J*, **6v** (13.3 mg, 37%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst **3g** (3.6 mg, 0.003 mmol), allene **1p** (30 mg, 0.07 mmol, 1 eq), DMDO solution in toluene (0.72 mL, 0.18 mmol), EtOAc (0.71 mL) and furan **2a** (70 µL, 0.93 mmol, 13 eq). dr: >20:1. ^{1}H NMR (500 MHz, DMSO-*d*$_6$, 100 °C) δ 7.11 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.89 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H), 6.11 (dd, *J* = 6.1, 1.8 Hz, 1H, H-6), 5.15 (d, *J* = 4.3 Hz, H-2), 5.05-5.01 (m, 1H, H-1), 4.76-4.74 (m, 1H, H-5), 4.74-4.70 (m, 1H, H-7), 3.78 (s, 3H, OCH$_3$), 3.75-3.64 (m, 2H, OCH$_2$), 2.44-2.38 (m, 1H, H-4), 1.98 (dt, *J* = 13.8, 6.8 Hz, 1H, C-4C**H**$_a$H$_b$), 1.88 (dt, *J* = 13.8, 6.8 Hz, 1H, C-4CH$_a$**H**$_b$), 1.33 (s, 9H, C(CH$_3$)$_3$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.07 (s, 3H, Si(CH$_3$)$_2$), 0.07 (s, 3H, Si(CH$_3$)$_2$). ^{13}C NMR (125 MHz, DMSO-*d*$_6$, 100 °C) δ 203.9 (C=O), 158.2 (C$_{arom}$), 154.1 (OC=O), 133.3 (C-6), 132.4 (C$_{arom}$), 131.5 (C-7), 130.6 (C$_{arom}$-H), 113.5 (C$_{arom}$-H), 80.6 (C-5), 79.7 (C-1), 79.1 (**C**(CH$_3$)$_3$), 68.7 (C-2), 59.9 (CH$_2$O), 54.9 (OCH$_3$), 51.1 (C-4), 32.6 (C-4**C**H$_2$), 27.4 (C(**C**H$_3$)$_3$), 25.3 (SiC(**C**H$_3$)$_3$), 17.3 (Si**C**(CH$_3$)$_3$), -5.9 (SiCH$_3$). IR (CH$_2$Cl$_2$): 2930 (C-H st), 1726 (C=O st), 1245 (C-O-C st as), 1049 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{27}$H$_{42}$NO$_6$Si]$^+$: 504.2781 [M+H]$^+$; found: 504.2784. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.00 mL/min; τ_{minor} = 19.8 min, τ_{major} = 33.1 min (10% ee).
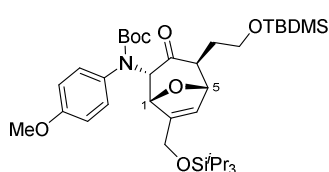
tert-Butyl   ((1S,2R,4R,5R)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-methyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6w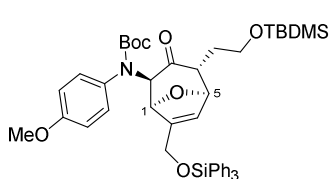. Following *GP-I*, **6w** (15.1 mg, 82%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2), as an oil after 16 h, starting from catalyst *ent-3g* (1.8 mg, 0.002 mmol), allene **1p** (75 mg, 0.18 mmol, 5 eq), DMDO solution in toluene (1.85 mL, 0.45 mmol, 12.5 eq), EtOAc (0.5 mL, 0.015M) and 3-methylfuran **2a** (3.2 µL, 0.04 mmol, 1 eq). Allene, DMDO and EtOAc were added in 5 portions (30 minutes per portion). R_f= 0.25 (petroleum ether/EtOAc 9:1). rr: 15:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 5.94-5.90 (m, 1H, H-6), 4.74 (d, *J* = 4.9 Hz, 1H, H-1), 4.69-4.64 (m, 1H, H-5), 4.62-4.54 (m, 1H, H-2), 3.77 (s, 3H, OCH$_3$), 3.75-3.69 (m, 2H, CH$_2$**CH$_2$**OTBS), 2.49-2.46 (m, 1H, H-4), 1.93-1.87 (m, 2H, **CH$_2$**CH$_2$OTBS), 1.30 (s, 9H, 3×CH$_3$), 0.89 (s, 9H, 3× CH$_3$), 0.06 (s, 6H, 2× CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.9 (C=O), 157.8 (C_{arom}), 146.0 (OC=O), 142.6 (C-7), 136.9 (C_{arom}), 129.1 (C_{arom}-H), 128.9 (C-6), 113.9 (C_{arom}-H), 81.6 (C-1), 80.5 (C-5), 79.5 (**C**(CH$_3$)$_3$), 70.4 (C-2), 58.1 (CH$_2$**CH$_2$**OTBS), 55.0 (OCH$_3$), 50.8 (C-4), 34.0 (**CH$_2$**CH$_2$OTBS), 27.4 (C(**CH$_3$**)$_3$), 25.3 (SiC(**CH$_3$**)$_3$), 17.5 (Si**C**(CH$_3$)$_3$), 17.2 (CH$_3$), -3.8 (SiCH$_3$). IR (CH$_2$Cl$_2$): 3009 (C-H st), 1698 (C=O st), 1242 (C-O-C st as), 1038 (C-O-C st sy) cm^{-1}. HRMS: Calculated for [C$_{28}$H$_{44}$NO$_6$Si]$^+$: 518.2938 [M+H]$^+$; found: 518.2945. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 8.0 min, τ_{minor} = 10.7 min (75% ee). [α]$_D^{20}$: -33.9 (*c* = 1.2, CH$_2$Cl$_2$).

tert-Butyl   ((1R,2S,4S,5S)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-oxo-7-(((tripropylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6x. Following *GP-I*, **6x** (8.4 mg, 34%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2) as an oil after 16 h, starting from catalyst **3g** (1.8 mg, 0.002 mmol), allene **1p** (75 mg, 0.18 mmol, 5 eq), DMDO solution in toluene (1.80 mL, 0.45 mmol, 12.5 eq), EtOAc (0.60 mL, 0.015M) and furan **2n** (9.2 mg, 0.04 mmol, 1 eq). Allene, DMDO and EtOAc were added in 5 portions (30 minutes per portion). R_f= 0.43 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR

(500 MHz, DMSO-d_6, 100 ºC) δ 7.16 (d, J = 8.6 Hz, 2H, C_{arom}-H), 6.89 (d, J = 8.6 Hz, 2H, C_{arom}-H), 6.18-6.14 (m, 1H, H-6), 4.96 (d, J = 4.8 Hz, 1H, H-1), 4.78-4.67 (m, 2H, H-5 + H-2), 3.91 (bs, 1H, C$\mathbf{H_a}$H$_b$), 3.77 (s, 3H, OCH$_3$), 3.73 (q, J = 6.3 Hz, 2H, CH$_2$OTBDMS), 3.53 (bs, 1H, CH$_a$$\mathbf{H_b}$), 2.53-2.50 (m, 1H, H-4), 1.98-1.86 (m, 2H, C-4CH$_2$), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.02 (s, 21H, Si(C$\mathbf{H}$(CH$_3$)$_2$)$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.4 (C=O), 157.9 (C_{arom}), 153.4 (OC=O), 147.4 (C-7), 134.6 (C_{arom}), 129.3 (C_{arom}-H), 128.7 (C-6), 113.7 (C_{arom}-H), 80.4 (C-5), 79.5 ($\mathbf{C}$(CH$_3$)$_3$), 79.0 (C-1), 70.0 (C-2), 59.9 (CH$_2$OTBDMS), 59.2 (C-7$\mathbf{C}$H$_2$), 54.8 (OCH$_3$), 50.6 (C-4), 33.8 (C-4$\mathbf{C}$H$_2$), 27.3 (C($\mathbf{C}$H$_3$)$_3$), 25.3 (SiC($\mathbf{C}$H$_3$)$_3$), 17.3 (Si$\mathbf{C}$(CH$_3$)$_3$), 17.2 (Si(CH($\mathbf{C}$H$_3$)$_2$)$_3$), 11.1 (Si($\mathbf{C}$H(CH$_3$)$_2$)$_3$), -5.9 (Si($\mathbf{C}$H$_3$)$_2$). IR (CH$_2$Cl$_2$): 2922 (C-H st), 1716 (C=O st), cm^{-1}. HRMS: Calculated for [C$_{37}$H$_{64}$NO$_7$Si$_2$]$^+$: 690.4221 [M+H]$^+$; found: 690.4222. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ$_{minor}$ = 4.3 min, τ$_{major}$ = 4.9 min (83% ee). [α]$_D^{20}$: -56.1 (c = 0.38, CH$_2$Cl$_2$).

tert-**Butyl** **((1*S*,2*R*,4*R*,5*R*)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-oxo-7-((((triphenylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-2-yl)(4-methoxyphenyl)carbamate, 6y.** Following *GP-I*, **6y** (13.7 mg, 73%) was isolated by FC (petroleum ether/EtOAc 19:1 to 8:2) as an oil after 16 h, starting from catalyst *ent*-**3b** (1.2 mg, 0.001 mmol), allene **1p** (50 mg, 0.12 mmol, 5 eq), DMDO solution in toluene (1.25 mL, 0.30 mmol, 12.5 eq), EtOAc (0.33 mL,) and furan **2m** (8.5 mg, 0.02 mmol, 1 eq). Allene, DMDO and EtOAc were added in 5 portions (30 minutes per portion). R$_f$= 0.35 (petroleum ether/EtOAc 9:1). rr: >20:1. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ºC) δ 7.55-7.35 (m, 15H, C_{arom}-H), 7.05 (d, J = 8.8 Hz, 2H, C_{arom}-H), 6.74 (d, J = 8.8 Hz, 2H, C_{arom}-H), 6.21-6.18 (m, 1H, H-6), 4.97 (d, J = 4.8 Hz, H-1), 4.76-4.72 (m, 1H, H-5), 4.62-4.53 (m, 1H, H-2), 4.03 (d, J = 14.2 Hz, C$\mathbf{H_a}$H$_b$), 3.91-3.81 (m, 1H, CH$_a$$\mathbf{H_b}$), 3.78-3.68 (m, 2H, CH$_2$OTBDMS), 3.67 (s, 3H, OCH$_3$), 2.52 (bs, 1H, H-4), 1.97-1.85 (m, 2H, C-4CH$_2$), 1.21 (s, 9H, C(CH$_3$)$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$). ^{13}C NMR (125 MHz, DMSO-d_6, 100 ºC) δ 203.2 (C=O), 157.7 (C_{arom}), 153.2 (OC=O), 146.3 (C-7), 136.3 (C_{arom}), 134.3 (C_{arom}-H), 134.1 (C_{arom}-H), 134.0 (C_{arom}-H), 133.2 (C_{arom}), 129.7 (C-6), 129.6 (C_{arom}-H), 129.5 (C_{arom}), 129.0 (C_{arom}), 128.9 (C_{arom}-H), 127.4 (C_{arom}-H), 127.3 (C_{arom}-H), 127.1

(C$_{arom}$-H), 113.7 (C$_{arom}$-H), 80.4 (C-5), 79.5 (**C**(CH$_3$)$_3$), 78.8 (C-1), 70.2 (C-2), 59.9 (CH$_2$OTBDMS), 59.8 (C-7**C**H$_2$), 54.8 (OCH$_3$), 50.4 (C-4), 33.9 (C-4**C**H$_2$), 27.3 (C(**C**H$_3$)$_3$), 25.3 (SiC(**C**H$_3$)$_3$), 17.3 (Si**C**(CH$_3$)$_3$), -5.9 (SiCH$_3$). IR (CH$_2$Cl$_2$): 2930 (C-H st), 1698 (C=O st), cm^{-1}. HRMS: Calculated for [C$_{46}$H$_{58}$NO$_7$Si$_2$]$^+$: 792.3752 [M+H]$^+$; found: 792.3752. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.00 mL/min; τ_{major} = 6.0 min, τ_{minor} = 7.5 min (86% ee). [α]$_D^{20}$: -48.9 (*c* = 0.98, CH$_2$Cl$_2$).

3. ALLYLATION OF IMINES USING ENANTIOPURE BORONATES

3.1 Synthesis of starting materials

SI14

3,4-Diethylhexane-3,4-diol (SI14): Diol **SI14** was prepared following a procedure described in a PhD dissertation and NMR spectral information are consistent with given data.[46] A round bottom flask was charged with magnesium powder (9.7g, 400 mmol, 8 eq) under Ar atmosphere. After that, SmI_2 0.1M solution in THF (50 mL, 5 mmol, 10 mol%) and TMSCl (3.15 mL, 25 mmol, 0.5 eq) were added at room temperature. A mixture of 3-pentanone (5.4 mL, 50 mmol, 1 eq) and TMSCl (6.3 mL, 50 mmol, 1 eq) was added dropwise to the reaction at the rate to maintain the blue colour. After 48h the reactions turned in grey colour and aqueous HCl 1M was added dropwise and extracted with Et_2O (3×20 mL), dried over Na_2SO_4, filtered and solvent was removed under reduced pressure. Residue was purified by FC (petroleum ether to petroleum ether/EtOAc 8:2) to afford a colorless oil (4 g, 22.9 mmol, 46%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 2H, 2×OH), 1.61 (q, J = 7.5, 8H, 4×CH_2), 0.94 (t, J = 7.5 Hz, 12H, 4×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.0 (C), 27.5 (CH_2), 9.2 (CH_3).

Allylboronates (±)-7a and (±)-7b

SI15a-b

(±)-7a R= Me
(±)-7b R= Et

General Procedure K (GP-K): (±)-7a and **(±)-7b** were synthesized following a procedure described in the literature with slight modifications.[47] A dried round bottom flask was charged with the corresponding diol (19.3 mmol, 1 eq) in dry THF (5.2 mL, 3.7M). The solution was cooled to 0ºC and BH_3·DMS 2M in THF (9.65 mL, 1 eq) was added dropwise to the mixture.

46   Incerti-Pradillos, Celia A. Asymmetric allylation of carbonyl compounds: kinetic resolution of sec-allylboronates and total synthesis of natural products, Loughborough University, 2014.

47   Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5338.

Then the reaction was stirred at 0ºC for 30 min and then at room temperature for 90 min. The resulting borane **SI15a-b** (1.3M in THF) was used in the next step in a without further purification when required. A two-necked round bottom flask fitted with a condenser was charged with magnesium powder (23.2 mmol, 1.2 eq). Dry THF (9.3 mL, 0.8M) was added to the flask followed by borane solution **SI15a-b** (1.3 M in THF) *via* cannula with vigorous stirring. Crotyl bromide (19.3 mmol, 1 eq) was added dropwise at room temperature to the solution (exotermic!) and let stirred for 30 minutes. Afterwards, crotyl bromide (19.3 mmol, 1 eq) was added to the reaction and the mixture was stirred for 90 minutes. The reaction was quenched carefully with aqueous HCl (0.1M) until the excess of magnesium was fully consumed. The mixture was extracted with EtOAc (3×15 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The crude mixture was purified by FC on silica gel (petroleum ether/CH_2Cl_2 10:0 to 5:5).
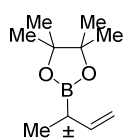
(±)-2-(But-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (±)-7a. Following *GP-K*, pinacol (4 g, 33.8 mmol, 1 eq) was used as starting material obtaining a colorless oil (4.3 g, 23.6 mmol, 70%) after purification by FC on silica gel (petroleum ether to 1:1 petroleum ether/CH_2Cl_2). R_f= 0.48 (petroleum ether/CH_2Cl_2 4.2:0.8). NMR spectral data are consistent with literature values.[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01-5.87 (m, 1H, **CH**=CH₂), 5.02-4.89 (m, 2H, CH=C**H₂**), 1.90 (t, *J* = 7.4 Hz, 1H, BC**H**), 1.24 (s, 12H, 4×CH₃), 1.10 (d, *J* = 7.3 Hz, 3H, CHC**H₃**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9 (**CH**=CH₂), 111.9 (CH=**CH₂**), 83.2 (**C**(CH₃)₂), 27.4 (CH₃), 27.6 (CH₃), 14.1 (CH₃). HC-B resonance was not observed due to quadrupolar effect of Boron.
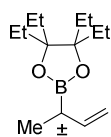
(±)-2-(But-3-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane, (±)-7b. (±)-7b was synthesized following *GP-K* using diol **SI14** (3.4 g, 19.3 mmol, 1 eq) as starting material obtaining a colorless oil (2.9 g, 12.2 mmol, 65%) after purification by FC on silica gel (petroleum ether to 1:1 petroleum ether:CH_2Cl_2). R_f= 0.40 (petroleum ether/CH_2Cl_2 4.8:0.2). NMR spectral data are consistent with literature values.[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H, **CH**=CH₂), 5.00-4.86 (m, 2H, CH=C**H₂**), 1.90 (t, *J* = 7.3 Hz, 1H, BC**H**), 1.71-1.58 (m, 8H, 4×CH₂), 1.10 (d, *J* = 7.3 Hz, 3H, CHC**H₃**), 0.90 (t, *J* = 7.4 Hz, 12H, 4×CH₃). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (**CH**=CH₂), 111.6 (CH=**CH₂**),

88.2 (**C**(CH$_2$CH$_3$)$_2$), 26.50 (CH$_2$), 26.44 (CH$_2$), 14.4 (CH$_3$), 8.93 (CH$_3$), 8.87 (CH$_3$). HC-B resonance was not observed due to quadrupolar effect of Boron.

3.2 Kinetic Resolution of racemic allylboronate (±)-7b
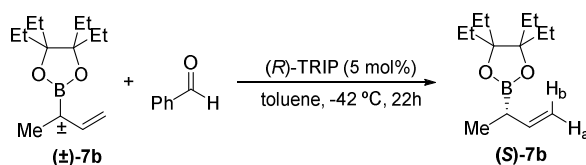
General Procedure for the Kinetic Resolution: A round bottom flask was charged with (*R*)-TRIP (40.5 mg, 0.05 mmol, 5 mol%) in dry toluene (1.56 mL, 0.03M). The reaction was cooled to -42 ºC and freshly distilled benzaldehyde (0.1 mL, 1.05 mmol, 1 eq) in dry toluene (1.54 mL, 0.68M) and boronate (±)-**7b** (500 mg, 2.1 mmol, 2 eq) in toluene (1.25 mL, 1.68M) was sequentially added dropwise to the mixture. After 22h, the reaction was quenched with NaHCO$_3$ aq. sat. (20 mL) and stirred at room temperature for 1h. The mixture was extracted with EtOAc (3×20 mL), dried over Na$_2$SO$_4$ and filtered. After the removal of the solvent under reduced pressure the oily residue was purified by FC on silica gel (petroleum ether to petroleum ether/CH$_2$Cl$_2$ 2:8) to afford (*S*)-**7b** (91%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.97 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H, **H**C=CH$_2$), 4.96 (ddd, *J* = 17.3, 1.9, 1.8 Hz, 1H, H$_b$), 4.90 (ddd, *J* = 10.3, 1.7, 1.6 Hz, 1H, H$_a$), 1.92 (t, *J* = 7.3 Hz, 1H, BCH), 1.72-1.59 (m, 8H, 4×CH$_2$), 1.10 (d, *J* = 7.3 Hz, 3H, CH$_3$), 0.90 (t, *J* = 7.5 Hz, 12H, 4×CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.6 (**C**H=CH$_2$), 111.6 (CH=**C**H$_2$), 88.3 (**C**(CH$_2$CH$_3$)$_2$), 26.51 (CH$_2$), 26.45 (CH$_2$), 14.4 (CH$_3$), 8.94 (CH$_3$), 8.89 (CH$_3$). HC-B resonance was not observed due to quadrupolar effect of Boron. [α]$_D$^{rt}: -4.7 (*c* = 0.4, CH$_2$Cl$_2$).

The enantiomeric excess of the enantiopure boronate (*S*)-**7b** was checked by HPLC analysis on chiral stationary phase at the corresponding alcohol **8** reproducing a reaction developed by Hoffmann.[48]

48   Hoffmann, R. W. *Pure & Appl. Chem.* **1988**, *60*, 123.
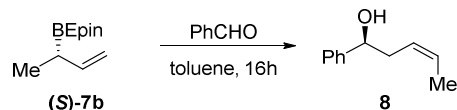
(**S**)-**7b** (25 mg, 0.11 mmol, 1 eq) was placed in a vial equipped with a stirring bar and toluene (0.5 mL, 0.22M) was added. After that, benzaldehyde (12 µL, 0.12 mmol, 1.1 eq) was added. After 16h, toluene was evaporated under reduced pressure and it was purified by FC (petroleum ether to petroleum ether/CH_2Cl_2 4:6) obtaining oily alcohol **8** as a mixture of diastereoisomers (12.7 mg, 0.08 mmol, 72%). *E*:*Z* ratio 1:5.3. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.42-7.23 (m, 5H, C$_{arom}$-H), 5.73-5.54 (m, 1H, **H**C=CH), 5.51-5.37 (m, 1H, HC=C**H**), 4.77-4.64(m, 1H, **H**COH), 2.65-2.33 (m, 2H, CH$_2$), 2.08* (bs, 1H, OH), 2.04 (bs, 1H, OH), 1.73-1.66* (m, 3H, CH$_3$), 1.66-1.56 (m, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 144.2 (C$_{arom}$), 129.6* (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 127.8 (**H**C=CH), 127.6 (HC=**C**H), 127.6* (**H**C=CH), 126.9* (HC=**C**H), 126.0 (C$_{arom}$-H), 125.9* (C$_{arom}$-H), 125.8 (C$_{arom}$-H), 74.0, 73.6* (HCOH), 43.0* (CH$_2$), 37.1 (CH$_2$), 18.2* (CH$_3$), 13.1 (CH$_3$). The ee was determined by HPLC analysis using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min at 21 ℃; *Z* isomer τ_{minor} = 14.28 min, τ_{major} = 16.79 min (99% ee); *E* isomer τ_{major} = 12.18 min, τ_{minor} = 15.22 min (99% ee).

3.3 Synthesis of primary amines 9a-l
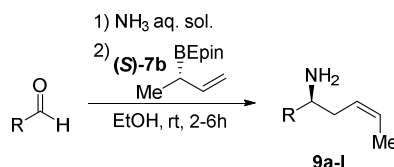
General Procedure for the Synthesis of Primary Amines (GP-L): Aldehyde (0.14 mmol, 1 eq) was placed in a vial equipped with a stirring bar. EtOH (0.28 mL, 0.5M) and aqueous ammonia (4.2 mmol, ~30 eq, 32% wt.) were added and the mixture was stirred for 1 h. **(*S*)-7b** (0.17 mmol, 1.2 eq) was added to the solution and the vial was rinsed with EtOH (0.14 mL). The mixture was stirred at room temperature for 2-6 h, until white precipitate appeared. The cap of the vial was removed to vaporize most of ammonia and HCl (5M aqueous, 2 mL) was added to acidify the solution (pH=1). Traces of alcohol were extracted with Et_2O (3×5 mL) and organic layer was washed with HCl (5M aqueous, 3×5 mL). Aqueous layer was alkalized with NaOH (6M aqueous, until pH=12-14) and extracted with CH_2Cl_2 (3×5 mL). Combined dichloromethane layers were washed with water, dried over anhydrous Na_2SO_4 and filtered. The removal of the solvent gave an oily residue that was purified by FC on silica gel with $CHCl_3$:NH_3 aq. (99:1) to $CHCl_3$:MeOH:NH_3 aq. (98:1:1) affording primary amine **9a-l**. TLCs were developed in PMA.

The racemic standards for HPLC analysis were prepared using boronate **(±)-7a**.
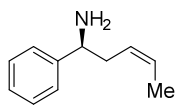
(*S,Z*)-1-Phenylpent-3-en-1-amine, 9a. Following *GP-L*, **9a** (14.9 mg, 0.09 mmol, 76%) was isolated by FC as pure oil after 2 h, starting from benzaldehyde (12.4 μL, 0.12 mmol), aqueous ammonia (0.22 mL, 3.67 mmol) in EtOH (0.24 mL) and adding boronate **(*S*)-7b** (35 mg, 0.15 mmol) diluted in EtOH (0.12 mL). *E:Z* ratio 1:8.3 (measured on the crude by quantitative ^{13}C-NMR spectra). R_f= 0.43 (EtOAc). ^{1}H NMR (300 MHz, CD_3OD) δ (*denotes minor isomer) 7.38-7.18 (m, 5H, C_{arom}-H), 5.59-5.44 (m, 1H, **H**C=CH), 5.39-5.25 (m, 1H, HC=C**H**), 3.86 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 2.59-2.30 (m, 2H, CH$_2$), 1.62* (dd, *J* =6.2, 1.1 Hz, 3H, CH$_3$), 1.55 (dd, *J* = 6.9, 0.7 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (*denotes minor isomer) 146.4 (C_{arom}), 129.4 (C_{arom}-H), 129.2* (HC=CH), 128.8* (**H**C=**C**H), 128.0 (HC=**C**H), 127.7 (C_{arom}-H), 127.6 (C_{arom}-H), 127.6* (C_{arom}-

H), 127.3 (H**C**=CH), 57.2 (H**C**NH$_2$), 57.1* (H**C**NH$_2$), 43.5* (**C**H$_2$), 37.6 (**C**H$_2$), 18.1* (**C**H$_3$), 13.0 (**C**H$_3$). IR (CH$_2$Cl$_2$): 3019, 2922 (NH$_2$ st), 2780 (C-H st), 1597 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 106 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{11}$H$_{16}$N]$^+$: 162.1283 [M+H]$^+$; found: 162.1280.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10a**.
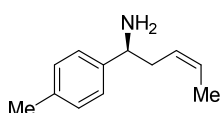
(*S*,*Z*)-1-(*p*-Tolyl)pent-3-en-1-amine, 9b. Following *GP-L*, **9b** (15.2 mg, 0.09 mmol, 62%) was isolated by FC as pure oil after 3 h, starting from *p*-tolualdehyde (16.5 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E*:*Z* ratio 1:6.0. R$_f$= 0.62 (CHCl$_3$:MeOH 5%). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.23-7.16 (d, *J* = 8.1 Hz, 2H. C$_{arom}$-H), 7.12 (d, *J* = 8.1 Hz, 2H, C$_{arom}$-H), 5.57-5.43 (m, 1H, HC=C**H**), 5.38-5.23 (m, 1H, **H**C=CH), 3.82 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 2.54-2.32 (m, 2H, CH$_2$), 2.30 (s, 3H, C$_{arom}$-CH$_3$), 1.62* (dd, *J* = 6.3, 1.3 Hz, 3H, CH$_3$), 1.55 (dd, *J* = 6.7, 0.7 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 143.3 (C$_{arom}$), 137.6 (**C**$_{arom}$-CH$_3$), 130.0 (C$_{arom}$-H), 129.1* (HC=**C**H), 128.9* (H**C**=CH), 127.8 (HC=**C**H), 127.51 (C$_{arom}$-H), 127.46* (C$_{arom}$-H), 127.2 (H**C**=CH), 56.9 (H**C**NH$_2$), 56.7* (H**C**NH$_2$), 43.5* (**C**H$_2$), 37.6 (**C**H$_2$), 21.1 (C$_{arom}$-**C**H$_3$), 18.1* (**C**H$_3$), 13.0 (**C**H$_3$). IR (CH$_2$Cl$_2$): 3019, 2922 (NH$_2$ st), 2831 (C-H st), 1512 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 120 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{12}$H$_{15}$]$^+$: 159.1171 [M-NH$_3$+H]$^+$; found: 159.1174.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10b**.
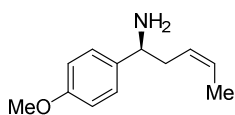
(*S*,*Z*)-1-(4-Methoxyphenyl)pent-3-en-1-amine, 9c. Following *GP-L*, **9c** (19.8 mg, 0.10 mmol, 74%) was isolated by FC as pure oil after 2 h, starting from *p*-anisaldehyde (17.0 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E*:*Z* ratio 1:5.7. R$_f$= 0.32 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.28-7.20 (d, *J* =8.7 Hz, 2H, C$_{arom}$-H), 6.90-6.83 (d, *J* =8.7 Hz, 2H, C$_{arom}$-H), 5.57-5.43 (m, 1H, HC=C**H**), 5.39-5.23 (m, 1H, **H**C=CH), 3.82 (t, *J* = 7.0

Hz, 1H, **H**CNH$_2$), 3.77 (s, 3H, OCH$_3$), 2.54-2.29 (m, 2H, CH$_2$), 1.62* (dd, *J* = 6.3, 1.3 Hz, 3H, CH$_3$), 1.55 (dd, *J* = 6.8, 0.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 158.64 (**C**$_{arom}$-OCH$_3$), 158.60* (**C**$_{arom}$-OCH$_3$), 138.4 (C$_{arom}$), 128.3* (H**C**=CH), 128.1* (H**C**=CH), 127.5 (C$_{arom}$-H), 127.2 (H**C**=CH), 126.6 (H**C**=CH), 113.8 (C$_{arom}$-H), 55.5* (OCH$_3$), 55.4 (OCH$_3$), 55.2 (HCNH$_2$), 43.2* (CH$_2$), 37.3 (CH$_2$), 18.2* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3011, 2937 (NH$_2$ st), 2932 (C-H st), 1609, 1243 (C-O-C st), 1609 (NH$_2$ δ), 1242 (C-O-C st as), 1034 (C-OC st sy) cm^{-1}. MS (EI) m/z (%): 136 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{12}$H$_{15}$O]$^+$: 175.1123 [M-NH$_3$+H]$^+$; found: 175.1127.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10c**.
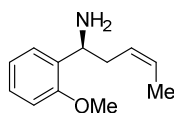
(S,Z)-1-(2-Methoxyphenyl)pent-3-en-1-amine, 9d. Following *GP-L*, **9d** (16.4 mg, 0.09 mmol, 61%) was isolated by FC as pure oil after 6 h, starting from *o*-anisaldehyde (19.4 mg, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate **(S)-7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E*:*Z* ratio 1:9.0. R$_f$= 0.14 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.29-7.17 (m, 2H, C$_{arom}$-H), 6.99-6.87 (m, 2H, C$_{arom}$-H), 5.57-5.43 (m, 1H, HC=C**H**), 5.40-5.28 (m, 1H, **H**C=CH), 4.15 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 3.85 (s, 3H, OCH$_3$), 2.60-2.26 (m, 2H, CH$_2$), 1.62* (dd, *J* = 6.2, 1.3 Hz, 3H, CH$_3$), 1.55 (dd, *J* = 6.7, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 158.3 (C$_{arom}$-O), 133.8 (C$_{arom}$), 129.0 (C$_{arom}$-H), 128.14 (H**C**=CH), 128.11 (H**C**=CH), 127.0 (C$_{arom}$-H), 121.5 (C$_{arom}$-H), 111.7 (C$_{arom}$-H), 55.8 (OCH$_3$), 52.2 (HCNH$_2$), 51.7* (HCNH$_2$), 41.5* (CH$_2$), 35.6 (CH$_2$), 18.2* (CH$_3$), 13.0 (CH$_3$). IR (CH$_2$Cl$_2$): 3012, 2919 (NH$_2$ st), 2818 (C-H st), 1601, 1583 (NH$_2$ δ), 1235 (C-O-C st as), 1051 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 136 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{12}$H$_{17}$NONa]$^+$: 214.1208 [M+Na]$^+$; found: 214.1208.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10d**.
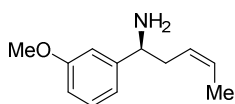
(S,Z)-1-(3-Methoxyphenyl)pent-3-en-1-amine, 9e. Following *GP-L*, **9e** (15.7 mg, 0.08 mmol, 59%) was isolated by FC as pure oil after 6 h, starting from *m*-anisaldehyde (17.1 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate **(S)-7b** (40 mg, 0.168 mmol) diluted in EtOH (0.14 mL). *E:Z* ratio 1:5.6. R_f= 0.32 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.22 (t, *J* = 7.7 Hz, 1H, C$_{arom}$-H), 6.94-6.85 (m, 2H, C$_{arom}$-H), 6.82-6.76 (m, 1H, C$_{arom}$-H), 5.59-5.44 (m, 1H, HC=C**H**), 5.40-5.25 (m, 1H, **H**C=CH), 3.84 (t, *J* = 7.0 Hz, 1H, **H**CNH$_2$), 3.79 (s, 3H, OCH$_3$), 2.56-2.30 (m, 2H, CH$_2$), 1.63* (dd, *J* = 6.2, 1.2 Hz, 3H, CH$_3$), 1.55 (dd, *J* = 6.7, 0.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 161.3 (C$_{arom}$-O), 148.0 (C$_{arom}$), 130.3 (C$_{arom}$-H), 129.2* (**H**C=CH), 128.8* (HC=**CH**), 127.7 (H**C**=CH), 127.3 (HC=**C**H), 119.93 (C$_{arom}$-H), 119.86* (C$_{arom}$-H), 113.4 (C$_{arom}$-H), 113.22 (C$_{arom}$-H), 113.16* (C$_{arom}$-H), 57.2 (OCH$_3$), 57.0* (OCH$_3$), 55.6 (HCNH$_2$), 43.5* (CH$_2$), 37.5 (CH$_2$), 18.1 (CH$_3$), 13.0* (CH$_3$). IR (CH$_2$Cl$_2$): 3012, 2940 (NH$_2$ st), 2840 (C-H st), 1601, 1583 (NH$_2$ δ), 1260 (C-O-C st as), 1049 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 136 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{12}$H$_{18}$NO]$^+$: 192.1388 [M+H]$^+$; found: 192.1392.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10e**.
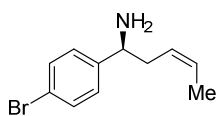
(S,Z)-1-(4-Bromophenyl)pent-3-en-1-amine, 9f. Following *GP-L,* **9f** (24.5 mg, 0.10 mmol, 73%) was isolated by FC as pure oil after 3 h, starting from 4-bromobenzaldehyde (25.9 mg, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate **(S)-7b** (40 mg, 0.17 mmol) diluted in EtOH (0.12 mL). *E:Z* ratio 1:5.7. R_f= 0.34 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.49-7.41 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 7.30-7.21 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 5.59-5.42 (m, 1H, HC=C**H**), 5.38-5.23 (m, 1H, **H**C=CH), 3.86 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 2.54-2.28 (m, 2H, CH$_2$), 1.62* (dd, *J* = 6.3, 1.4 Hz, 3H, CH$_3$), 1.53 (dd, *J* = 6.8, 1.0 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 145.7 (C$_{arom}$), 132.4 (C$_{arom}$-H), 129.7 (C$_{arom}$-H), 129.6* (C$_{arom}$-H), 129.5* (HC=**CH**), 128.4* (**H**C=CH), 127.6 (H**C**=CH), 127.4 (HC=**C**H), 121.53 (C$_{arom}$-Br), 121.51* (C$_{arom}$-Br), 56.6 (HCNH$_2$), 56.5* (HCNH$_2$), 43.4* (CH$_2$), 37.5 (CH$_2$), 18.1* (CH$_3$), 13.0 (CH$_3$). IR (CH$_2$Cl$_2$): 3019, 2919 (NH$_2$ st),

2850 (C-H st), 1590 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 184 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{11}$H$_{15}$NBr]$^+$: 240.0388 [M+H]$^+$; found: 240.0394.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10f**.
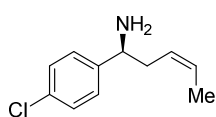
(S,Z)-1-(4-Chlorophenyl)pent-3-en-1-amine, 9g. Following *GP-L*, **9g** (22.5 mg, 0.11 mmol, 82%) was isolated by FC as pure oil after 5 h, starting from 4-chlorobenzaldehyde (20 mg, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E:Z* ratio 1:5.5. R$_f$= 0.51 (petroleum ether/EtOAc 2:8). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.36-7.27 (s, 4H. C$_{arom}$-H), 5.60-5.42 (m, 1H, HC=C**H**), 5.39-5.24 (m, 1H, **H**C=CH), 3.87 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 2.55-2.29 (m, 2H, CH$_2$), 1.62* (dd, *J* = 6.2, 1.3 Hz, 3H, CH$_3$), 1.53 (dd, *J* = 6.8, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 145.3 (C$_{arom}$), 133.6 (C$_{arom}$-Cl), 129.5* (HC=**C**H), 129.4 (C$_{arom}$-H), 129.3 (C$_{arom}$-H), 129.3* (C$_{arom}$-H), 128.5* (**H**C=CH), 127.5 (HC=**C**H), 127.4 (**H**C=CH), 56.6 (HCNH$_2$), 56.5* (HCNH$_2$), 43.4* (CH$_2$), 37.5 (CH$_2$), 18.1* (CH$_3$), 13.0 (CH$_3$). IR (CH$_2$Cl$_2$): 3012, 2926 (NH$_2$ st), 2851 (C-H st), 1591 (NH$_2$ δ), 1088 (C-Cl st) cm^{-1}. MS (EI) m/z (%): 140 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{11}$H$_{15}$NCl]$^+$: 196.0893 [M+H]$^+$; found: 196.0895.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10g**.
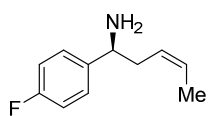
(S,Z)-1-(4-Fluorophenyl)pent-3-en-1-amine, 9h. Following *GP-L*, **9h** (15.2 mg, 0.08 mmol, 61%) was isolated by FC as pure oil after 5 h, starting from 4-fluorobenzaldehyde (15.1 μL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E:Z* ratio 1:5.4. R$_f$= 0.33 (petroleum ether/EtOAc 2:8). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.39-7.28 (m, 2H, C$_{arom}$-H), 7.08-6.97 (m, 2H, C$_{arom}$-H), 5.58-5.43 (m, 1H, HC=C**H**), 5.39-5.23 (m, 1H, **H**C=CH), 3.88 (t, *J* = 6.9 Hz, 1H, **H**CNH$_2$), 2.54-2.28 (m, 2H, CH$_2$), 1.62* (dd, *J* = 6.3, 1.4 Hz, 3H, CH$_3$), 1.53 (dd, *J* = 6.8, 1.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 163.3 (d, $^1J_{C-F}$ = 243.3 Hz,

C_{arom}-F), 142.4 (d, $^4J_{C-F}$ = 3.3 Hz, **C**$_{arom}$-C), 129.4 (d, $^3J_{C-F}$ = 7.9 Hz, C_{arom}-H), 129.4* (d, $^3J_{C-F}$ = 8.0 Hz, C_{arom}-H), 128.6* (HC=**C**H), 127.5 (HC=**C**H), 127.4 (**H**C=CH), 115.9 (d, $^2J_{C-F}$ = 21.4 Hz, C_{arom}-H), 56.5 (**H**CNH$_2$), 56.4* (**H**CNH$_2$), 43.6* (CH$_2$), 37.6 (CH$_2$), 18.1* (CH$_3$), 13.0 (CH$_3$). IR (CH$_2$Cl$_2$): 3010, 2985 (NH$_2$ st), 2930 (C-H st), 1217 (C-F st) cm^{-1}. MS (EI) m/z (%): 124 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{11}$H$_{15}$NF]$^+$: 180.1189 [M+H]$^+$; found: 180.1188.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10h**.
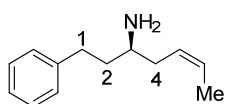
(*R*,*Z*)-1-Phenylhept-5-en-3-amine, 9i. Following *GP-L,* **9i** (19.3 mg, 0.1 mmol, 73%) was isolated by FC as pure oil after 4 h, starting from hydrocinnamaldehyde (18.8 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E*:*Z* ratio nd. R$_f$= 0.23 (petroleum ether/EtOAc 2:8). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 7.29-7.10 (m, 5H, C$_{arom}$-H), 5.68-5.50 (m, 1H, HC=C**H**), 5.49-5.35 (m, 1H, **H**C=CH), 2.83-2.55 (m, 3H, 2×H-1+H-3), 2.29-2.08 (m, 2H, H-4ab), 2.07-1.94* (m, 2H, H-4ab), 1.84-1.52 (m, 5H, 2×H-2+CH$_3$). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 143.5 (C$_{arom}$), 129.39 (C$_{arom}$-H), 129.35 (C$_{arom}$-H), 129.2* (HC=**C**H), 128.8* (**H**C=CH), 127.9 (HC=**C**H), 127.4 (**H**C=CH), 126.8 (C$_{arom}$-H), 51.9 (C-3), 51.5* (C-3), 41.2* (C-2), 39.8 (C-2), 35.3 (C-4), 33.5 (C-1), 33.4* (C-1), 18.2* (CH$_3$), 13,2 (CH$_3$). IR (CH$_2$Cl$_2$): 3026, 2919 (NH$_2$ st), 2857 (C-H st), 1605, 1583 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 134 (81, [M$^+$-C$_4$H$_7$]), 91 (100, [M$^+$-C$_6$H$_{12}$N]). HRMS: Calculated for [C$_{13}$H$_{20}$N]$^+$: 190.1596 [M+H]$^+$; found: 190.1599.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10i**.
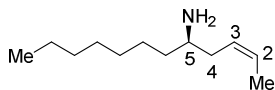
(*R*,*Z*)-Dodec-2-en-5-amine, 9j. Following *GP-L*, **9j** (15.5 mg, 0.08 mmol, 60%) was isolated by FC as pure oil after 3 h, starting from octanal (21.9 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate (*S*)-**7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E*:*Z* ratio 1:5.6. R$_f$= 0.25 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer) 5.67-5.49 (m, 1H, HC=C**H**), 5.49-5.36 (m, 1H, **H**C=CH), 2.80-2.65 (m, 1H, H-5), 2.25-2.03 (m, 2H, H-4ab), 2.02-1.89* (m, 2H, H-4ab), 1.68* (dd, *J* = 6.0, 1.2 Hz, 3H, 3×H-1), 1.64 (dd, *J* = 6.8,

0.8 Hz, 3H, 3×H-1), 1.46-1.25 (m, 12H, 6×CH$_2$), 0.95-0.86 (m, 3H, CH$_2$**CH$_3$**). ^{13}C NMR (75 MHz, CD$_3$OD) δ (*denotes minor isomer) 129.1* (H**C**=CH), 128.9* (H**C**=CH), 128.0 (H**C**=CH), 127.3 (H**C**=CH), 52.3 (C-5), 51.9* (C-5), 41.2* (C-4), 37.74 (C-4), 37.67* (CH$_2$), 35.3 (CH$_2$), 33.0 (CH$_2$), 30.9 (CH$_2$), 30.4 (CH$_2$), 27.2 (CH$_2$), 27.1* (CH$_2$), 23.7 (CH$_2$), 18.2* (CH$_3$), 14.4 (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 2959, 2930 (NH$_2$ st), 2851 (C-H st), 1454 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 128 (100, [M$^+$-C$_4$H$_7$]).

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding benzoylated product **10j**.
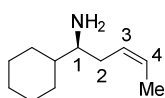
(S,Z)-1-Cyclohexylpent-3-en-1-amine, 9k. Following *GP-L*, **9k** (8.0 mg, 0.05 mmol, 34%) was isolated by FC as pure oil after 3 h, starting from cyclohexanecarboxaldehyde (17.0 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate **(S)-7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E:Z* ratio 1:6.3. R$_f$= 0.25 (EtOAc). ^{1}H NMR (300 MHz, CD$_3$OD) δ (*denotes minor isomer). 5.67-5.49 (m, 1H, H-4), 5.47-5.35 (m, 1H, H-3), 2.58-2.51 (m, 1H, H-1), 2.31-2.17 (m, 1H, H-2a), 2.15-2.02 (m, 1H, H-2b), 1.99-1.86* (m, 1H, H-2b), 1.85-1.59 (m, 8H, 2×C$_{cy}$H$_2$+C$_{cy}$H+CH$_3$), 1.39-0.96 (m, 6H, 3×C$_{cy}$H$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 129.5* (H**C**=CH), 129.0* (H**C**=CH), 128.6 (H**C**=CH), 127.2 (H**C**=CH), 57.2 (C-1), 56.7* (C-1), 44.1 (C$_{cy}$H), 44.0* (C$_{cy}$H), 38.2* (C-2), 32.4 (C-2), 30.7 (C$_{cy}$H$_2$), 30.6* (C$_{cy}$H$_2$), 29.5* (C$_{cy}$H$_2$), 29.5 (C$_{cy}$H$_2$), 27.7 (C$_{cy}$H$_2$), 27.6 (C$_{cy}$H$_2$), 27.6* (C$_{cy}$H$_2$), 27.5 (C$_{cy}$H$_2$), 18.2* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 2922, 2851 (NH$_2$ st), 1451 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%):126 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{11}$H$_{22}$N]$^+$: 168.1752 [M+H]$^+$; found: 168.1749.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding benzoylated product **10k**.
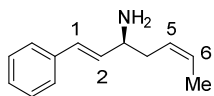
(S,1E,5Z)-1-Phenylhepta-1,5-dien-3-amine, 9l. Following *GP-L*, **9l** (17.3 mg, 0.14 mmol, 66%) was isolated by FC as pure oil after 3 h, starting from *trans*-cinnamaldehyde (17.6 µL, 0.14 mmol), aqueous ammonia (0.25 mL, 4.2 mmol) in EtOH (0.28 mL) and adding boronate **(S)-7b** (40 mg, 0.17 mmol) diluted in EtOH (0.14 mL). *E:Z* ratio 1:6.0. R$_f$= 0.44 (CHCl$_3$:MeOH 5%). ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.41-7.18 (m, 5H, C$_{arom}$-H), 6.51 (dd, *J* = 15.9, 1.2 Hz, 1H, H-1), 6.21

(dd, J = 15.9, 6.8 Hz, 1H, H-2), 5.69-5.52 (m, 1H, H-6), 5.51-5.38 (m, 1H, H-5), 3.56 (qd, J = 6.6, 1.2 Hz, 1H, H-3), 2.30 (t, J = 6.9 Hz, 2H, H-4), 2.22-2.08* (m, 2H, H-4), 1.68 (dd, J = 6.7, 0.9 Hz, 3H, CH$_3$), 1.48 (brs, 2H, NH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 137.34* (C$_{arom}$), 137.30 (C$_{arom}$), 134.7* (C-6), 134.6 (C-6), 128.9 (C$_{arom}$-H), 128.9* (C$_{arom}$-H), 128.65 (C$_{arom}$-H), 128.56* (C$_{arom}$-H), 127.5* (C$_{arom}$-H), 127.4 (C$_{arom}$-H), 126.9 (C-1), 126.6 (C-2), 126.4 (C-5), 54.0 (C-3), 53.7* (C-3), 41.4* (C-4), 35.5 (C-4), 18.2* (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 3019, 2915 (NH$_2$ st), 2830 (C-H st), 1490 (NH$_2$ δ) cm^{-1}. MS (EI) m/z (%): 186 (1, [M$^+$-H]), 132 (100, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{13}$H$_{18}$N]$^+$: 188.1439 [M+H]$^+$; found: 188.1444.

The enantiomeric excess of the product was measured by HPLC analysis on chiral stationary phase at the corresponding acetylated product **10l**.

3.4 <u>Synthesis of protected amines 10a-l</u>
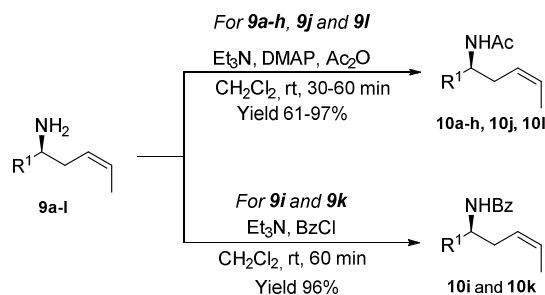
General Procedure for acetylation: A vial equipped with a magnetic stirring bar was charged with the amine **9a-h**, **9j** and **9l** (0.09 mmol, 1 eq), CH$_2$Cl$_2$ (0.25M), DMAP (0.009 mmol, 10 mol%), Et$_3$N (0.28 mmol, 3 eq) and Ac$_2$O (0.14 mmol, 1.5 eq). The crude mixture was stirred at room temperature until completion (30-60 min). The residue was concentrated *in vacuo* and purified by FC on silica gel (petroleum ether/EtOAc 8:2 to 6:4) affording the corresponding acetylated product as white solid. TLCs were developed in PMA.

The racemic standards for HPLC analysis were prepared through an acetylation reaction of racemic amines **9a-h**, **9j** and **9l**, which were previously synthesized using boronate (±)-**7a**.

General Procedure for benzoylation: A vial equipped with a magnetic stirring bar was charged with the primary amine **9i** or **9k** (0.03 mmol, 1 eq), CH$_2$Cl$_2$ (0.25M), Et$_3$N (0.05 mmol, 1.5 eq) and benzoyl chloride (0.04 mmol, 1.2 eq). The crude mixture was stirred at room temperature until completion (60 min). The mixture was concentrated *in vacuo* and purified by FC on silica gel (petroleum ether/EtOAc 19:1 to 7:3) affording the corresponding benzoylated product as a white solid. TLC was developed in PMA.

The racemic standards for HPLC analysis were prepared through a benzoylation reaction of racemic amines **9i** and **9k**, which were previously synthesized using boronate (±)-**7a**.
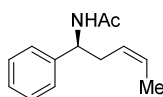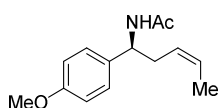
(*S,Z*)-*N*-(1-Phenylpent-3-en-1-yl)acetamide, 10a. Following *GP for acetylation*, **10a** (9.9 mg, 0.05 mmol, 89%) was isolated by FC, starting from primary amine **9a** (8.8 mg, 0.05 mmol) in CH_2Cl_2 (0.22 mL), Et_3N (22.3 µL, 0.16 mmol), DMAP (1.1 mg, 0.009 mmol) and acetic anhydride (7.8 µL, 0.08 mmol). *E:Z* ratio 1:6.3 ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.37-7.21 (m, 5H, C$_{arom}$-H), 5.80 (d, *J* = 7.0 Hz, 1H, NH), 5.63-5.45 (m, 1H, HC=C**H**), 5.35-5.23 (m, 1H, **H**C=CH), 5.11-4.99 (m, 1H, **H**CNH), 2.57 (tdd, *J* = 7.0, 1.7, 0.9 Hz, 2H, CH$_2$), 2.52-2.45* (m, 2H, CH$_2$), 1.99 (s, 3H, COC**H**$_3$), 1.63* (dd, *J* = 6.4, 1.4 Hz, 3H, CH$_3$), 1.59 (dd, *J* = 6.8, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.4 (C=O), 142.0* (C$_{arom}$), 141.9 (C$_{arom}$), 128.9* (C$_{arom}$-H), 128.7 (C$_{arom}$-H), 127.4 (HC=**C**H), 127.3* (HC=**C**H), 127.2 (C$_{arom}$-H), 126.6 (C$_{arom}$-H), 126.6* (C$_{arom}$-H), 126.4* (H**C**=CH), 125.5 (H**C**=CH), 53.1 (HCNH), 53.0* (HCNH), 39.4* (CH$_2$), 33.5 (CH$_2$), 23.5 (COCH$_3$), 18.1* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3282 (NH st), 1645 (C=O st) cm^{-1}. MS (EI) m/z (%): 148 (64, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{13}$H$_{18}$NO]$^+$: 204.1388 [M+H]$^+$; found: 204.1396. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; *Z* isomer τ$_{minor}$ = 44.24 min, τ$_{major}$ = 51.01 min (97% ee); *E* isomer τ$_{major}$ = 47.61 min, τ$_{minor}$ = 56.93 min (96% ee).
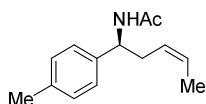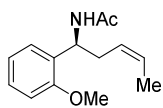
(*S,Z*)-*N*-(1-(p-tolyl)pent-3-en-1-yl)acetamide, 10b. Following *GP for acetylation*, **10b** (16.1 mg, 0.07 mmol, 80%) was isolated by FC, starting from primary amine **9b** (16.4 mg, 0.09 mmol) in CH_2Cl_2 (0.37 mL), Et_3N (39 µL, 0.28 mmol), DMAP (1.1 mg, 0.009 mmol) and acetic anhydride (13.2 µL, 0.14 mmol). *E:Z* ratio 1:6.0. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.23-7.10 (m, 4H, C$_{arom}$-H), 5.82 (d, *J* = 8.1 Hz, 1H, NH), 5.64-5.47 (m, 1H, HC=C**H**), 5.36-5.23 (m, 1H, **H**C=CH), 5.07-4.93 (m, 1H, **H**CNH), 2.60-2.52 (m, 2H, CH$_2$), 2.53-2.40* (m, 2H, CH$_2$), 2.32 (s, 3H, C$_{arom}$C**H**$_3$), 1.97 (s, 3H, COC**H**$_3$), 1.59 (dd, *J* = 6.7, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.3 (C=O), 139.0* (C$_{arom}$), 138.9 (C$_{arom}$), 137.1 (**C**$_{arom}$-CH$_3$), 137.0* (**C**$_{arom}$-CH$_3$), 129.4 (C$_{arom}$-H), 128.8* (HC=**C**H), 127.1 (HC=**C**H), 126.6 (C$_{arom}$-H), 126.5* (H**C**=CH), 125.7 (H**C**=CH), 52.9 (HCNH), 52.7* (HCNH), 39.4* (CH$_2$), 33.4 (CH$_2$), 23.6 (COCH$_3$), 21.2 (C$_{arom}$**C**H$_3$), 18.1* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3289 (NH st), 2926 (C-H st), 1644 (C=O st) cm^{-1}. MS (EI) m/z (%):162 (92, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{14}$H$_{20}$NO]$^+$: 218.1545 [M+H]$^+$; found: 218.1549. The ee was determined by HPLC using a *Chiralpak AY-3*

column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; *Z* isomer τ_{minor} = 25.78 min, τ_{major} = 41.14 min (>99% ee); *E* isomer τ_{minor} = 38.28 min, τ_{major} = 55.80 min (95% ee).

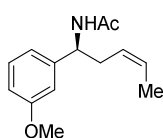**(*S*,*Z*)-*N*-(1-(4-Methoxyphenyl)pent-3-en-1-yl)acetamide,   10c.** Following *GP for acetylation*, **10c** (17.8 mg, 0.08 mmol, 90%) was isolated by FC, starting from primary amine **9c** (16.2 mg, 0.08 mmol) in CH$_2$Cl$_2$ (0.34 mL), Et$_3$N (38.5 µL, 0.28 mmol), DMAP (1.0 mg, 0.008 mmol) and acetic anhydride (7.8 µL, 0.08 mmol). *E*:*Z* ratio 1:5.7. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.20 (d, *J* = 8.7 Hz, 2H, C$_{arom}$-H), 6.86 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 5.75 (d, *J* = 8.2 Hz, 1H, NH), 5.62-5.44 (m, 1H, HC=C**H**), 5.35-5.22 (m, 1H, **H**C=CH), 5.06-4.91 (m, 1H, **H**CNH), 3.79 (s, 3H, OCH$_3$), 2.60-2.51 (m, 2H, CH$_2$), 2.50-2.42* (m, 2H, CH$_2$), 1.97 (s, 3H, COCH$_3$), 1.63* (dd, *J* = 6.4, 1.0 Hz, 3H, CH$_3$), 1.59 (dd, *J* = 6.8, 0.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.3 (C=O), 158.9 (C$_{arom}$-O), 134.2* (C$_{arom}$), 134.0 (C$_{arom}$), 128.8* (HC=CH), 127.8 (C$_{arom}$-H), 127.7* (C$_{arom}$-H), 127.1 (HC=**C**H), 126.6* (**H**C=CH), 125.7 (H**C**=CH), 114.1* (C$_{arom}$-H), 55.4 (HCNH), 52.6 (OCH$_3$), 52.5* (OCH$_3$), 39.3* (CH$_2$), 33.4 (CH$_2$), 23.6 (COCH$_3$), 18.1* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3282 (NH st), 1644 (C=O st), 1245 (C-O-C st as), 1020 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 178 (98, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{14}$H$_{20}$NO$_2$]$^+$: 234.1494 [M+H]$^+$; found: 234.1499. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; *Z* isomer τ_{minor} = 55.28 min, τ_{major} = 124.25 min (98% ee); *E* isomer τ_{major} = 99.91 min, τ_{minor} = 106.38 min (95% ee).

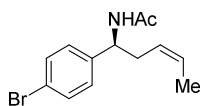**(*S*,*Z*)-*N*-(1-(2-Methoxyphenyl)pent-3-en-1-yl)acetamide, 10d.** Following *GP for acetylation*, **10d** (14.9 mg, 0.06 mmol, 68%) was isolated by FC, starting from primary amine **9d** (18 mg, 0.09 mmol) in CH$_2$Cl$_2$ (0.38 mL), Et$_3$N (39.3 µL, 0.28 mmol), DMAP (1.1 mg, 0.009 mmol) and acetic anhydride (13.3 µL, 0.14 mmol). *E*:*Z* ratio 1:9.0. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.25-7.19 (m, 1H, C$_{arom}$-H), 7.15 (dd, *J* = 7.6, 1.8 Hz, 1H, C$_{arom}$-H), 6.95-6.86 (m, 2H, C$_{arom}$-H), 6.43 (d, *J* = 8.7 Hz 1H, NH), 5.55-5.41 (m, 1H, HC=C**H**), 5.35-5.23 (m, 1H, **H**C=CH), 5.22-5.10 (m, 1H, **H**CNH), 3.89 (s, 3H, OCH$_3$), 2.63-2.42 (m, 2H, CH$_2$), 1.97 (s, 3H, COCH$_3$), 1.65-1.56* (m, 3H, CH$_3$), 1.51 (dd, *J* = 6.7, 0.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.0 (C=O), 157.2 (C$_{arom}$-O), 129.3 (C$_{arom}$), 129.2 (C$_{arom}$-H), 128.6 (HC=**C**H), 126.5 (C$_{arom}$-H), 126.4

(H**C**=CH), 120.8 (C_{arom}-H), 111.1 (C_{arom}-H), 55.5 (OCH_3), 51.8 (H**C**NH), 32.6 (CH_2), 23.8 (CO**C**H_3), 18.1* (CH_3), 12.9 (CH_3). IR (CH_2Cl_2): 3307 (NH st), 2930 (C-H st), 1641 (C=O st), 1245 (C-OC st as), 1027 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 178 (100, $[M^+$-$C_4H_7]$). HRMS: Calculated for $[C_{14}H_{20}NO_2]^+$: 234.1494 $[M+H]^+$; found: 234.1498. The ee was determined by HPLC using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; *Z* isomer τ_{minor} = 35.75 min, τ_{major} = 106.07 min (85% ee); *E* isomer τ_{major} = 33.85 min, τ_{minor} = 97.60 min (73% ee).

(*S*,*Z*)-*N*-(1-(3-Methoxyphenyl)pent-3-en-1-yl)acetamide, 10e. Following *GP for acetylation*, **10e** (14.4 mg, 0.06 mmol, 89%) was isolated by FC as an oil, starting from primary amine **9e** (13.3 mg, 0.07 mmol) in CH_2Cl_2 (0.28 mL), Et_3N (29 µL, 0.21 mmol), DMAP (0.8 m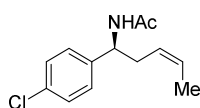g, 0.007 mmol) and acetic anhydride (9.8 µL, 0.1 mmol). *E*:*Z* ratio 1:5.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ (*denotes minor isomer) 7.31-7.20 (m, 1H, C_{arom}-H), 6.93-6.75 (m, 3H, C_{arom}-H), 5.78 (d, *J* = 6.8 Hz, 1H, NH), 5.65-5.48 (m, 1H, HC=C**H**), 5.36-5.23 (m, 1H, **H**C=CH), 5.09-4.92 (m, 1H, **H**CNH), 3.80 (s, 3H, OCH_3), 2.62-2.51 (m, 2H, CH_2), 2.51-2.42* (m, 2H, CH_2), 1.99 (s, COCH_3), 1.60 (dd, *J* = 6.8, 0.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (*denotes minor isomer) 169.4 (C=O), 159.9 (C_{arom}-O), 143.6 (C_{arom}), 129.8 (C_{arom}-H), 129.7* (C_{arom}-H), 129.0* (HC=**C**H), 127.3 (HC=**C**H), 126.4* (H**C**=CH), 125.5 (H**C**=CH), 118.9 (C_{arom}-H), 118.8* (C_{arom}-H), 112.8 (C_{arom}-H), 112.7* (C_{arom}-H), 112.5 (C_{arom}-H), 112.4* (C_{arom}-H), 55.4 (OCH_3), 53.1 (H**C**NH), 52.9* (H**C**NH), 39.4* (CH_2), 33.5 (CH_2), 23.6 (CO**C**H_3), 18.1* (CH_3), 13.1 (CH_3). IR (CH_2Cl_2): 3285 (NH st), 2940 (C-H st), 1648 (C=O st), 1260 (C-O-C st as), 1045 (C-O-C st sy) cm^{-1}. MS (EI) m/z (%): 178 (100, $[M^+$-$C_4H_7]$). HRMS: Calculated for $[C_{14}H_{20}NO_2]^+$: 234.1494 $[M+H]^+$; found: 234.1498. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 0.7 mL/min; *Z* isomer τ_{minor} = 139.35 min, τ_{major} = 172.43 min (>99% ee); *E* isomer τ_{major} = 134.51 min, τ_{minor} = 192.95 min (96% ee).
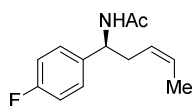

(*S*,*Z*)-*N*-(1-(4-Bromophenyl)pent-3-en-1-yl)acetamide, 10f. Following *GP for acetylation*, **10f** (20.8 mg, 0.07 mmol, 83%) was isolated by FC, starting from primary amine **5c** (21.4 mg, 0.09 mmol) in CH_2Cl_2 (0.36 mL), Et_3N (37.2 µL, 0.27 mmol), DMAP (1.1 mg, 0.009 mmol) and acetic anhydride (12.6 µL, 0.13 mmol). *E*:*Z* ratio 1:5.7 ^{1}H NMR (300 MHz, $CDCl_3$) δ (*denotes minor isomer) 7.43 (d, *J* = 8.4

Hz, 2H, C$_{arom}$-H), 7.14 (d, *J* = 8.4 Hz, 2H, C$_{arom}$-H), 5.87 (d, *J* = 7.3 Hz, 1H, NH), 5.67-5.47 (m, 1H, HC=C**H**), 5.31-5.19 (m, 1H, **H**C=CH), 5.03-4.89 (m, 1H, **H**CNH), 2.56-2.48 (m, 2H, CH$_2$), 2.47-2.39* (m, 2H, CH$_2$), 1.98 (s, 3H, COCH$_3$), 1.63* (dd, *J* = 6.4, 1.4 Hz, 3H, CH$_3$), 1.58 (dd, *J* = 6.8, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.5 (C=O), 141.2* (C$_{arom}$), 141.1 (C$_{arom}$), 131.7 (C$_{arom}$-H), 129.5* (HC=CH), 128.4 (C$_{arom}$-H), 128.3* (C$_{arom}$-H), 127.7 (HC=CH), 125.9* (H**C**=CH), 125.0 (H**C**=CH), 121.2 (C$_{arom}$-Br), 52.7 (HCNH), 52.5* (HCNH), 39.3* (CH$_2$), 33.3 (CH$_2$), 23.5 (COCH$_3$), 18.1* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3282 (NH st), 1648 (C=O st) cm^{-1}. MS (EI) m/z (%): 226 (44, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{13}$H$_{17}$NOBr]$^+$: 282.0494 [M+H]$^+$; found: 282.0504. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; *Z* isomer τ_{minor} = 27.18 min, τ_{major} = 51.42 min (98% ee); *E* isomer τ_{minor} = 44.41 min, τ_{major} = 54.08 min (98% ee).

(*S*,*Z*)-*N*-(1-(4-Chlorophenyl)pent-3-en-1-yl)acetamide, 10g. Following *GP for acetylation*, **10g** (13.6 mg, 0.06 mmol, 84%) was isolated by FC, starting from primary amine **9g** (13.4 mg, 0.07 mmol) in CH$_2$Cl$_2$ (0.27 mL), Et$_3$N (28.4 μL, 0.2 mmol), DMAP (1.0 mg, 0.008 mmol) and acetic anhydride (9.6 μL, 0.1 mmol). *E*:*Z* ratio 1:5.5. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.29 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 7.20 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 5.81 (d, *J* = 7.1 Hz, 1H, NH), 5.66-5.47 (m, 1H, HC=C**H**), 5.33-5.18 (m, 1H, **H**C=CH), 5.07-4.90 (m, 1H, **H**CNH), 2.58-2.49 (m, 2H, CH$_2$), 2.47-2.40* (m, 2H, CH$_2$), 1.98 (s, 3H, COCH$_3$), 1.64* (dd, *J* = 6.4, 1.4 Hz, 3H, CH$_3$), 1.58 (dd, *J* = 6.8, 0.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.4 (C=O), 140.7* (C$_{arom}$), 140.5 (C$_{arom}$), 133.1 (C$_{arom}$-Cl), 133.0* (C$_{arom}$-Cl), 129.5* (HC=**C**H), 128.8 (C$_{arom}$-H), 128.0 (C$_{arom}$-H), 127.9* (C$_{arom}$-H), 127.8 (HC=**C**H), 126.0* (H**C**=CH), 125.0 (H**C**=CH), 52.6 (HCNH), 52.4* (HCNH), 39.3* (CH$_2$), 33.4 (CH$_2$), 25.5* (COCH$_3$), 23.6 (COCH$_3$), 18.1* (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 3285 (NH st), 1648 (C=O st) cm^{-1}. MS (EI) m/z (%): 182 (49, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{13}$H$_{17}$NOCl]$^+$: 238.1001 [M+H]$^+$; found: 238.0999. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; *Z* isomer τ_{minor} = 23.02 min, τ_{major} = 44.60 min (>99% ee); *E* isomer τ_{minor} = 38.71 min, τ_{major} = 41.73 min (>99% ee).

(S,Z)-N-(1-(4-Fluorophenyl)pent-3-en-1-yl)acetamide, 10h. Following *GP for acetylation*, **10h** (5.5 mg, 0.02 mmol, 61%) was isolated by FC, starting from primary amine **9h** (7.4 mg, 0.04 mmol) in CH_2Cl_2 (0.16 mL), Et$_3$N (16.7 µL, 0.12 mmol), DMAP (0.5 mg, 0.004 mmol) and acetic anhydride (5.8 µL, 0.06 mmol). *E:Z* ratio 1:5.4. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.31-7.20 (m, 2H, C$_{arom}$-H), 7.06-6.96 (m, 2H, C$_{arom}$-H), 5.74 (d, *J* = 6.0 Hz, 1H, NH), 5.66-5.48 (m, 1H, HC=C**H**), 5.35-5.19 (m, 1H, **H**C=CH), 5.07-4.93 (m, 1H, **H**CNH), 2.59-2.50 (m, 2H, CH$_2$), 2.49-2.41* (m, 2H, CH$_2$), 1.99 (s, 3H, COCH$_3$), 1.59 (dd, *J* = 6.7, 0.8 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.4 (C=O), 162.1 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, C$_{arom}$-F), 162.0* (d, $^1J_{C\text{-}F}$ = 245.2 Hz, C$_{arom}$-F), 137.9* (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C$_{arom}$), 137.8 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C$_{arom}$), 129.3* (HC=CH), 128.2 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C$_{arom}$-H), 128.1* (d, $^3J_{C\text{-}F}$ = 7.2 Hz, C$_{arom}$-H), 127.6 (HC=**C**H), 126.1* (H**C**=CH), 125.2 (H**C**=CH), 115.5 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, C$_{arom}$-H), 115.4* (d, $^2J_{C\text{-}F}$ = 21.4 Hz, C$_{arom}$-H), 52.6 (HCNH), 52.4* (HCNH), 39.5* (CH$_2$), 33.5 (CH$_2$), 23.5 (COCH$_3$), 18.1* (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3289 (NH st), 2927 (C-H st), 1644 (C=O st), 1220 (C-F st). MS (EI) m/z (%): 166 (49, [M$^+$-C$_4$H$_7$]), 124 (100, [M$^+$-C$_6$H$_4$F]). HRMS: Calculated for [C$_{13}$H$_{17}$NOF]$^+$: 222.1294 [M+H]$^+$; found: 222.1292. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; *Z* isomer τ$_{minor}$ = 17.30 min, τ$_{major}$ = 34.12 min (>99% ee); *E* isomer τ$_{major}$ = 24.23 min, τ$_{minor}$ = 30.90 min (99% ee).

**10h** was crystallized in vapour diffusion conditions with Et$_2$O:*n*-hexane at -20 ºC.
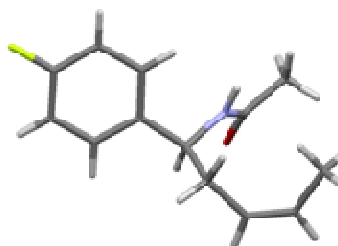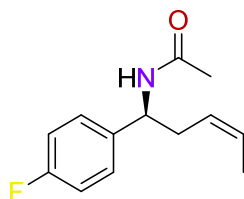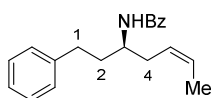
(R,Z)-N-(1-Phenylhept-5-en-3-yl)benzamide, 10i. Following *GP for benzoylation*, **10i** (9.3 mg, 0.03 mmol, 96%) was isolated by FC, starting from primary amine **9i** (6.3 mg, 0.03 mmol) in CH$_2$Cl$_2$ (0.13 mL), Et$_3$N (7 μL, 0.05 mmol) and benzoyl chloride (4.6 μL, 0.04 mmol). *E:Z* ratio nd. R$_f$= 0.51 (petroleum ether/EtOAc 8:2). ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 7.72-7.65 (m, 2H, C$_{arom}$-H), 7.53-7.38 (m, 3H, C$_{arom}$-H), 7.32-7.23 (m, 2H, C$_{arom}$-H), 7.24-7.14 (m, 3H, C$_{arom}$-H), 5.94 (d, *J* = 8.8 Hz, 1H, NH), 5.71-5.56 (m, 1H, HC=C**H**), 5.56-5.40 (m, 1H, **H**C=CH), 4.38-4.18 (m, 1H, H-3), 2.74 (t, *J* = 8.0 Hz, 2H, 2×H-1), 2.54-2.41 (m, 1H, H-4a), 2.40-2.25 (m, 1H, H-4b), 2.07-1.78 (m, 2H, 2×H-2), 1.67* (dd, *J* = 5.9, 0.9 Hz, 3H, CH$_3$), 1.63 (dd, *J* = 6.7, 0.7 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 167.1 (C=O), 142.0* (C$_{arom}$), 141.9 (C$_{arom}$), 135.1* (C$_{arom}$), 135.0 (C$_{arom}$), 131.4 (C$_{arom}$-H), 129.0* (HC=**C**H), 128.7 (HC=**C**H), 128.6 (H**C**=CH), 128.5 (C$_{arom}$-H), 127.4 (C$_{arom}$-H), 126.9 (C$_{arom}$-H), 126.5* (H**C**=CH), 126.1 (C$_{arom}$-H), 125.6 (C$_{arom}$-H), 49.7 (C-3), 49.5* (C-3), 38.1* (C-2), 36.3* (C-4), 36.2 (C-2), 32.75 (C-4), 32.67* (C-1), 32.1 (C-1), 18.2* (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 3303 (NH st), 2926 (C-H st), 1630 (C=O st) cm^{-1}. MS (EI) m/z (%): 238 (38, [M$^+$- C$_4$H$_7$]), 105 (100, [M$^+$-C$_{13}$H$_{18}$N]). HRMS: Calculated for [C$_{20}$H$_{24}$NO]$^+$: 294.1858 [M+H]$^+$; found: 294.1859. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; *E* isomer τ$_{minor}$ = 61.18 min, τ$_{major}$ = 129.93 min (93% ee); *Z* isomer τ$_{majorr}$ = 83.30 min, τ$_{minor}$ = 87.76 min (93% ee).
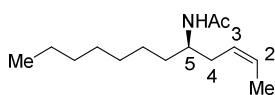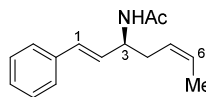
(R,Z)-N-(Dodec-2-en-5-yl)acetamide, 10j. Following *GP for acetylation*, **10j** (10.2 mg, 0.04 mmol, 81%) was isolated by FC, starting from primary amine **9j** (10.2 mg, 0.06 mmol) in CH$_2$Cl$_2$ (0.22 mL), Et$_3$N (23.4 μL, 0.17 mmol), DMAP (1.0 mg, 0.008 mmol) and acetic anhydride (8 μL, 0.08 mmol). *E:Z* ratio 1:5.6. ^{1}H NMR (300 MHz, CDCl$_3$) δ (*denotes minor isomer) 5.66-5.52 (m, 1H, HC=C**H**), 5.47-5.31 (m, 1H, **H**C=CH), 5.24 (d, *J* = 8.4 Hz, 1H, NH), 4.07-3.86 (m, 1H, **H**CNH), 2.36-2.23 (m, 1H, H-4a), 2.21-2.07 (m, 1H, H-4b), 1.95 (s, 3H, COCH$_3$), 1.66* (dd, *J* = 6.0, 1.3 Hz, 3H, CH$_3$), 1.61 (dd, *J* = 6.7, 1.1 Hz, 3H, CH$_3$), 1.41-1.16 (m, 13H, 6×CH$_2$), 0.91-0.83 (m, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.64 (C=O), 169.59* (C=O), 128.4* (HC=**C**H), 126.9 (HC=**C**H), 126.8* (H**C**=CH), 125.9 (H**C**=CH), 49.4 (HCNH), 49.1* (HCNH), 37.9* (CH$_2$), 34.4 (CH$_2$), 32.0 (CH$_2$), 31.9 (CH$_2$), 29.7 (CH$_2$), 29.4

(CH$_2$), 26.2 (CH$_2$), 26.1* (CH$_2$), 23.7 (COCH$_3$), 18.2* (CH$_3$), 14.2 (CH$_3$), 13.1 (CH$_3$). IR (CH$_2$Cl$_2$): 3278 (NH st), 2926 (C-H st), 1645 (C=O st) cm^{-1}. MS (EI) m/z (%):170 (35, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{14}$H$_{28}$NO]$^+$: 226.2171 [M+H]$^+$; found: 226.2177. The ee was determined by HPLC using a *Chiralpak AY-3* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; Z isomer τ_{minor} = 12.85 min, τ_{major} = 22.86 min (96% ee); E isomer τ_{major} = 19.99 min, τ_{minor} = 26.17 min (99% ee).
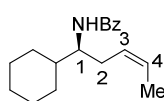
(S,Z)-N-(1-Cyclohexylpent-3-en-1-yl)benzamide, 10k. Following *GP for benzoylation*, **10k** (3.9 mg, 0.01 mmol, 96%) was isolated by FC, starting from primary amine **9k** (2.5 mg, 0.01 mmol) in CH$_2$Cl$_2$ (0.1 mL), Et$_3$N (3.2 µL, 0.02 mmol) and benzoyl chloride (2.1 µL, 0.02 mmol). R$_f$= 0.5 (petroleum ether/EtOAc 8:2). E:Z ratio 1:6.3 ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77-7.70 (m, 2H, C$_{arom}$-H), 7.53-7.38 (m, 3H, C$_{arom}$-H), 5.91 (d, *J* = 9.3 Hz, 1H, NH), 5.66-5.52 (m, 1H, HC=**C**H), 5.51-5.37 (m, 1H, **H**C=CH), 4.14-4.01 (m, 1H, H-1), 2.50-2.37 (m, 1H, H-2a), 2.34-2.15 (m, 1H, H-2b), 1.88-1.71 (m, 4H, 2×C$_{cy}$H$_2$), 1.71-1.42 (m, 4H, C$_{cy}$H+CH$_3$), 1.36-0.98 (m, 6H, 3×C$_{cy}$H$_2$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 167.3 (C=O), 135.4* (C$_{arom}$), 135.3 (C$_{arom}$), 131.4* (C$_{arom}$-H), 128.7 (C$_{arom}$-H), 128.4* (HC=**C**H), 127.1* (H**C**=CH), 126.9 (C$_{arom}$-H), 126.8 (HC=**C**H), 126.3 (H**C**=CH), 54.1 (C-1), 53.8* (C-1), 41.4 (C$_{cy}$H), 35.2* (C-2), 30.1 (C-2), 29.9* (C$_{cy}$H$_2$), 29.8* (C$_{cy}$H$_2$), 29.3 (C$_{cy}$H$_2$), 29.0 (C$_{cy}$H$_2$), 26.5 (C$_{cy}$H$_2$), 26.3 (C$_{cy}$H$_2$), 18.2* (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 3310 (NH st), 2851 (C-H st), 1630 (C=O st) cm^{-1}. MS (EI) m/z (%): 216 (59, [M$^+$-C$_4$H$_7$]), 105 (100, [M$^+$-C$_{11}$H$_{20}$N]). HRMS: Calculated for [C$_{18}$H$_{26}$NO]$^+$: 272.2018 [M+H]$^+$; found: 272.2014. The ee was determined by HPLC using a *Chiralcel OD-3* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; E isomer τ_{major} = 13.05 min, τ_{minor} = 16.15 min (94% ee), Z isomer τ_{minor} = 14.19 min, τ_{major} = 18.47 min (91% ee).

N-((S,1E,5Z)-1-Phenylhepta-1,5-dien-3-yl)acetamide, 10l. Following *GP for acetylation*, **10l** (17.3 mg, 0.07 mmol, 97%) was isolated by FC, starting from primary amine **9l** (14.6 mg, 0.08 mmol) in CH$_2$Cl$_2$ (0.31 mL), Et$_3$N (32.6 µL, 0.23 mmol), DMAP (1.0 mg, 0.008 mmol) and acetic anhydride (11 µL, 0.12 mmol). E:Z ratio 1:6.0 ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41-7.18 (m, 4H, C$_{arom}$-H), 6.51 (dd, *J* = 16.0, 1.5 Hz, 1H, H-1), 6.14 (dd, *J* = 16.0, 6.0 Hz, 1H, H-2), 5.72-5.49 (m, 2H, H-6+NH), 5.49-5.35 (m, 1H, H-5), 4.80-4.64 (m, 1H, H-3), 2.56-2.29 (m, 2H, CH$_2$), 2.03 (s, 3H, COCH$_3$), 1.73-

1.60 (m, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (*denotes minor isomer) 169.4 (C=O), 136.8 (C$_{arom}$), 130.6 (C-1), 130.5* (C-1), 129.5 (C-6), 128.7 (C$_{arom}$-H), 127.7 (C-2), 127.6 (C$_{arom}$-H), 126.5 (C$_{arom}$-H), 126.1*(C-5), 125.2 (C-5), 50.7 (C-3), 50.5* (C-3), 38.3* (C-4), 32.5 (C-4), 23.7 (COCH$_3$), 18.2* (CH$_3$), 13.2 (CH$_3$). IR (CH$_2$Cl$_2$): 3289 (NH st), 2926 (C-H st), 1644 (C=O st) cm^{-1}. MS (EI) m/z (%): 229 (1, M$^+$), 174 (72, [M$^+$-C$_4$H$_7$]). HRMS: Calculated for [C$_{15}$H$_{20}$NO]$^+$: 230.1545 [M+H]$^+$; found: 230.1546. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/EtOH (97:3)]; flow rate 1.0 mL/min; *Z* isomer τ$_{minor}$ = 32.04 min, τ$_{major}$ = 34.47 min (94% ee).

Appendix

ABBREVIATIONS, ACRONYMS AND SYMBOLS[1]

Ac	Acetyl
acac	Acetylacetonate
ACDC	Asymmetric Counterion Directed Catalysis
Ac$_2$O	Acetic anhydride
aq.	Aqueous
Ar	Aryl
BINOL	1,1´-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	broad signal
c	Concentrarion (measured in g/100 mL)
C$_{arom}$	Aromatic carbon
CBA	Chiral Brønsted Acid
CPA	Chiral Phosphoric Acid
D-A	Diels-Alder
DFT	Densitiy Functional Theory
DMDO	Dimethyldioxirane
DMSO	Dimethylsulfoxide
dpp	diphenyl phosphate
d.r.	diastereomeric ratio
EDG	Electron-donating group
e.e.	enantiomeric excess
et al.	*Et alii* (and others)
eV	Electron volt
EWG	Electron-withdeawing group
FC	Flash chromatography
GC	Gas chromatography
GP	General Procedure
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
J	Coupling constant
LUMO	Lowest Unoccupied Molecular Orbital
Mes	mesityl
M.p.	Melting point
MS	molecular sieves or Mass Spectrometry

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[1] For standard Abbreviations and Acronyms, see: *"Guidelines for Authors" J. Org. Chem.* **2017**.

| **n.d.** | not determined |
NHC	*N*-heterocyclic carbene
n.r.	no reaction
PMP	*para*-methoxyphenyl
PTC	Phase Transfer Catalysis
R	alkyl group or substituent
r.r.	regioisomeric ratio
r.t.	room temperature
SOMO	Single Occupied Molecular Orbital
SPINOL	1,1´-spirobiindane-7,7´-diol
SI	Supporting Information
TADDOL	(α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol)
Tf	Trifluoromethanesulfonyl
Ts	Tosyl
TS	transition state
X	halogen, heteroatom or leaving group
δ	chemical shift
τ_{major}	Retention time for major enantiomer
τ_{minor}	Retention time for minor enantiomer

El empleo de catalizadores quirales que contienen enlaces de hidrógeno dadores ha abierto una estrategia muy útil para la afinidad entre el catalizador y el sustrato ya que confiere una mejor organización y estados de transición más rígidos que otorgan mejores estereoselectividades. En este sentido, los ácidos de Brønsted han demostrado ser catalizadores altamente eficaces y versátiles para un gran número de transformaciones sintéticas relevantes. Debido a la necesidad de activar un mayor rango de sustratos mediante la utilización de ácidos más fuertes, Terada y Akiyama desarrollaron un nuevo grupo de ácidos fosfóricos quirales basados en la estructura del BINOL capaces de actuar de forma bifuncional en un gran número de reacciones.

Siguiendo la línea de investigación del grupo en el área de la organocatálisis asimétrica, la presente memoria recoge el estudio y desarrollo de varias metodologías bajo catálisis de ácidos de Brønsted quirales los cuales participan generando especies reactivas y a su vez proporcionando un entorno asimétrico conduciendo a la formación de productos de forma enantioenriquecida.

En un primer capítulo, se ha expuesto un breve resumen con perspectiva histórica de las características más generales de la organocatálisis asimétrica, haciendo especial mención a los avances en los diferentes modos de activación de compuestos carbonílicos e iminas empleando catalizadores de ácidos de Brønsted tipo ácidos fosfóricos o triflamidas. Se detallan los modos de activación con recientes ejemplos bibliográficos aclarando el mecanismo de cada uno de ellos.

El principal proyecto de la tesis doctoral consiste en el estudio del comportamiento de compuestos con estructura 1,3-dipolo frente a dienos ricos en electrones en un caso típico de cicloadición (4+3). Pretendemos explorar el uso de cationes alílicos estabilizados por heteroátomos como fuente de la unidad que aporta tres átomos de carbono, los cuales son conocidos por reaccionar de manera eficaz con dienos

via cicloadición (4+3) rindiendo una estructura carbocatiónica cíclica de siete eslabones que posteriormente evoluciona hasta el producto final (ver Esquema 1).

Esquema 1
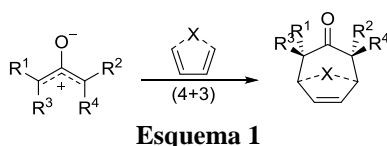
Inicialmente se trabajó en la síntesis de los diferentes precursores de catión oxaalílico como son los metilidenoxiranos. De esta forma, la formación *in situ* de los cationes oxaalílicos mediante la epoxidación de alenos estabilizados por nitrógeno con la consiguiente apertura del metilidenoxirano resultó ser la estrategia más viable. La primera aproximación se basó en la apertura de alquilidenoxiranos mediante catálisis por ácidos de Brønsted fuertes que se fundamenta en la protonación o activación del sustrato mediante enlaces de hidrógeno por el catalizador ácido, la base conjugada obtenida, que contiene el entorno quiral, se mantiene próxima al protón por interacciones iónicas o electrostáticas. La posterior transformación sobre este intermedio asimétrico da lugar al producto final enantioenriquecido. Se realizó un estudio con los reactivos epoxidantes clásicos como pueden ser *mCPBA*, CH_3COOH, ^tBuOOH o H_2O_2 sin observar el producto de cicloadición en ninguno de los casos. Al acudir a la bibliografía se observó la utilización del dimetildioxirano (DMDO) en reacciones de epoxidación de alenos. Asimismo, se decidió preparar dicho compuesto y ensayarlo en la reacción obteniendo el cicloaducto con un rendimiento del 35% en presencia de furano y un ácido fosfórico (Esquema 2).
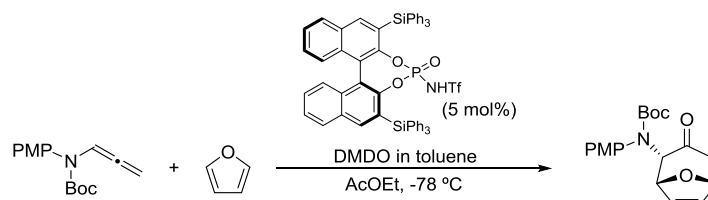

Esquema 2
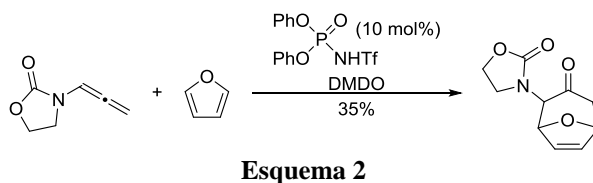
En 2004, para compensar las limitaciones observadas hasta la fecha con el empleo de tioureas quirales, Akiyama y Terada presentaron los ácidos fosfóricos derivados del BINOL. Estas especies presentan la acidez adecuada para generar interacciones electrostáticas más estables, y una situación más restringida del grupo ácido gracias a su

entorno quiral. Además, el grupo fosfato es a la vez ácido y base, confiriendo un carácter bifuncional al catalizador. De esta forma, se procedió a verificar la viabilidad de la reacción variando la acidez de los catalizadores empleados para promover la reacción entre una alenamida conocida y furano como dieno rico en electrones. Se observó que una mayor acidez en el sistema catalítico promovía la reacción de manera más eficaz en términos de rendimiento y estereocontrol.

De esta forma, se evaluaron diferentes alenos con grupos dadores y electron-atractores modulando de esta forma la electrofilia del catión oxaalílico con el fin de lograr los mejores resultados encontrando necesaria la incorporación tanto de un grupo electron-atractor tipo alcoxicarbonilo como un sustituyente aromático sobre el átomo de nitrógeno. A continuación se realizaron estudios de temperatura, diversos modos de adición, variaciones en la concentración, estudio de equivalentes, disolventes y co-disolventes observando una mejora significativa bajo el empleo de acetato de etilo como co-disolvente en el sistema de reacción. De esta forma, también se estudió el empleo de otros acetatos sin observar ninguna mejora.

Con el fin de mejorar los resultados, se reevaluaron diferentes catalizadores bajo las condiciones óptimas de reacción incluyendo sistemas tipo SPINOL o bifosfóricos que han demostrado buenos resultados en otras reacciones descritas en la bibliografía sin lograr una mejora en los resultados.

Tras un extenso proceso de exploración de las variables de reacción, se determina que el empleo de triflamida sustituida por triphenylsilyl en posiciones 3,3´del BINOL como catalizador en DMDO en tolueno y acetato de etilo como disolvente a -78 ºC conducen a la formación de 8-oxabiciclo[3.2.1]-octano (Esquema 3).
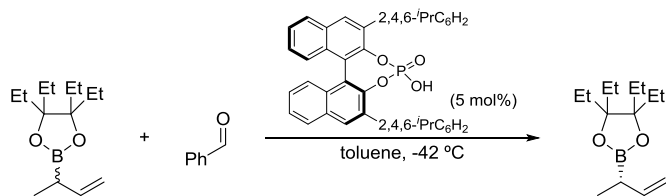

Esquema 3

A continuación se decidió estudiar la influencia de la sustitución y naturaleza electrónica del dieno, observando que la reacción es muy dependiente de este parámetro, estando limitada al uso de furanos como dienos ricos en electrones capaces de proporcionar resultados aceptables en cuanto a rendimiento y estereocontrol. Se realizó el alcance de la reacción con buenos rendimientos y enantioselectividades bajo una absoluta diastereoselectividad y casi completa regioselectividad. Sin embargo, la reacción queda limitada al uso de furanos sustituidos en posición 3.

Con el fin de completar el trabajo se utilizaron los furanos que mejores resultados aportaron al estudio de alenos sustituidos en posición γ con sustituyentes de diferente naturaleza como grupos alquilo o funcionalizados obteniendo excelentes resultados (Esquema 4).
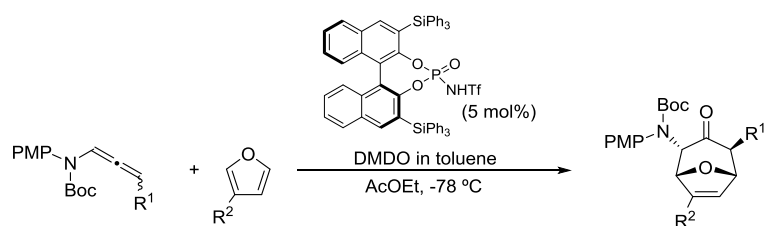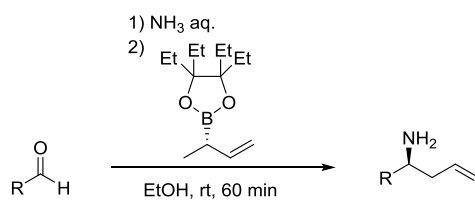

Esquema 4

Finalmente, el tercer capítulo trata sobre el trabajo realizado en la Universidad de Loughborough (UK) bajo la supervisión del Prof. Andrei V. Malkov y la posterior colaboración con nuestro grupo en la UPV/EHU trabajando con el objetivo de establecer las condiciones óptimas para la resolución cinética de mezclas racémicas de alilboronatos secundarios mediante la alilación selectiva facial de aldehídos empleando condiciones de ácidos de Brønsted quirales (Esquema 5) para posteriormente utilizarlos como productos de partida en la alilación de iminas.

Esquema 5

Los boronatos resueltos serán utilizados para la síntesis de aminas quirales homoalílicas. Desarrollaremos la alilación asimétrica de iminas primarias mediante el empleo de alilboronatos enantioenriquecidos con el objetivo de lograr un proceso de absoluta transferencia de quiralidad al producto final. Los boronatos resueltos se añadirán tras la condensación del correspondiente aldehído en imina bajo amoniaco en disolución de etanol a temperatura ambiente (Esquema 6).

Esquema 6