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Novel Stereoselective Transformations under Lewis Base Catalysis

MEMORIA PRESENTADA POR

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Summary

Since the necessity of pharmaceutical industries to commercialize enantiopure compounds, the synthesis of enantiomerically pure molecules has gained much interest over the years. Although different strategies such as the resolution of racemates or the c*hiral pool* strategy have been widely exploited, asymmetric synthesis has constituted a breakthrough in this area. Within the field of asymmetric synthesis, the asymmetric induction can be performed by the use of chiral auxiliaries or catalysts, being the catalysis employing small organic molecules as reaction promoters the one which has been most exploited in recent years. This catalysis, known as organocatalysis, employs a large variety of organocatalysts which can be classified by its mode of action as Brønsted acids, Brønsted bases, Lewis acids and Lewis bases. The work complied in this manuscript is focused on the development of novel transformations promoted by Lewis bases.

In this sense, we first evaluated 2-vinyl cyclopropylacetaldehydes as suitable substrates for the development of an enantioselective organocatalyzed vinylcyclopropane-cyclopentene (VCP-CP) rearrangement. We established the capability of chiral secondary amine catalysts to promote the ring-opening reaction of the vinylcyclopropanes leading to the formation of a wide variety of differently substituted cyclopentenes in good yields and enantiocontrol.

Secondly, the metal-free activation of bis(pinacolato)diboron and its reactivity towards allenylamides, unexplored compounds in the field of borylation reactions, was studied. The alkoxide activation of B_2pin_2 afforded a nucleophilic boryl moiety which could react with different electrophilic positions of allenylamides. The stereoselective metal-free borylation of allenylamides gave access to trisubstituted olefins, valuable building blocks for further transformations such as metal-catalyzed cross-coupling reactions.

Finally, as part of a short stay in the group of Prof. Nuno Maulide in the University of Vienna (Austria), research in the triflic anhydride-mediated activation of amides was carried out. The objective of the short stay was to extend the scope of the asymmetric version of [3,3]-sigmatropic rearrangement previously developed by the group, which involved an amide activation step. The induction of chirality was obtained by the use of 2-substituted pyrrolidines as chiral auxiliaries.

Resumen

Dada la necesidad por parte de las empresas farmacéuticas de comercializar compuestos enantiomericamente puros, la síntesis de moléculas enantiopuras ha atraído mucho interés en los últimos años. Aunque estrategias tales como la resolución de mezclas racémicas y la estrategia c*hiral pool* han sido muy explotadas, la síntesis asimétrica constituye hoy en día uno de los principales métodos para la obtención de compuestos enantiomericamente puros. Ésta puede llevarse a cabo mediante el uso de auxiliares quirales o mediante catálisis asimétrica. Dentro de esta última, el empleo de moléculas orgánicas de pequeño tamaño como catalizadores ha adquirido una importante relevancia en las últimas dos décadas. Este tipo de catálisis, conocida como organocatálisis, emplea una gran variedad de organocatalizadores que pueden clasificarse en función de su modo de activación en ácidos de Brønsted, bases de Brønsted, ácidos de Lewis y bases de Lewis. El trabajo presentado en este manuscrito se centra en el desarrollo de nuevas transformaciones promovidas por bases de Lewis.

En este sentido, en primer lugar se evaluaron ciclopropanoacetaldehidos sustituidos con un grupo vinilaceptor como sustratos susceptibles de ser sometidos a una reacción de reagrupamiento vinilciclopropano-ciclopenteno (VCP-CP) organocatalítica enantioselectiva. Se estudió la capacidad de llevar a cabo la reacción de apertura del vinilciclopropano por parte de aminas secundarias quirales para promover el acceso a ciclopentenos sustituidos con buenos rendimientos y alto grado de enantiocontrol.

En segundo lugar, se estudió la activación del bis(pinacolato)diboro y su reactividad frente a alenilamidas, compuestos no explorados en el campo de reacciones de borilación, en ausencia de metales. La activación del B_2pin_2 a través de un alcóxido generó una especie de boro nucleófila capaz de reaccionar con las posiciones electrófilas de las alenilamidas. Esta borilación organocatalítica estereoselectiva de alenilamidas permitió el acceso a olefinas trisustituidas, que pueden actuar como excelentes “building blocks” en futuras transformaciones como reacciones de acoplamiento cruzado catalizadas por metales.

Finalmente, como parte de una estancia breve en el grupo del Prof. Nuno Maulide en la Universidad de Viena (Austria), se trabajó en la activación de amidas mediante el uso de anhídrido tríflico. El objetivo de la estancia consistió en la extensión del alcance de la versión asimétrica de un reagrupamiento sigmatrópico [3,3] descubierto previamente por el grupo, el cual incluía un paso de activación de amidas. La inducción de quiralidad se llevó a cabo mediante el empleo de pirrolidinas 2-sustituidas como auxiliares quirales.

Laburpena

Konposatu enantiomerikoki puruak komertzializatzeko enpresa farmazeutikoen nahia ikusita, azken urteotan molekula enantiopuruen sintesiak arreta handia jaso du. Nahiz eta nahaste errazemikoen erresoluzioa eta *chiral pool* estrategiak asko erabiliak izan diren, gaur egun, konposatu enantiomerikoki puruak lortzeko metodorik erabilienetarikoa sintesi asimetrikoa da, bai laguntzaile kiralak erabiliz zein katalisi asimetrikoaren bidez. Azken honetan, katalizatzaile moduan molekula organiko txikiek garrantzi handia lortu dute azken bi hamarkadetan. Katalisi mota honetan, organokatalisis moduan ezaguna, hainbat organokatalizatzaile erabili ohi dira, zeinak haiek aktibatzeko moduaren arabera Brønsted azidoetan, Brønsted baseetan, Lewis azidoetan eta Lewis baseetan sailka daitezkeen. Eskuizkribu honetan aurkezten den lana Lewisen baseetan sustatutako eraldaketa berrien garapenean zentratzen da.

Horri dagokionez, binilhartzaile taldeaz ordezkatutako ziklopropanoazetaldehidoak ebaluatu ziren substratu modura binilziklopropano-ziklopenteno (BZP-ZP) berrantolaketa erreakzio organokatalitiko eta enantioselektibo batean. Amina sekundario kiralen bidez, binilziklopropanoaren irekiera-erreakzioaren gaitasuna ikertu zen, ziklopenteno desberdinak etekin onekin eta enantiokontrol handiarekin isolatzen.

Beste alde batetik, bis(pinakolato)diboroaren metalik gabeko aktibazioa eta haren erreaktibitatea alenilamideekin ikertu ziren, zeinak ez diren aztertu borilazio erreakzioetan. Alkoxido baten formazioaren bitartez aktibatutako B_2pin_2, alenilamidaren posizio elektrofilikoekin erreakzionatzeko gai zen, sortutako boro espezie nukleofilikoaren bidez. Alenilamiden borilazio erreakzio organokataliko eta enantioselektiboak, olefina triordezkatuen lorpena bermatu zuen. Hauek, “building block” modura joka dezakete metalek, adibidez, katalizatutako akoplamendu gurutzatutako erreakzioetan.

Azkenik, Vienako Unibertsitateko (Austria) Prof. Nuno Maulideren taldean egindako egonaldi labur baten parte gisa, amidak aktibatzeko anhidrido triflikoaren erabilpenean lan egin zen. Egonaldiaren helburua “berrantolaketa” [3,3]-sigmatropikoaren bertsio asimetrikoaren hedapenean zatzan, zeina aldez aurretik ikerkuntza taldean aurkitu zen. Kiralitatearen indukzioa, laguntzaile kiral moduan pirrolidina 2-ordezkatuen bidez burutu zen.

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Chapter 1

1

Introduction

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1. ASYMMETRIC SYNTHESIS

The necessity of synthesizing enantiopure compounds has gained more and more attention over the years since in 1992 the FDA (Food and Drug Administration) banned the marketing of racemates in which both enantiomers present different physiological effects.[1] Due to the necessity of pharmaceutical industries to commercialize enantiopure compounds, much effort has been made in the last decades in the preparation of enantioenriched molecules.[2] Three are the general methodologies which can be taken for that purpose: the *resolution of racemates*, c*hiral pool* strategy and *asymmetric synthesis*. The resolution of racemic mixtures consists on the separation of both enantiomers through simple methods such as crystallization, or differences on reactivity.[3] On the other hand, the *chiral pool* strategy is based on the use of enantiomerically pure natural products as starting materials which introduce the initial stereogenic centers and induce enantiocontrol in the final product.[4] Asymmetric synthesis allows the chirality transfer through a chiral element present in the molecule or a reagent present in the media, therefore converting an achiral starting material into an enantioenriched product. This methodology comprises the use of the stereocontrolling element either in stoichiometric (chiral auxiliaries strategy) or substoichiometric (enantioselective catalysis) amount. Regarding their chemical composition, chiral catalysts can be enzymatic, metallic or organic in nature (Figure 1.1).

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[1] (a) Stinson, S. C. *Chem. Eng. News* **1992**, *70*, 46. (b) Stinson, S. C. *Chem. Eng. News* **1993**, *71*, 38.

[2] Seebach, D.; Hungerbüler, E. *Synthesis of Enantiomerically Pure Compounuds (EPC-Synthesis) in Modern Synthetic Methods*, (Eds.: Scheffold, R.), Salle & Sauerländer, Frankfurt, 1980.

[3] Faber, K. *Chem. Eur. J*. **2001**, *7*, 5004.

[4] Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon Press, Oxford, 1983.

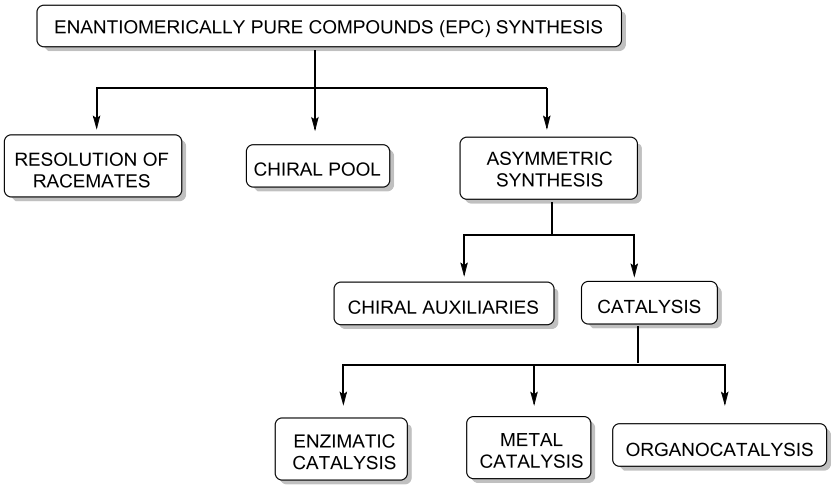

Figure 1. 1. Methods for the synthesis of enantiomerically pure compounds

Although the use of metals has implied the development of a wide range of novel catalytic transformations in the synthesis of enantiopure compounds, in the last two decades a new area, known as organocatalysis, has emerged as a very important tool in the development of asymmetric transformations.

2. ORGANOCATALYSIS

Organocatalysis consists on the use of substoichiometric amounts of small organic molecules as highly selective catalysts in stereocontrolled reactions. Over the years a wide range of transformations have been developed using this methodology allowing the access to complex enantiomerically pure molecules in an easy manner. The term “organocatalysis” was introduced in 2000 by Prof. MacMillan and since then, an enormous breakthrough was achieved both in the design of novel catalysts and in the development of new catalytic methodologies. A lot of types of catalysts have been used in this area involving different activation modes for the formation of new C-C bonds. In 2005, List reported a classification of

organocatalysts categorizing them as Brønsted base, Brønsted acid, Lewis acid and Lewis base catalysts according to its participation in the mechanism (Figure 1.2).[5,6]

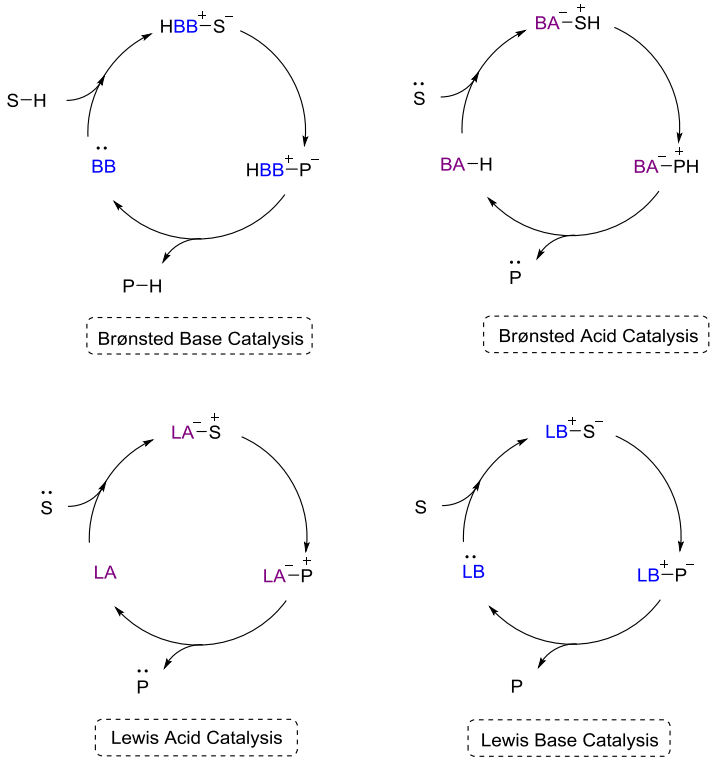

Figure 1. 2. Mechanistic classification of organocatalysts

In the following pages, a short overview of the field according to each catalyst category will be discussed.

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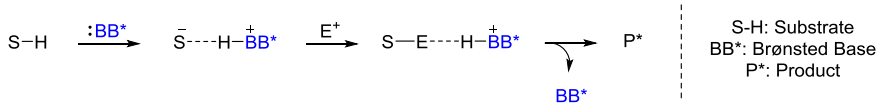
[5] Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.

[6] For some reviews on organocatalysis, see: (a) Yang, J. W.; List, B. *Science* **2006**, 1584. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (c) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178. (d) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618. (e) Marqués-Lopez, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep*. **2010**, *27*, 1138. (f) Marson, C. M. *Chem. Rev*. **2012**, *41*, 7712.

2.1. Brønsted bases

Brønsted bases activate the substrate through a partial deprotonation process generating a new species with enhanced nucleophilicity due to the formation of an ion-pair which is able to react with an electrophile furnishing the reaction product after the release of the catalyst (Scheme 1.1).[7]



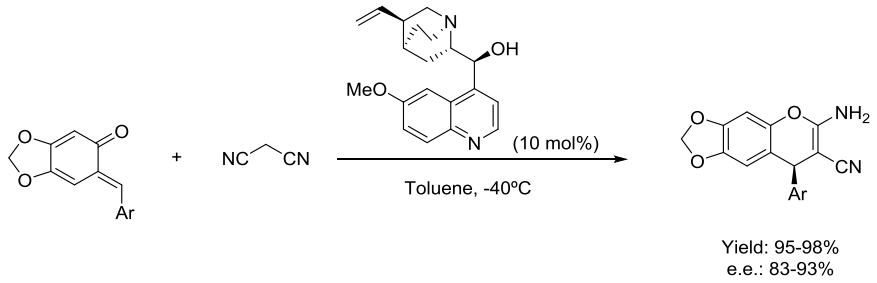
Scheme 1. 1. Brønsted base catalysis

Cinchona alkaloids are one of the most employed Brønsted base catalysts nowadays promoting a wide range of enantioselective transformations, such as, conjugate additions, cycloaddition reactions, epoxidations or hydrogenations.[8] Mechanistically, they are categorized as Brønsted bases when the nitrogen moiety abstracts a proton resulting in a chiral intermediate species which determines the facial selectivity of the transformation. The commercially available pseudoenantiomeric forms of several cinchona alkaloids convert them in one of the most chirality inducers, among which quinine and quinidine (pseudoenantiomer) or cinchonine and cinchonidine (pseudoenantiomer) stand out in asymmetric synthesis. Moreover, they present a bifunctional activity due to the presence of quinuclidine nitrogen and the hydroxyl group which present a basic character and Brønsted acidic character, respectively. The 1,2-aminoalcohol functionality is the responsible of the catalytic activity acting the quinuclidine as a base. As an example of this type of Brønsted base organocatalysts, a (4+2) cycloaddition of *ortho*-quinone methides (*o*-QMs) and malononitrile was reported by Han and

[7] (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev*. **2009**, *38*, 632. (b) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem*. **2010**, *291*, 145.

[8] (a) Tian, S.-K.; Chen, Y.; Huang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res*. **2004**, *37*, 621. (b) Park, H.-G.; Jeong, B.-S. Cinchona Alkaloids in Synthesis and Catalysis: *Cinchona-catalyzed nucleophilic α-substitution of carbonyl derivatives*. (Eds.: Song, C. E.), WILEY-VCH, pp 131-169, 2009. (c) Jang, H. B.; Lee, J. W.; Song, C. E. Cinchona Alkaloids in Synthesis and Catalysis: *Cinchona-catalyzed nucleophilic 1,2-addition to C=O and C=N bonds*. (Eds.: Song, C. E.), WILEY-VCH, pp 197-247, 2009. (d) Liu, Y.-K.; Chen, Y.-C. Cinchona Alkaloids in Synthesis and Catalysis: *Cinchona-catalyzed cycloaddition reactions.* (Eds.: Song, C. E.), WILEY-VCH, pp 297-324, 2009. (e) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *8*, 1229. (f) Gui, Y.-Y.; Yang, J.; Qi, L.-W.; Wang, X.; Tian, F.; Li, X.-N.; Peng, L.; Wang, L.-X. *Org. Biomol. Chem*. **2015**, *13*, 6371.

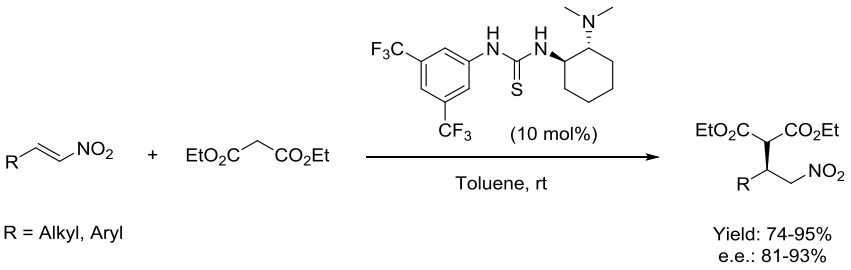
coworkers.[9] They provided a novel approach for the synthesis of 4*H*-chromenes in excellent yields and enantioselectivities employing quinine as reaction promoter (Scheme 1.2).



Scheme 1. 2. Quinine-catalyzed (4+2) cycloaddition

Sometimes, Brønsted bases are not able to activate less acidic substrates. In this case, the incorporation of other active functionality in the catalyst can overcome the pk_a issues. Thus, bifunctional catalysts were extended, which by combination of a Brønsted base character site and another site with hydrogen-bond donor ability, both electrophilic and nucleophilic counterparts of the reactions would be activated in the transition state, making the catalyst more selective. Michael reaction is the most common transformation carried out by these catalysts, being the enantioselective Michael reaction of malonates and nitroolefins carried out by the group of Takemoto one of the pioneers works in this field.[10] They proposed that both the nitroolefin and the malonate could be activated by the introduction of an additional basic, nucleophile-activating group in the catalyst, leading to a synergistic interaction between the functional groups. While diethyl malonate was activated by the tertiary amine, the thiourea activated the nitroolefin by hydrogen bond interactions. By the application of the bifunctional catalyst, Michael addition adducts were obtained in high yields and high enantiocontrol (Scheme 1.3).

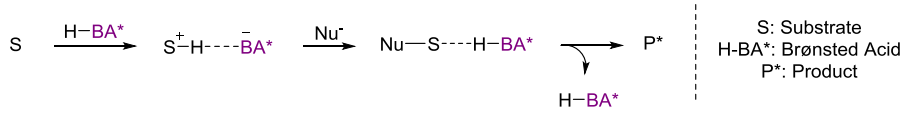
[9] Adili, A.; Tao, Z.-L.; Chen, D.-F.; Han, Z.-Y. *Org. Biomol. Chem*. **2015**, *13*, 2247.
[10] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672.



Scheme 1. 3. Bifunctional organocatalyst-catalyzed enantioselective Michael reaction

2.2. Brønsted acids

Brønsted acids interact with substrates through non-covalent interactions increasing the electrophilicity of the substrates and making them more susceptible towards the nucleophilic attack. Depending on the strength of the acid, the activation can be performed by protonation or by hydrogen-bonding interactions. In the case of strong acids, the substrate is protonated by the catalyst and the conjugate base stays next to the proton due to ionic interactions, being the conjugate base the responsible of inducing chirality. On the other hand, weaker acids can establish hydrogen-bonding interactions with the substrate, increasing its negative charge density and inducing the enantioselectivity. The main difference between the two activation modes relies on the bond distance, which is longer in the case of hydrogen-bonding interactions (Scheme 1.4).

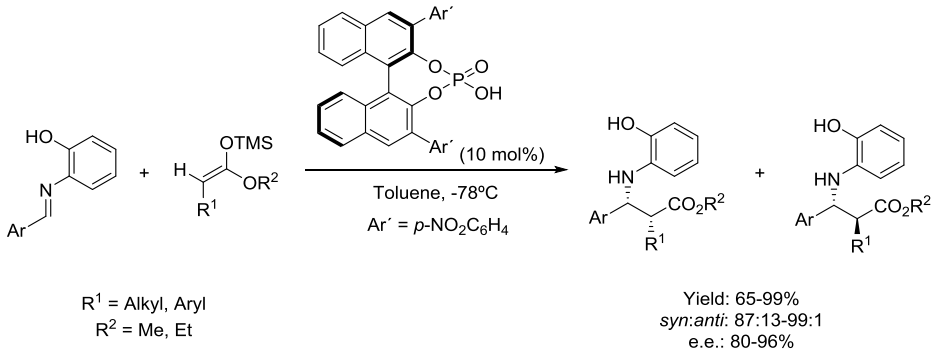


Scheme 1. 4. Brønsted acid catalysis

Among all the most employed chiral Brønsted acids, chiral phosphoric acids, chiral triflyl phosphoramides and chiral sulfonic acids stand out.[11] Chiral phosphoric acids are the archetypical chiral Brønsted acids used as catalysts in the last decade due to the wide range of enantioselective transformations which have been carried out with them. One of the most

[11] (a) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem*. **2010**, *291*, 395. (b) Cheon, C.-H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043. (c) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115,* 9277. (c) Akiyama, T. *Hydrogen Bonding in Organic Synthesis*, (Eds.: Pihko, P. M.) Wiley-VCH, Weinheim, 2009.

important properties of phosphoric acids is their bifunctionality. Apart from the acidic nature given by the hydroxyl group, the oxygen lone pair electrons of the P=O bond make the catalyst act also as a Brønsted base. Thus, they act as proton donors and acceptors, accelerating the reaction and increasing its selectivity. Nowadays, BINOL-derived chiral phosphoric acids are considered the most important Brønsted acid catalysts.[12] They are axially chiral with C2 symmetry and are able to prevent free rotation. Moreover, both enantiomers of BINOL are commercially available and the possibility of modulating their structure by the incorporation of substituents in 3 and 3´ positions, gives us the possibility of synthesizing a wide range of structurally similar catalysts with different electronic and steric properties. The group of Akiyama reported the first enantioselective Mannich-type reaction of silyl enolates with aldimines in which the C-N double bond was activated by a strong Brønsted acid (Scheme 1.5).[13] Both aromatic groups in 3 and 3´ positions, which were not coplanar with the BINOL structure, lead to an excellent asymmetric induction.



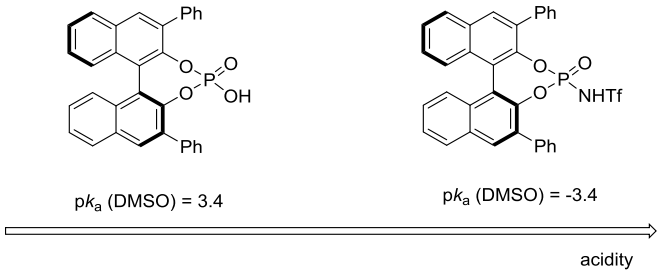
Scheme 1. 5. Chiral phosphoric acid-catalyzed enantioselective Mannich-type reaction

However, chiral phosphoric acids present some limitations towards some substrates such as carbonyl compounds. In these particular cases, BINOL-derived phosphoric acids are not acid

[12] Selected examples: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 11804. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558. (d) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1679. (e) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (f) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (g) Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal*. **2008**, *350*, 1457. (h) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc*. **2008**, *130*, 5652. (i) Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8225. (j) Zabaleta, N.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun*. **2018**, *54*, 8905. (k) Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev*. **2018**, *47*, 1142.

[13] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed*. **2004**, *43*, 1566.

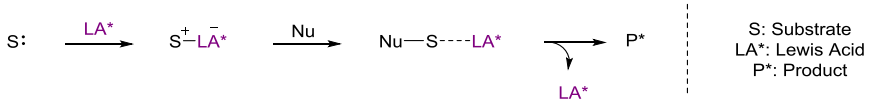
enough to activate them. To solve this limitation, in 2006, Yamamoto suggested that the use of phosphoramide as functional group could enhance the acidity of the catalyst significantly (Scheme 1.6).[14]



Scheme 1. 6. Enhancement of the acidity of a Brønsted acid: *N*-Triflylphosphoramide *vs* phosphoric acid

2.3. Lewis acids

Compounds containing carbocations, silyl or phosphonium cations present Lewis acid catalytic properties, as well as phase transfer catalysts. However the number of asymmetric transformations catalyzed by a Lewis acid organocatalyst is limited, not observing high levels of enantiocontrol, being the majority of the transformations carried out by achiral catalysts.[15] Lewis acids activate the substrates through electrostatic interactions by pulling away electrons making the substrate more electrophilic. As consequence, the nucleophilic attack is favored, generating the new species as reaction product (Scheme 1.7).

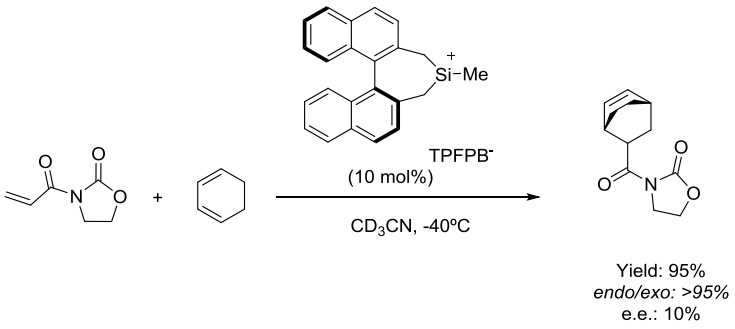


Scheme 1. 7. Lewis acid catalysis

[14] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc*. **2006**, *128*, 9626. For more transformations involving *N*-Triflylphosphoramides, see: (a) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097. (b) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 593. (c) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2008**, *47*, 2411. (d) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5661. (e) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem. Int. Ed*. **2008**, 47, 6798. (f) Held, F. E.; Grau, D.; Tsogoeva, S. B. *Molecules*, **2015**, *20*, 16103. (g) Villar, L.; Uria, U.; Martinez, J. I.; Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed*. **2017**, *56*, 10535.

[15] Sereda, O.; Tabassum, S.; Wilhelm, R. *Top. Curr. Chem*. **2010**, *291*, 349.

Chiral silane Lewis acid catalysts have acquired importance in organocatalysis due to their compatibility with many carbon nucleophiles which gives them the possibility to be part of nucleophilic additions or cycloaddition reactions, among others.[16] Jørgensen and coworkers were the pioneers synthesizing the first chiral silyl cation and reporting its application in an enantioselective Diels-Alder reaction.[17] The acidity of these catalysts comes from vacant *d* orbitals at silicon atom, which give to it capability of valence shell expansion. Lewis bases interact with the vacant *d* orbitals on tetravalent silicon, with the consequent expansion of its coordination number to five. The formal hybridization on silicon changes from tetravalent (sp^3) to pentavalent (sp^3d). After this interaction an increasement of the electron density at ligands and the silicon atom takes place, making the silicon be more positively charged, acting as a Lewis acid. The authors suggested that polar solvents contributed to the improvement of the catalytic system. By performing the reaction in deuterated acetonitrile, the solvent coordinated too strongly to the silyl cation allowing the reaction to take place stereoselectively (Scheme 1.8).



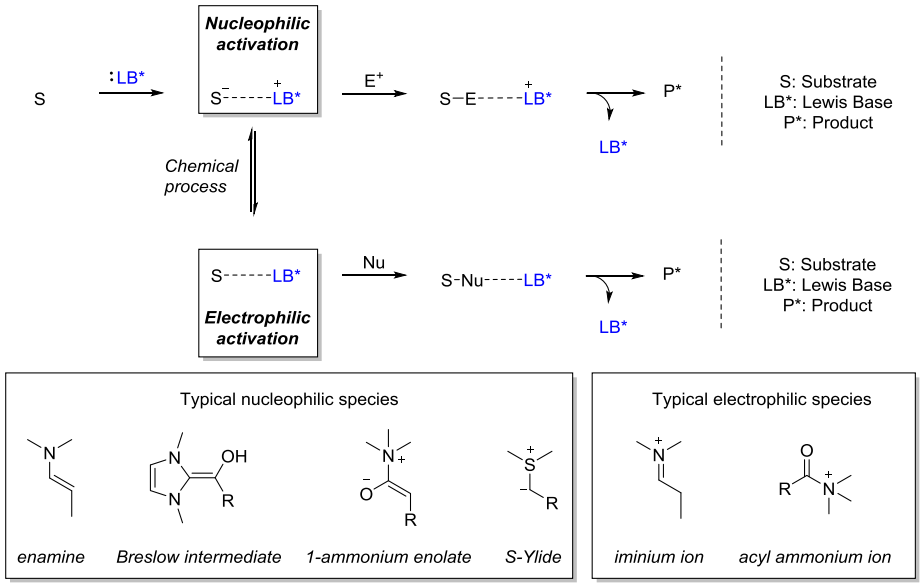
Scheme 1. 8. Axial chiral silyl salt-catalyzed Diels-Alder reaction

[16] (a) Hara, K.; Akiyama, R.; Sawamura, M. *Org. Lett*. **2005**, *7*, 5621. (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc*. **2005**, *127*, 2858. (c) Tang, Z.; Mathieu, B.; Tinant, B.; Dive, G.; Ghosez, L. *Tetrahedron* **2007,** *63*, 8449.

[17] Johannsen, M.; Jørgensen, K. A.; Helmchen, G. *J. Am. Chem. Soc*. **1998**, *120*, 7637.

2.4. Lewis bases

The majority of the organocatalysts are classified as Lewis bases. They can activate substrates by the formation of a covalent bond converting them in activated nucleophiles or electrophiles, and promote the reaction in an enantioselective manner (Scheme 1.9). Among all Lewis base organocatalysts, enamine, iminium, carbene catalysis and catalysis *via* ylides stand out as the most developed ones.

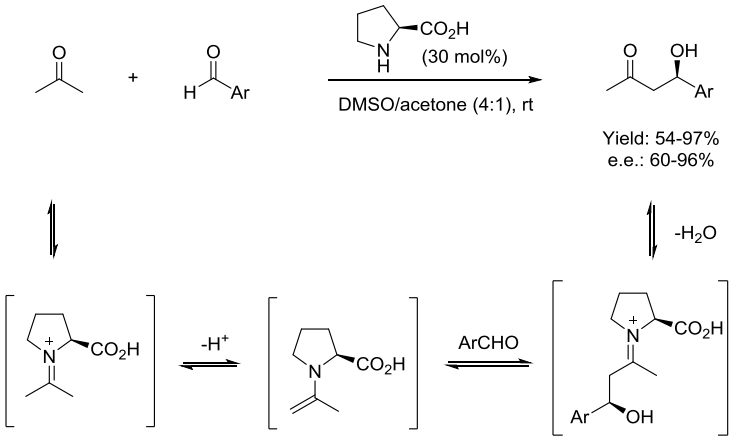


Scheme 1. 9. Lewis base catalysis

One of the pioneer examples in enamine catalysis was reported by List, Lerner and Barbas III.[18] It was the first example of the use of an organocatalyst for the intramolecular asymmetric aldol reaction. Proline was used as catalyst in the aldol reaction between acetone and differently substituted aromatic aldehydes, obtaining the corresponding aldol products in high yields and high enantioselectivities (Scheme 1.10). The mechanism of the reaction can be explained by an initial condensation of proline with ketone generating an iminium ion which is easily deprotonated rendering a nucleophilic enamine species. This enamine reacts with aromatic aldehyde electrophiles, furnishing an iminium ion species which is then hydrolyzed to

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

the final aldol product.[19] Enamine formation is facilitated by the dramatic increase in C-H acidity of the alfa-proton upon initial conversion of the carbonyl compound into an iminium ion. This is due to the catalyst-substrate iminium-type adduct has a LUMO lower in energy compared to the carbonyl compound. As consequence, an enamine with a HOMO higher in energy is formed which presents a major nucleophilicity than the corresponding enol. This strategy has been employed for the α-functionalization of aldehydes and ketones.[20]

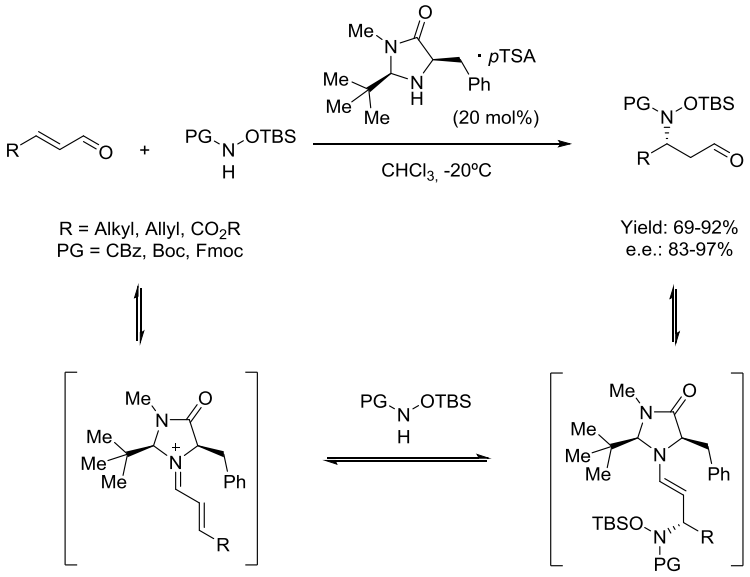


Scheme 1. 10. Enamine catalysis

In iminium catalysis the active species consists on an iminium ion which is generated after the condensation of the amine with α,β-unsaturated aldehydes.[21] In this field, Macmillan developed a variety of chiral secondary amine catalysts which participate in asymmetric iminium activation of enals and enones. One of the first examples in this field was the enantioselective organocatalytic amine conjugate addition to α,β-unsaturated aldehydes.[22] This chemo- and stereoselective transformation led to the formation of enantioenriched β-amino aldehydes in high yields (Scheme 1.11). The reaction starts by the condensation of the catalyst with the carbonyl compound generating an iminium ion which posseses an electrophilic character. The iminium intermediate is very reactive at β position due to the

[19] List, B. *Acc. Chem. Res*. **2004**, *37*, 548.
[20] (a) Mukherjee, S.; Woon Yang, J.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Sulzer-Massé, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123. (c) Kano, T.; Maruoka, K. *Chem. Sci*. **2013**, *4*, 907.
[21] (a) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79. (b) Erkkilä, A.; Mojander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
[22] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2006**, *128*, 9328.

LUMO energy lowering effect being able to react with nucleophiles, such as *N*-silyloxycarbamates. After the nucleophilic addition, an enamine species is formed which after enamine/iminium tautomerism and hydrolysis furnishes the final β-functionalized product.



Scheme 1. 11. Iminium catalysis

As it can be observed, both mechanistic cycles present common species such as enamine and iminium ion intermediates. The reaction presents the ability of moving from one intermediate to the other which led to the combination of both mechanistic cycles promoting iminium/enamine cascade catalysis.[23] The generated enamine species formed after the β-functionalization of the iminium ion, can react with an electrophile leading to α,β-difunctionalized compounds.

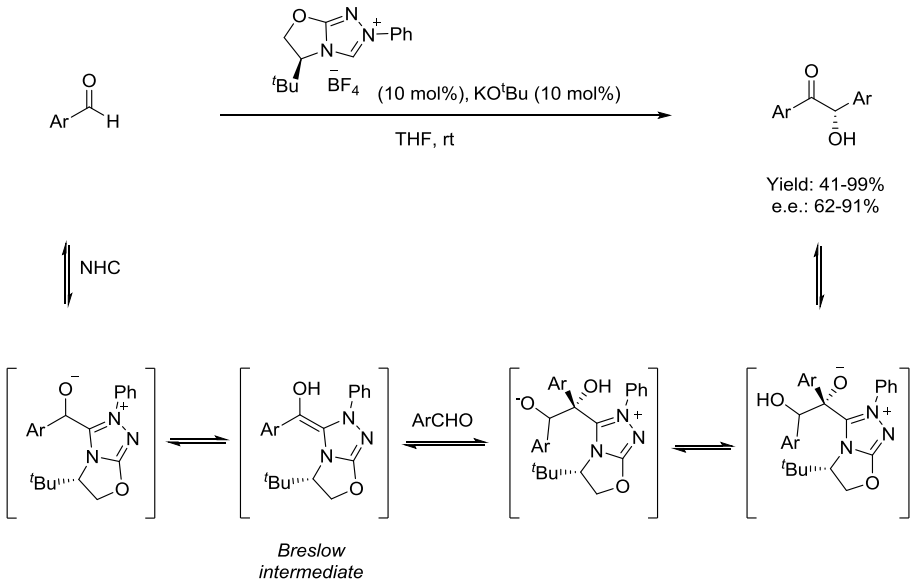
[23] For reviews on organocatalytic iminium/enamine cascade catalysis, see: (a) Pellisier, H. *Adv. Synth. Catal*. **2012**, *354*, 237. (b) Pellisier, H. *Chem. Rev*. **2013**, *113*, 442. (c) Volla, C. M. R.; Atodiresei, L.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390. (d) Vetica, F. de Figueriedo, R. M.; Orsini, M.; Tofani, D.; Gasperi, T. *Synthesis* **2015**, *47*, 2139.

N-heterocyclic carbenes (NHC) have been also considered Lewis base catalysts.[24] These singlet carbenes present a higher stability due to the presence of at least one nitrogen atom adjacent to the open shell atom. This nitrogen atom is able to donate electron density to the unoccupied *p*-orbital (LUMO) while it removes electron density from the carbine carbon through a σ-bond.[25] *N*-heterocyclic carbenes have gained much attention in organocatalysis due to their capability of generating reaction intermediates, such as Breslow intermediate, with the potential to interact with additional reagents. In this field, Enders described the synthesis of a bicyclic chiral triazolium salt as a novel precatalyst to promote an asymmetric version of the benzoin condensation (Scheme 1.12).[26] The authors synthesized a variety of aromatic α-hydroxyketones in moderate to good yields and high values of enantioselectivity. The nucleophilic addition of the catalyst to the aldehyde generated a tetrahedral intermediate which furnished the Breslow intermediate after a proton shift. This nucleophilic intermediate was able to react with a second molecule of the aldehyde leading to an alkoxide intermediate, which after a proton transfer furnished the final product releasing the catalyst. The high asymmetric induction observed could be resulted from the conformational rigidity of the bicyclic nucleophilic catalyst and the shielding of the Breslow intermediate by the *tert*-butyl group.

[24] For selected reviews on the use of NHCs as organocatalyst, see: (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Biju, A. K.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (e) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed*. **2012**, *51*, 314. (f) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (g) Chen, X.-Y.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 7991. (h) Flanigan, D. M.; Romanov-Michaidilis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (i) Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14912. (j) Walden, D. M.; Ogba, O. M.; Johnston, R. C.; Cheong, P. H. *Acc. Chem. Res.* **2016**, *49*, 1279. (k) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Synthesis* **2017**, *49*, 451.

[25] (a) Cazin, C. S. J. *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Springer: London, 2011. (b) Díez-Gónzalez, S. *From Laboratory Curiosities to Efficient Synthetic Tools*; RSC Publishing: Cambridge, 2011. (c) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.

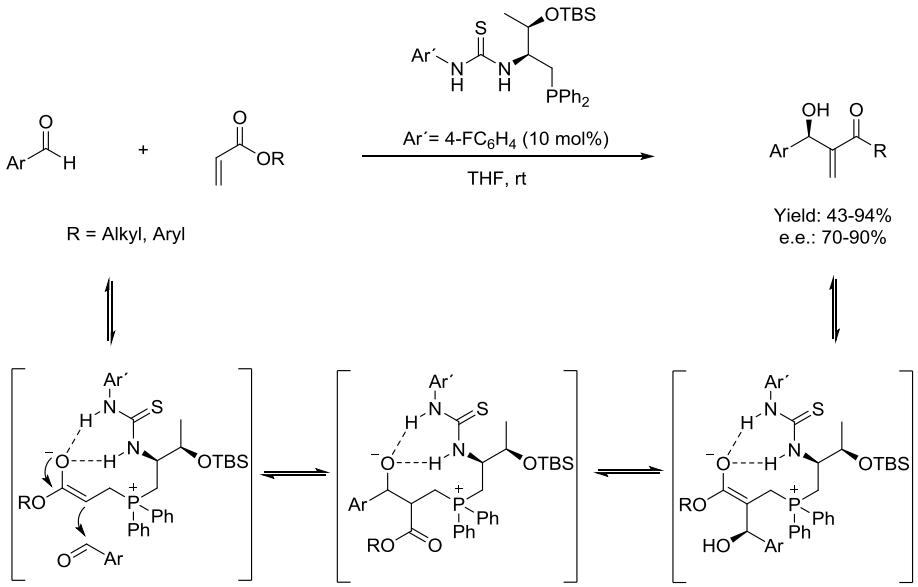
[26] Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed*. **2002**, *41*, 1743.



Scheme 1. 12. NHC-catalyzed enantioselective benzoin condensation

Phosphanes can also act as Lewis base catalysts being their contribution to this field remarkably over the years.[27] An example of phosphane-catalyzed transformation is the Morita-Baylis-Hillman (MBH) reaction which has been widely studied in the last decades. In the field of asymmetric synthesis, Lu and coworkers developed a bifunctional phosphane-thiourea organocatalyst which could promote the MBH reaction between acrylates and aromatic aldehydes (Scheme 1.13).[28] The reaction mechanism is explained by the reversible conjugate addition of the phosphane catalyst to the acrylate generating a phosphonium enolate intermediate. This structurally well-defined intermediate underwent an intermolecular aldol reaction with the aromatic aldehyde in a high stereochemically selective manner, being the responsible of the high enantioselectivity observed. The generated intermediate furnished the final MBH adduct after a proton transfer process and a β-elimination, regenerating the catalyst.

[27] (a) Marinetti, A.; Voituriez, A. *Synlett*, **2010**, *2*, 174. (b) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. *Chem. Rev*. **2018**, *118*, 10049.
[28] Han, X.; Wang, Y.; Zhang, F.; Lu, Y. *Org. Biomol. Chem*. **2011**, *9*, 6734.



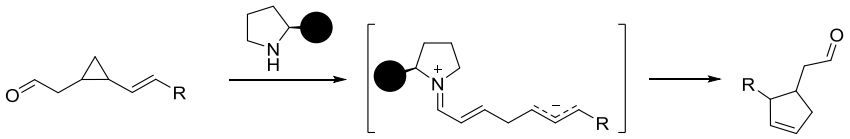
Scheme 1. 13. MBH reaction between acrylates and aromatic aldehydes

As it can be appreciated in this section, catalysis promoted by Lewis bases constitutes nowadays one of the most important features for the construction of new C-C, C-N or other bonds in an enantioselective fashion by the use of structurally different catalysts such as amines, phosphanes or carbenes. The work complied in this manuscript will be focused on the development of novel stereoselective transformations promoted by Lewis bases.

3. GENERAL OBJECTIVES

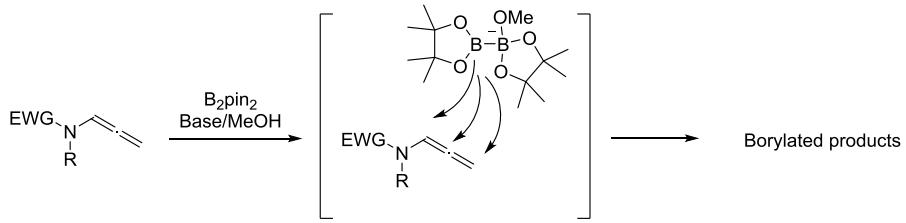
The work summarized in this thesis has been developed in line with the current research activity of the group, focused on the study of novel transformations within the field of organocatalysis. This research work will be present in different parts.

In the first part and based on the experience achieved by the group in the field of aminocatalysis and the use of this activation manifold in reactions involving the ring-opening of strained cyclopropanes containing molecules, the **aminocatalyzed vinylcyclopropane-cyclopentene rearrangement** will be studied (Scheme 1.14). This is an underdeveloped reaction that typically requires harsh conditions and long reaction times. Remarkably, there is not any catalytic enantioselective example of this reaction. For this purpose, we have envisaged the possibility of using cyclopropylacetaldehydes with a vinyl substituent as suitable substrates for this transformation. Our hypothesis relies on the formation of a donor-acceptor cyclopropane after the condensation of a chiral aminocatalyst with the formyl group. Donor-acceptor cyclopropane would undergo a ring-opening reaction leading to a zwitterionic intermediate which would go through a ring-closing process furnishing the corresponding cyclopentene product. The enantioselection of the reaction is planned to be controlled by the geometry of the catalyst.



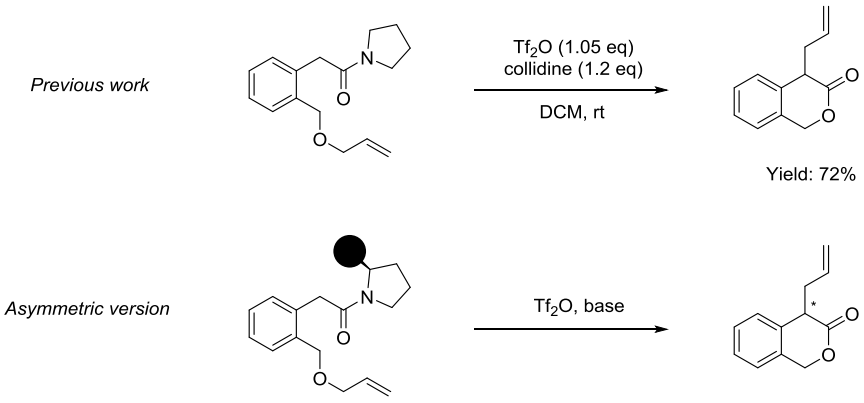
Scheme 1. 14. Aminocatalyzed vinylcyclopropane-cyclopentene rearrangement

In the second part, the **transition metal-free borylation of allenylamides** will be presented. Joining with the experience of Prof. Elena Fernández of University Rovira i Virgilli in Tarragona the metal-free activation of B_2pin_2 and its reactivity towards allenylamides will be studied. The borylation will be developed by alkoxide activation of B_2pin_2 which afford a nucleophilic boron moiety which can be added to the different electrophilic positions of the allenylamide system (Scheme 1.15).



Scheme 1. 15. Transition metal-free boylation of allenylamides

Finally a research performed during a short stay at the University of Vienna under the supervision of Prof. Nuno Maulide will be discussed. This chapter deals with the use of triflic anhydride for the activation of amides which is nowadays one of the main research lines of the group. Besides, the group has previously developed a [3,3]-sigmatropic rearrangement of keteniminium salts and different variants of this rearrangement were carried out over a wide variety of substrates. The main objective of this short stay was extending the scope of the **asymmetric version of this [3,3]-sigmatropic rearrangement which involved an amide activation step** (Scheme 1.16), using chiral auxiliaries in order to control the stereochemical outcome of the reaction.



Scheme 1. 16. Amide activation/[3,3]-sigmatropic rearrangement

Chapter 2

2

Aminocatalytic Enantioselective Vinylcyclopropane-cyclopentene (VCP-CP) Rearrangement

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1. INTRODUCTION

Cyclopropanes are considered privileged structures in organic synthesis due to they can participate in many different transformations, playing an important role in the chemical synthesis. Since Freund first synthesized cyclopropane in 1882,[1] it has become an important scaffold, especially from the point of view of its structural features that is also present in a wide number of natural products and pharmaceuticals. These three-membered rings present a ring strain of 115 KJ/mol which can be attributed to both angular and torsional strain.[2] On the one hand, the angular strain makes cyclopropanes to have a bond angle of 60° (C-C-C) instead of 109.5° corresponding to a sp^3 hybridized carbon atom and, on the other the torsion strain derived from the eclipsed conformation of the hydrogen atoms due to the planar structure of the cyclopropane. Furthermore, cyclopropane presents shorter C-H and C-C bonds than propane, and present higher reactivity than their acyclic analogues.

Despite the high ring strain of cyclopropanes, their C-C bonds are kinetically inert and therefore, cyclopropanes must be activated towards a ring-opening reaction using different approaches which widens the number of potential reactions in which these compounds can be involved in. Thereby, cyclopropanes can be activated placing acceptor substituents (electrophilic cyclopropanes), donor substituents (nucleophilic cyclopropanes), or both donor and acceptor substituents (donor-acceptor cyclopropanes) (Scheme 2.1). An electrophilic cyclopropane is generated when an electron-withdrawing group is located in the cyclopropane, which can stabilize the negative charge generated after the ring-opening event, showing the typical reactivity as homo-Michael acceptor (Scheme 2.1 a).[3] On the other hand, the introduction of a donor substituent in the cyclopropane moiety generates a nucleophilic cyclopropane being the ring-opening process initiated by an electrophile generating a positive charged intermediate (Scheme 2.1 b).[4] This chemical behavior can be visualized as if the nucleophilic cyclopropane could be considered as an homo-enolate equivalent. Finally, it is also possible to place substituents with different electronic properties in vicinal positions of the

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[1] Freund, A. *J. Prakt. Chem*. **1882**, *26*, 367.

[2] De Meijere, A. *Angew. Chem. Int. Ed*. **1979**, *18*, 809.

[3] Reviews on acceptor cyclopropanes: (a) Verhé, R.; de Kimpe, N. *In the Chemistry of Cyclopropyl Group*, (Eds.: Rappoport, Z.), Wiley, pp 445-564, Great Britain, 1987. (b) de Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051.

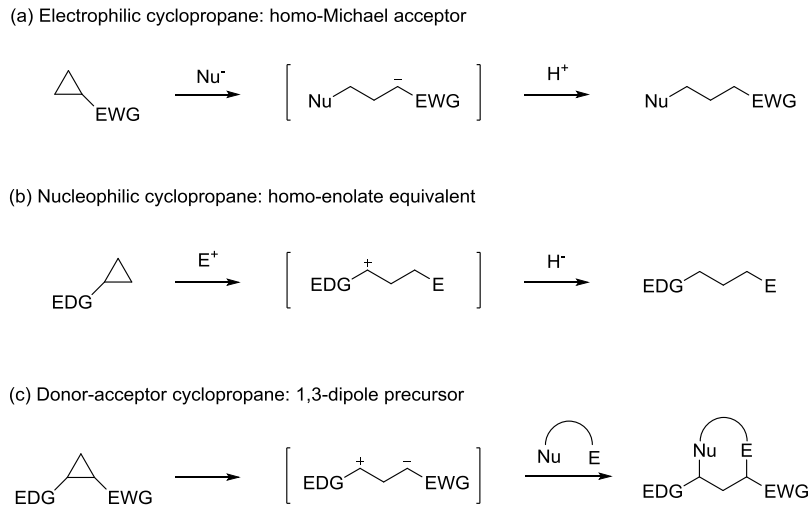
[4] Reviews on donor cyclopropanes: (a) Gibson, D. H.; DePuy, C. H. *Chem. Rev*. **1974**, *74*, 605. (b) Salaun, J. *Chem. Rev*. **1983**, *83*, 619. (c) Kulinkovich, O. G. *Chem. Rev*. **2003**, *103*, 2597. (d) Guijarro, D.; Yus, M. *Curr. Org. Chem*. **2005**, *9*, 1713.

cyclopropane, leading to donor-acceptor cyclopropanes.[5] Vicinally substituted donor-acceptor cyclopropanes present a synergistic effect inducing high polarization to the C-C bond (Scheme 2.1 c). This leads to a weaker bond that has increased kinetic tendency to undergo ring-opening, generating a 1,3-zwitterionic species (1,3-dipole), in which the positive charge is stabilized by the donor and the negative charge is stabilized by the acceptor moiety. Typically, the 1,3-dipole makes the donor-acceptor cyclopropane to take part in cycloaddition reactions[6] acting as a dipole and reacting with dipolarophiles or substrates bearing nucleophile and electrophile in the same molecule, this case affording five- ((3+2) cycloaddition), six- ((3+3) cycloaddition), or seven- ((3+4) cycloaddition) membered cyclic structures. It has to be mentioned that computational and experimental studies in several particular cases have demonstrated that the effect of the electron-donating substituents on the polarization of the C-C bond of the donor-acceptor cyclopropanes is more relevant than the effect of electron-withdrawing substituents.[7] Cyclopropanes substituted by both electron-withdrawing and electron-donating groups, known as donor-acceptor (D-A) cyclopropanes, are nowadays powerful reagents that can be used in a wide range of chemical transformations.

[5] Reviews on donor-acceptor cyclopropanes: (a) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (b) Mel´nikov, M. Y.; Budyna, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendelv. Commun*. **2011**, *21*, 293. (c) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804. (d) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem*. **2015**, *13*, 655. (e) Gharpure, S. J.; Nanda, L. N. *Tetrahedron Lett*. **2017**, *58*, 711.

[6] Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed*. **2014**, *53*, 5504.

[7] Schneider, T. F. Werz, D. B. *Org. Lett*. **2011**, *13*, 1848.



Scheme 2. 1. Reactivity modes of differently activated cyclopropanes

The chemistry of vinylcyclopropanes deserves special attention.[8] The combination of the alkene moiety with the presence of the strained cyclopropane scaffold provides a very particular reactivity pattern to these compounds. In addition, the principle of vinylogy anticipates that the nucleophilic or electrophilic character of the cyclopropane moiety is transmitted across the π bond of the alkene, providing different reactivity patterns and possibilities for other chemical reactions.[9] In fact, vinylcyclopropanes present an *s-trans-gauche* conformation which allows the maximum orbital overlap of the asymmetric component of cyclopropane orbitals with the π or π* orbitals of the ethylene unit (Figure 2.1). This behavior together with the high strain energy of 27.5 kcal/mol makes them present diverse modes of reactivity, and in some cases, different to those presented before.[10]

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[8] For selected reviews on vinylcyclopropanes: (a) Willcott, M. R.; Cargle, V. H. *J. Am. Chem. Soc.* **1967**, *89*, 723. (b) Sarel, S.; Jovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 5. (c) Willcot, M. R.; Cargill, R. L.; Sears, A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25. (d) Dolbier, W. R. *Acc. Chem. Res.* **1981**, *14*, 195. (e) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (f) Thakur, A.; Louie, J. *Molecular Rearrangements in Organic Synthesis,* (Eds.: Rojas, C. M.), Wiley & Sons, pp 323-362, Utah, 2016. (g) Vshyvenko, S.; Reed, J. W.; Piers, E. C*omprehensive Organic Synthesis II*, (Eds.:Trost, B.), Elsvevier, pp 999-1076, Canada, 2014.

[9] (a) Fuson, R. C. *Chem. Rev*. **1935**, *16*, 1. (b) Curti, C.; Battistini, L.; Sartori, A.; Zanardi, F. *Chem. Rev*. **2020**, *120*, 2448.

[10] Hudlicky, T.; Reed, J. W. *Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry*: Rearrangements of vinylcyclopropanes and related systems. (Eds.: Trost, B.; Paquette, L. A.), Elsevier, pp 899-970, Oxford, 1991,.

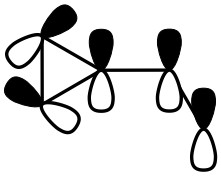
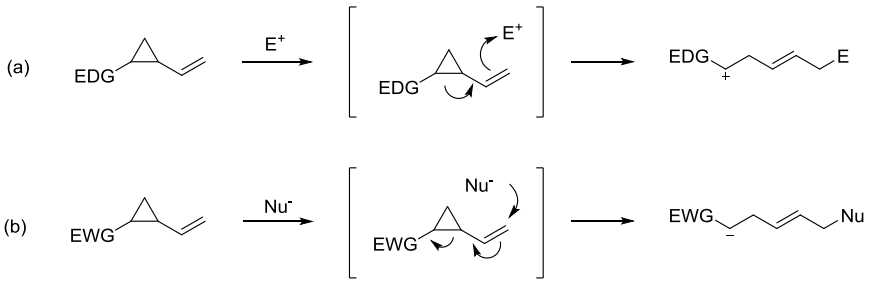


Figure 2. 1. Vinylcyclopropane

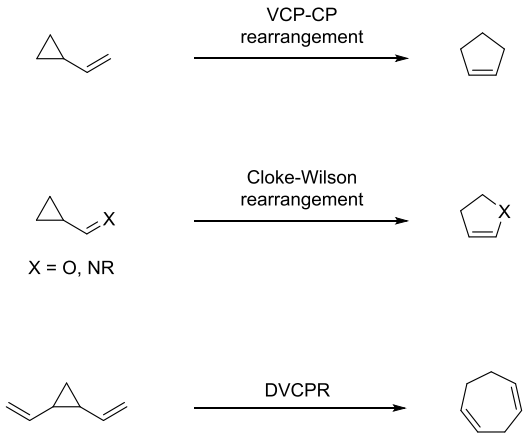
Different reactivity modes can be observed depending on the substituents located in the cyclopropane ring and/or in the vinyl moiety. The ring-opening reaction of the vinylcyclopropane can be mediated by an electrophile or a nucleophile (Scheme 2.2). Vinylcyclopropanes bearing an electron-donating substituent undergo electrophile-promoted ring-opening reaction, which involves the cleavage of the cyclopropane C-C bond to form a carbocation stabilized by the EDG group (Scheme 2.2 a). On the other hand, vinylcyclopropanes with electron-withdrawing groups in their structure undergo a nucleophile-promoted ring-opening process, generating an electron-withdrawing group-stabilized carbanion (Scheme 2.2 b).



Scheme 2. 2. Electrophile- and nucleophile-promoted vinylcyclopropane ring-opening reactions

Apart from ring-opening reactions, vinylcyclopropanes can take part in other transformations (Scheme 2.3). On the one hand, *cis*-disubstituted vinylcyclopropanes can undergo a concerted [1,5]-H shift to 1,4-dienes. On the other hand, *trans*-disubstituted vinylcyclopropanes can suffer from a [1,3]-sigmatropic alkyl shift to form cyclopentenes. The latter process, which is known as the vinylcyclopropane-cyclopentene (VCP-CP) rearrangement, can be easily performed due to the lower energy associated to the structure of cyclopentenes. Apart from the vinylcyclopropane-cyclopentene rearrangement, other related rearrangements

have been also reported, such as the heteroatom variants, the Cloke-Wilson rearrangement[11] and the rearrangement of vinylaziridines and vinyloxiranes[12] and its vinylogous version, the divinylcyclopropane-cycloheptadiene rearrangement (DVCPR) (Scheme 2.3).[13]



Scheme 2. 3. Rearrangement processes of vinylcyclopropanes

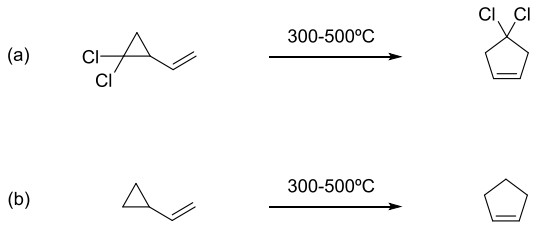
As mentioned, the vinylcyclopropane-cyclopentene (VCP-CP) rearrangement, which is the most developed mode of reactivity of vinylcyclopropanes, consists on a [1,3]-sigmatropic carbon shift involving the formation of a cyclopentene from the ring expansion of the

[11] For some examples of Cloke-Wilson rearrangement, see: (a) Stevens, R. V. *Acc. Chem. Res*. **1977**, *10*, 193. (b) Howell, A. R.; Martin, W. R.; Sloan, J. W.; Smith, W. T. *J. Heterocyclic Chem*. **1991**, *28*, 1147. (c) Funke, C.; Es-Sayed, M.; De Meijere, A. *Org. Lett*. **2000**, *2*, 4249. (d) Ydav, U. K.; Balamurugan, R. *Org. Lett*. **2001**, *3*, 2717. (e) Pinnick, H. W.; Chang, Y.-H. *Tetrahedron Lett*. **2001**, 3, 2717. (f) Honda, M.; Naitou, T.; Hoshino, H; Takagi, S.; Segi, M.; Nakajima, J. *Tetrahedron Lett*. **2005**, *46*, 7345. (g) Gräbe K; Zwafelink, B.; Doye, S. *Eur. J. Org. Chem*. **2009**, *5*, 565. (h) Tomilov, Y. V.; Platonov, D. N.; Frumkin, A.-E.; Lipilin, D. L.; Salikov, R. F. *Tetrahedron Lett*. **2010**, *51*, 5120. (i) Saha, S.; Reedy, U. R.; Patro, B. *Tetrahedron Lett*. **2011**, *52*, 4014. (j) Gropi, E.; Namboothiri, I. N. N. *J. Org. Chem*. **2013**, *78*, 910. (k) Kaschel, J.; Schneider, T. F.; Schirmer, P.; Maaβ, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem*. **2013**, 4539. (l) Cai, J.; Li, F.; Deng, G.-J.; Ji, X.; Huang, H. *Green Chem*. **2016**, *18*, 3503. (m) Zhang, J.; Jang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. *Org. Lett*. **2017**, *19*, 3043.

[12] For some examples of heteroatom containing VCP-CP rearrangement, see: (a) Atkinson R. S.; Rees, C. W. *Chem. Commun*. **1967**, 1232. (b) Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem*. **1968**, *33*, 481. (c) Paladini, J. C.; Chuche, J. *Tetrahedron Lett*. **1971**, *12*, 4383. (d) Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054. (e) Brichacek, M.; Lee, D.; Njardarson J. T. *Org. Lett*. **2008**, *10*, 5023. (f) Brichacek, M.; Njardarson, J. T. *Org. Biomol. Chem*. **2009**, *7*, 1761. (g) Brichacek, M.; Villalobos, M. N.; Plichta, A.; Njardarson, J. T. *Org. Lett*. **2011**, *13*, 1110.

[13] For some examples of DVCPR, see: (a) Arai, M.; Crawford, R. J. *Can. J. Chem*. **1972**, *50*, 2158. (b) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, 1. (c) Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2013**, *52*, 6396. (d) Wu, J.; Jong, Y.; Wei, W.; Wu, Y.; Li, Y.; Xhang, J.; Zheng, Y.; Xu, S. *Angew. Chem. Int. Ed*. **2018**, *57*, 6284. (e) Apel, C.; Hartmann, S. S.; Lentz, D.; Christmann, M. *Angew. Chem. Int. Ed*. **2019**, *58*, 5075.

vinylcyclopropane *via* C-C bond cleavage. Through this transformation it is possible to access in a selective manner to cyclopentene building blocks which are presented in a wide range of natural products.[14] This reaction was discovered by Neureiter in 1959 who synthesized 4,4-dichlorocyclopentenes from 1,1-dichloro-2-vinylcyclopropane under thermal conditions (Scheme 2.4 a).[15] One year later, Vogel[16] and Overberger and Borchert[17] described independently the conversion of simple vinylcyclopropanes into cyclopentenes under similar conditions as those used by Neureiter (Scheme 2.4 b).



Scheme 2. 4. Pioneering works in vinylcyclopropane-cyclopentene rearrangements

Since the discovery of these pioneering examples of the vinylcyclopropane-cyclopentene rearrangement, thermal conditions were the selected method for overcoming the high energy barrier associated to the process. Despite the wide range of examples of VCP-CP rearrangement presented in the last century, the necessary drastic conditions showed poor functional group compatibility and in most of the cases unfunctionalized substrates should be used for performing this rearrangement. In order to widen the scope of this transformation, a lot of efforts have been made over the years which have ended up in the development of new strategies for carrying out the transformation in mild conditions. Thus, photochemical or transition metal-catalyzed rearrangements have been developed. In the following pages, an overview of the most relevant examples of VCP-CP rearrangements will be provided.

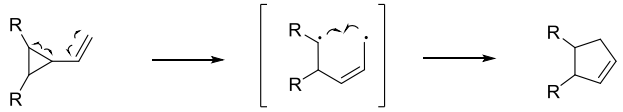
[14] (a) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React*. **1985**, *33*, 247. (b) Hudlicky, T.; Reed, J. W. *Angew. Chem. Int. Ed*. **2010**, *49*, 4864.
[15] Neureiter, N. P. *J. Org. Chem.* **1959**, *24*, 2044.
[16] Vogel, E. *Angew. Chem*. **1960**, *72*, 4.
[17] Overberger, C. G.; Borchert, A. E. *J. Am. Chem. Soc*. **1960**, *82*, 1007.

1.1. Thermal VCP-CP rearrangement

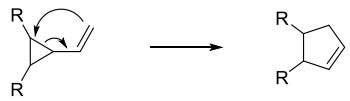
1.1.1. Mechanism

Generally, it is thought that thermal vinylcyclopropane-cyclopentene rearrangement takes place by two different mechanistic pathways: homolytic fission or a pathway involving a concerted, orbital symmetry-controlled process (Scheme 2.5).[8e,14a,18]

(a) Homolytic fission or diradical-mediated pathway



(b) [$2\sigma_s + 2\pi_s$] concerted pathway



Scheme 2. 5. Mechanistic pathways for thermal VCP-CP rearrangement

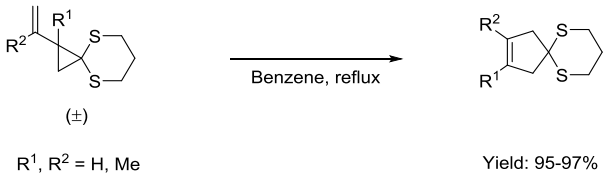
Distinguishing between the two mechanistic pathways is not trivial because the activation energy for the concerted rearrangement is not low enough to exclude a non concerted biradical mechanism. While kinetic studies support a biradical mechanism, the stereoespecific nature of most of the VCP-CP rearrangements reported, lead to the idea that thermal VCP-CP rearrangement could be considered a concerted process. The bond-dissociation energy of the cyclopropane ring cleavage is 65 kcal/mol, which decrease up to 50 kcal/mol in the case of vinylcyclopropanes. This fact would propose the participation of a biradical intermediate due to the resonance stabilization energy of the allyl radical is 13 kcal/mol.

As a consequence, it can be concluded that nowadays the mechanism for the thermal vinylcyclopropane-cyclopentene rearrangement is not clear. It is mostly believed that the rearrangement takes place through a biradical pathway; however, there are some cases in which the concerted pathway might operate as well.

[18] (a) Baldwin, J. E. *Chem. Rev*. **2003**, *103*, 1197. (b) Baldwin, J. E.; Leber, P. A. *Org. Biomol. Chem*. **2008**, *6*, 36.

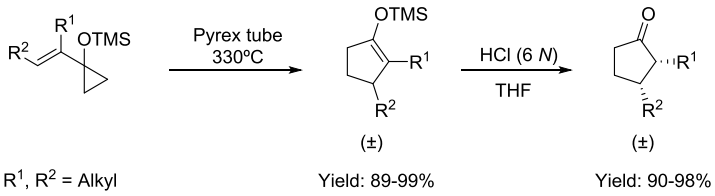
1.1.2. Scope of the reaction

After its discovery in the early 60s, the first example of a vinylcyclopropane-cyclopentene thermal rearrangement for synthetic purposes was reported by Corey in 1972. He described the rearrangement of thioacetals derived vinylcyclopropanones to the corresponding substituted cyclopentenes in benzene refluxing solution (Scheme 2.6).[19]



Scheme 2. 6. Thermal rearrangement of vinylcyclopropanone dithioacetals

One year later, the thermolysis of silyloxy substituted vinylcyclopropanols was reported by Trost leading to the quantitative formation of the corresponding cyclopentenes.[20] The role of this protecting group was to decrease the bond-dissociation energy for the vinylcyclopropane from 51 kcal/mol to 42 kcal/mol. This methodology enabled the synthesis of differently substituted cyclopentanones after hydrolysis of the silyl enol ether moiety (Scheme 2.7).[21]

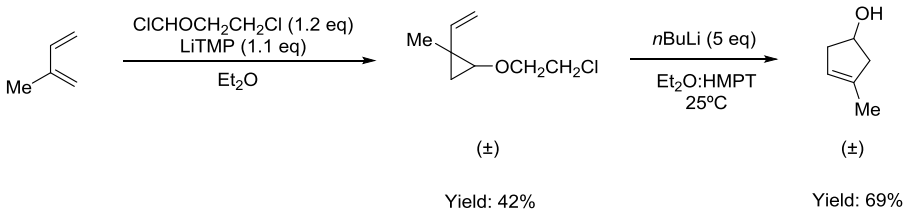


Scheme 2. 7. VCP-CP rearrangement of silyloxycyclopropanes

One of the drawbacks of thermal rearrangements is the high temperature that reaction requires to take place. Some progress regarding the reaction temperature has been made over the years. The group of Danheiser demonstrated that the reaction rate would be enhanced by the use of lithium salts of vinylcyclopropanols. This brought the possibility of decreasing the

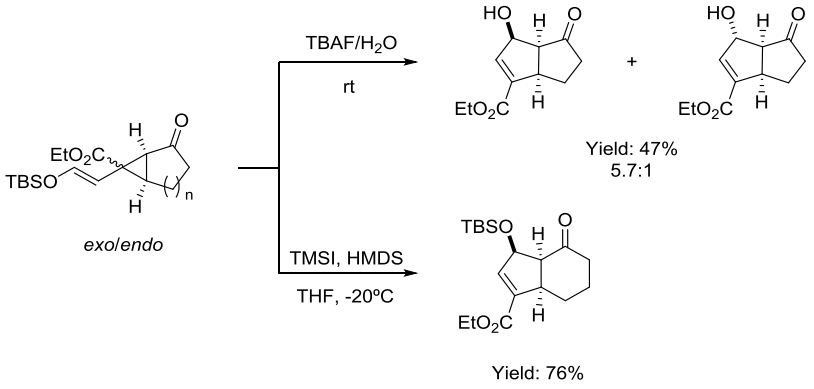
[19] Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc*. **1972**, *94*, 8932.
[20] Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc*. **1973**, *95*, 5311.
[21] Trost, B. M.; Keeley, D. E. *J. Am. Chem. Soc*. **1976**, *98*, 248.

reaction temperature up to room temperature, obtaining cyclopentenols in good yields in a two-step synthesis starting from 1,3-dienes (Scheme 2.8).[22]



Scheme 2. 8. Thermal rearrangement of lithium vinylcyclopropanolates

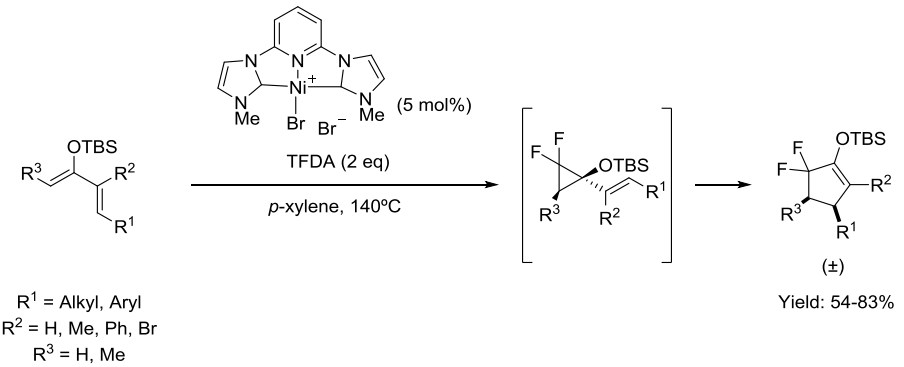
Further progress in the thermal VCP-CP rearrangement involves the use of donor-acceptor cyclopropanes. By the incorporation of an electron-withdrawing group, the C-C bond of the corresponding cyclopropane weakens, not requiring extremely high temperatures for the rearrangement to take place. In this sense, Hudlicky and coworkers were able to carry out the rearrangement of fused cyclopropanes at lower temperatures.[23] By treating the cyclopropanes with TBAF or TMSI in the presence of HMDS the rearrangement took place at room temperature or -20ºC affording fused cyclopentenes in good yields. The obtained bicycloalkane structures can be considered precursors of cyclopentanoids such as prostaglandins (Scheme 2.9).



Scheme 2. 9. Rearrangement of 1-(silyloxyvinyl)cyclopropane derivatives

[22] Danheiser, R. L.; Martinez-Davila, C.; Morin, J. *J. Org. Chem.* **1980**, *45*, 1340.
[23] Hudlicky, T.; Heard, N. E.; Fleming, A. *J. Org. Chem*. **1990**, *55*, 2570.

In this field, the group of Ichikawa extended the methodology by the incorporation of two geminal fluorine atoms in the vinylcyclopropane structure under the hypothesis that fluorine substitution would increase the ring strain, elongating the C-C distal bond to the geminal fluorine substituents. In this sense, a sequential difluorocyclopropanation/VCP-CP rearrangement of silyl dienol ethers was performed, which afforded synthetically useful derivatives of di- and monofluorinated cyclopentanones and cyclopentenones in good yields.[24] They were able to carry out the rearrangement spontaneously over *in situ* generated vinylcyclopropanes after a Ni-catalyzed difluorocyclopropanation reaction in a domino process (Scheme 2.10).



Scheme 2. 10. Domino cyclopropanation/VCP-CP rearrangement of silyl enol ethers

1.2. Photochemical VCP-CP rearrangement

1.2.1 Mechanism

Vinylcyclopropanes have the absorption maxima for the π→π* olefin band in the 189-201 nm region, which indicates that to undergo photochemically induced vinylcyclopropane-cyclopentene rearrangement, the vinylcyclopropane may bear additional chromophoric functional groups extending its absorption to 254 nm. Photochemical rearrangements can take place by both direct and sensitized methods. While direct irradiation in n-π* systems of the vinylcyclopropane involves low energy excitations, more selective processes can be achieved,

[24] Aono, T.; Sasagawa, H.; Fuchibe, K.; Ichikawa, J. *Org. Lett.* **2015**, *17*, 5736.

converting this pathway very useful from a synthetic point of view. However, sensitized methods imply higher energy due to the formation of the triplet states (80 kcal/mol) so that they involve lower conversions and reaction yields at the expense of the formation of some by-products.[8f]

The more extended mechanism of many photochemical vinylcyclopropane-cyclopentene rearrangements generally involves singlet-excited vinylcyclopropanes intercrossing to T1 that lead to a ring-opened diradical species which generates the final cyclopentene product upon ring closure.[8e,14a] These initially found T1 intermediate can also generate a bicyclo[2.1.0]pentane that is itself photolabile and can isomerize to a cyclopentene (Figure 2.2).

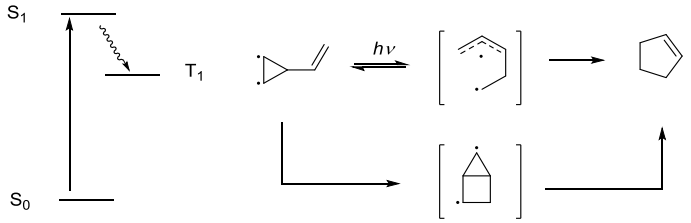
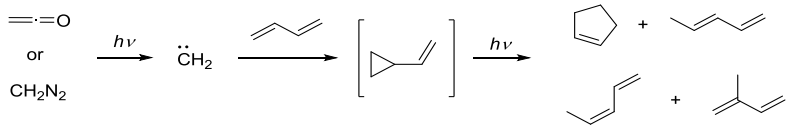


Figure 2. 2. Biradical-mediated photochemical VCP-CP rearrangement

1.2.2. Scope of the reaction

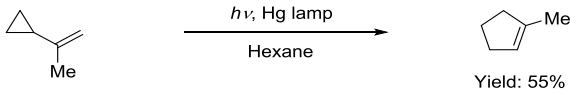
The first example of photochemical vinylcyclopropane-cyclopentene rearrangement was reported by Frey.[25] He studied the photolysis of ketene and diazomethane in the presence of butadiene at 65°C, observing that after decomposition of both reagents, methylene was generated. This extremely endothermic carbene, reacted rapidly with the diene generating a vinylcyclopropane molecule, which subsequently evolved to a mixture of different products among which cyclopentene was detected (Scheme 2.11).

[25] Frey, H. M. *Trans. Faraday Soc*. **1962**, *58*, 516.



Scheme 2. 11. First example of photochemical VCP-CP rearrangement

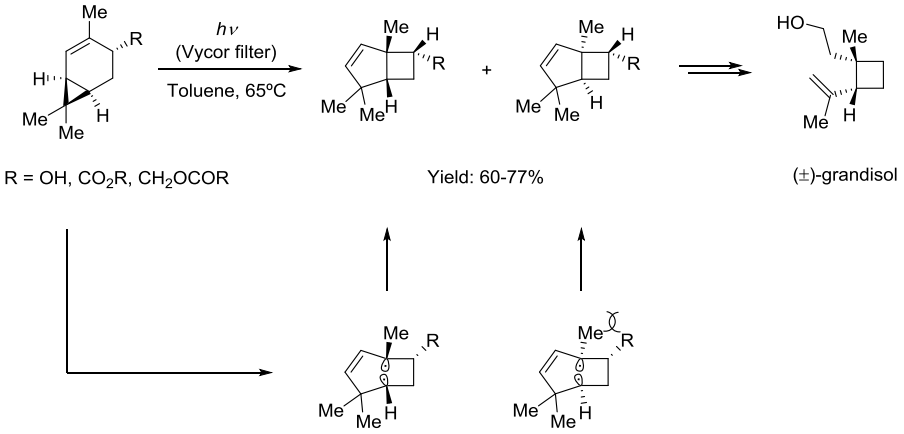
Since this discovery, different examples of photochemical vinylcyclopropane-cyclopentene rearrangements were published. One of the first examples reported was the isomerization of isopropenylcyclopropane to methylcyclopentene described by Cooke in 1970.[26] It was suggested that the reaction proceeded through a singlet state, being the electronic excitation localized in the vinylcyclopropane because triplet-sensitized conditions did not turn to be efficient in the formation of the cyclopentene, regardless the employed sensitizer (Scheme 2.12).



Scheme 2. 12. Photochemical rearrangement of isopropenylcyclopropane

Sonawane and coworkers reported years later a photolytic approach for the synthesis of bicyclo[3.2.0]heptene derivatives starting from bicyclo[4.1.0]heptenes.[27] A solution of cyclopropane in toluene, the last also acting as the photosensitizer, was irradiated with 200 W high pressure lamp, affording two diastereomeric cyclobutane fused cyclopentene products. The authors proposed that the transformation occurred *via* biradical intermediates where the diastereomeric distribution was controlled by both the nature of R substituent and the interactions between R substituent and the adjacent methyl group. This methodology was appealing from a synthetic point of view, since it brought the possibility of synthesizing products with bicyclo[3.2.0]heptenes core which is a framework present in different families of natural products such as grandisol (Scheme 2.13).

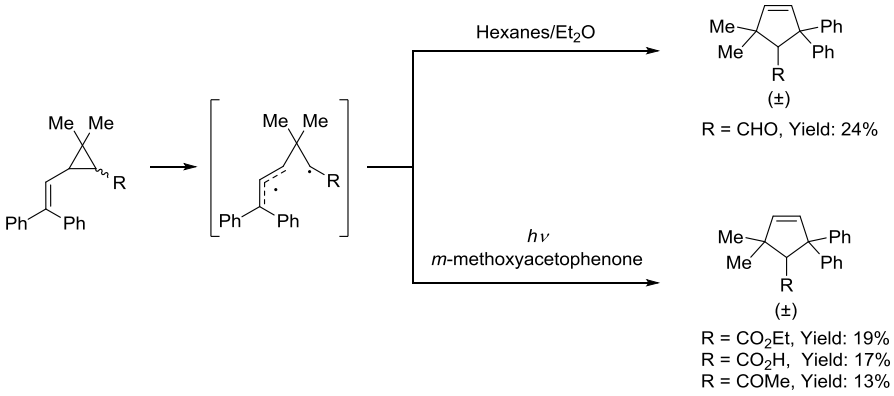
[26] Cooke, R. S. *Chem. Commun*. **1970**, 454.
[27] Sonawane, H. R.; Nanjundiah, B. S.; Kumar, M. V. *Tetrahedron Lett*. **1985**, *26*, 1097.



Scheme 2. 13. Photochemical rearrangement of fused vinylcyclopropanes

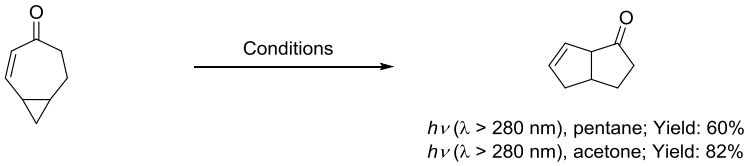
Years later, Armesto and coworkers developed a deep study about the vinylcyclopropane-cyclopentene photorearrangement employing 1-substituted-2-vinylcyclopropanes as model substrates.[28] They explained that the diphenyl substitution pattern at the vinyl unit would favor the generation of the biradical intermediate, resulting from photoinduced homolytic cleavage of the allylic cyclopropane C-C bonds. This fact would enable carrying out the reaction both under direct irradiation and triplet-sensitized conditions. Direct irradiation of this type of vinylcyclopropanes with a Pyrex glass filtered light at λ > 300 nm yielded the corresponding cyclopentenes in a very low yield and only when the R substituent was a formyl group. On the other hand, by *m*-methoxyacetophenone-sensitized irradiation of differently substituted vinylcyclopropanes, the corresponding five-membered rings were obtained in low yields broadening the scope of the reaction to cyclopentenes bearing acyl, hydroxyl and carboxylate groups. In view of these results they concluded that the substituent in position 1 of the cyclopropane was crucial for the stabilization of the biradical intermediate (Scheme 2.14).

[28] Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R. *J. Org. Chem*. **1999**, *64*, 1056.



Scheme 2. 14. Photochemical rearrangement of 1-substituted 2-vinylcyclopropanes

Better performance was obtained by Paquette and coworkers during the synthesis of bicycle[3.3.0]octanones by the rearrangement of bicyclic VCPs using both direct and sensitized reaction conditions.[29] Although singlet state of the vinylcyclopropane was able to undergo C-C bond cleavage due to the thermal behavior of the ketone, pyrolisis of pentane solution of the vinylcyclopropane through a Pyrex filter (λ > 280 nm) rendered the photoproduct in a moderate 60% yield. However, photorrearrangement of fused vinylcyclopropane under sensitized conditions employing acetone as sensitizer lead to a high 82% yield of the bicycle (Scheme 2.15).



Scheme 2. 15. Photochemical rearrangement of bicyclic VCP under both direct and sensitized conditions

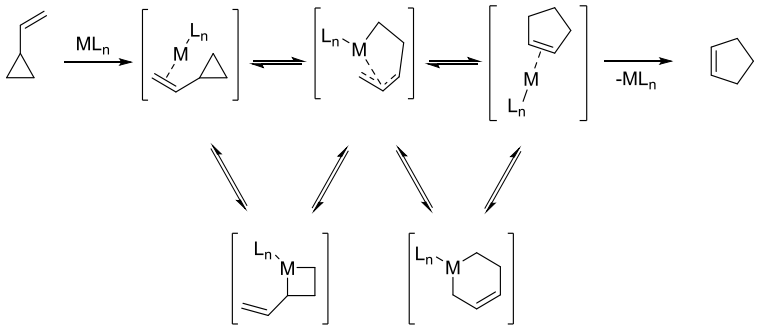
[29] Paquette, L. A.; Henzel, R. P.; Eizember, R. F. *J. Org. Chem.* **1973***, 38*, 3250.

1.3. Transition metal-catalyzed VCP-CP rearrangement

1.3.1. Mechanism

The ability of a transition metal to undergo insertion in the C-C bond of cyclopropanes can be used to activate vinylcyclopropanes towards rearrangement to form cyclopentenes.

The mechanism that explains the vinylcyclopropane-cyclopentene rearrangement under a transition metal catalyst is based on the formation of η^2-alkene complex of the metal which is followed by an oxidative addition leading to a η^1-alkyl/η^3-allyl metal complex in a direct way. This allyl metal complex can also happen through the formation of an allyl metallacyclobutane. Afterwards, the rearrangement takes place together with a reductive elimination process, which can occur over the allyl metal complex, either directly or *via* a metallacyclohexene intermediate (Scheme 2.16).[30] Literature shows that transition metals such as Rh(I), Ni(0) and Pd(0) are proficient catalysts for the vinylcyclopropane-cyclopentene rearrangement.

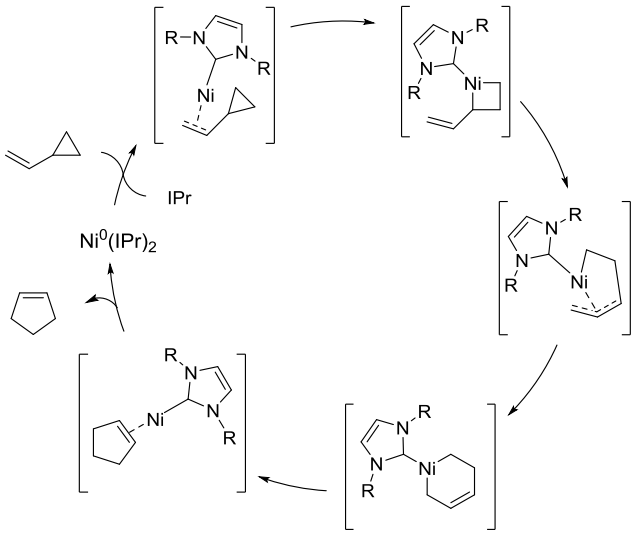


Scheme 2. 16. Mechanism of metal-catalyzed vinylcyclopropane-cyclopentene rearrangement

In particular, Tantillo performed kinetic and computational studies to understand the mechanism of the rearrangement of vinylcyclopropanes to cyclopentenes catalyzed by a Ni(0)-NHC complex.[31] The data are in line with the general mechanism proposed before, demonstrating that the reaction starts with the complexation of the vinylcyclopropane with the metal to generate a η^2-alkene complex, which next forms a vinyl nickellacyclobutane after

[30] Wang, S. C.; Tantillo, D. J. *J. Organomet. Chem*. **2006**, *691*, 4386.
[31] Wang, S. C.; Troast, D. M.; Conda-Sheridan, M.; Zuo, G.; LaGarde, D.; Louie, J.; Tantillo, D. J. *J. Org. Chem*. **2009**, *74*, 7822.

oxidative addition. This complex rearranges to a nickellacyclohexene intermediate *via* a η^1-alkyl, η^3-allyl-nickel complex, which after a reductive elimination step affords the cyclopentene product (Scheme 2.17).



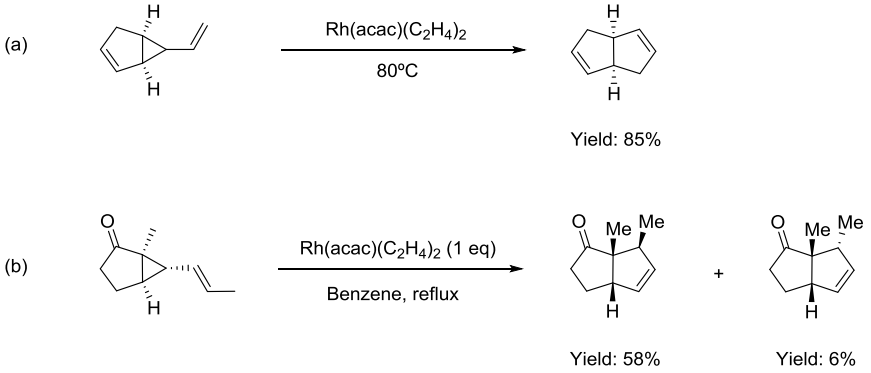
Scheme 2. 17. Mechanism for Ni(0)/IPr-catalyzed VCP-CP rearrangement

1.3.2. Scope of the reaction

The first two examples in transition metal-mediated vinylcyclopropane-cyclopentene rearrangement were made by the groups of Aris and Hudlicky, independently.[32] In both publications the authors reported the rhodium-mediated vinylcyclopropane-cyclopentene rearrangement of differently substituted fused vinylcyclopropanes. Aris and coworkers synthesized some Rh based catalysts and studied their effect in the rearrangement reaction observing the formation of tetrahydropentalene derived product which came from a concerted mechanism (Scheme 2.18 a). Employing the same catalyst, Hudlicky and coworkers performed the VCP-CP rearrangement being this process a suitable methodology for larger complex

[32] (a) Aris, V.; Brown, J. M.; Conneely, J. A.; Golding, B. T.; Williamson, D. H. *J. Chem. Soc. Perkin Trans. 2,* **1975**, 4. (b) Hudlicky, T.; Koszyk, F. F.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

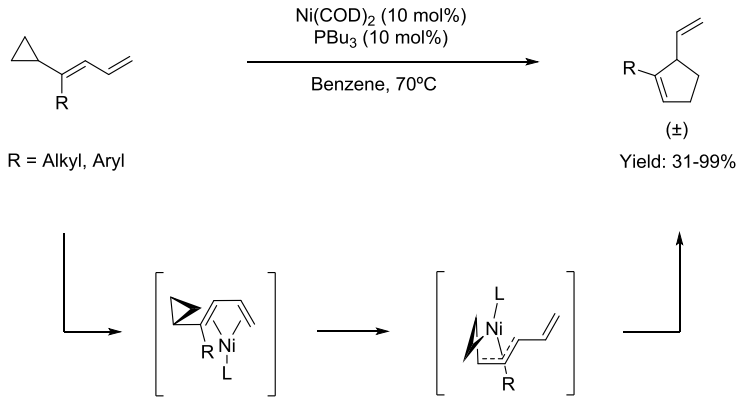
molecules. It was suggested that the presence of a carbonyl group would avoid the regiochemistry problems that thermal methods eventually presented (Scheme 2.18 b).



Scheme 2. 18. First examples of Rh-catalyzed VCP-CP rearrangement

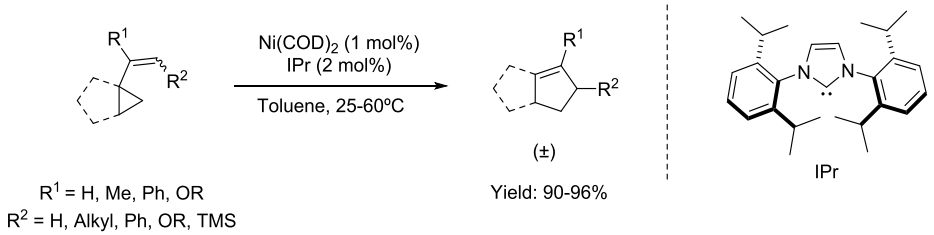
The group of Murakami reported in 1979 the ability of a Ni(0)/PBu_3 catalytic system to perform the rearrangement of vinylcyclopropanes with dienyl or styrenyl substituents (Scheme 2.19).[33] The reaction proceeded through the formation of a butadiene-nickel (0) complex which underwent a ring-opening reaction involving the coordinative interaction of the vinylcyclopropane moiety with the metal and generating a *cisoid* σ,π-allyl complex which was required for cyclopentene formation. This transformation could be considered diastereoconvergent due to whatever the conformation of the diene was, the same reaction product was obtained as consequence of an isomerization process which took place prior to the rearrangement. The role of the phosphane was explained in terms of the stabilization of the Ni(II) intermediate by its σ-donating ability.

[33] Murakami, M.; Nishida, S. *Chem. Lett*. **1979**, 927.



Scheme 2. 19. Ni(0)/PBu_3-catalyzed rearrangement of dienyl-substituted vinylcyclopropanes

Although all these examples show that Rh and Ni allow performing VCP-CP rearrangement under milder conditions, in most of the cases activated substrates are needed to undergo the required transformation. As a possible solution to overcome this limitation, the group of Louie suggested that a metal with higher electron density would present a higher nucleophilicity, favoring the attack to the corresponding vinyl moiety, and facilitating the ring-opening reaction. To accomplish with their proposal, they performed the isomerization of vinylcyclopropanes employing *N*-heterocyclic carbenes as ligands for the nickel catalyst due to the higher σ-donating ability of these ligands and their high affinity for nickel. Using this type of Ni-NHC complexes, differently substituted cyclopentenes were obtained in high yields from activated and non-activated vinylcyclopropanes using mild reaction conditions (Scheme 2.20).[34]

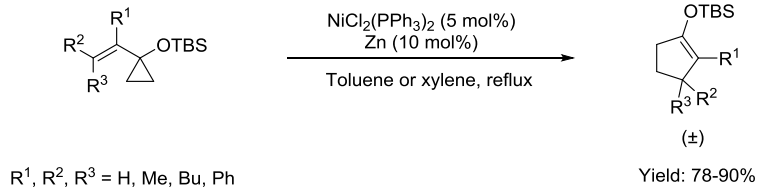


Scheme 2. 20. Ni(0)/IPr-catalyzed rearrangement of vinylcyclopropanes

It should be mentioned that through the use of transition metals it is also possible to carry out other previously reported transformations in milder conditions. One example was the

[34] Zuo, G.; Louie, J. *Angew. Chem. Int. Ed*. **2004**, *43*, 2277.

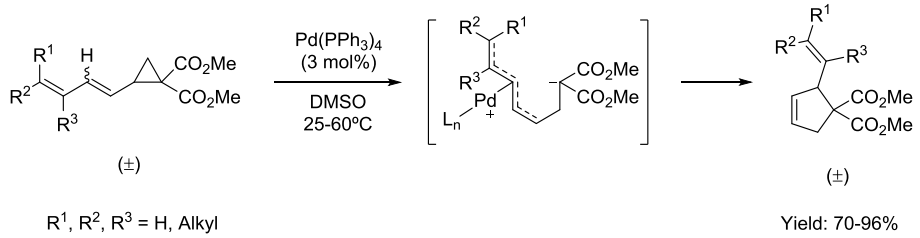
rearrangement of 1-silyloxy-1-vinylcyclopropanes to 1-silyloxycyclopentenes which was previously described under thermal conditions involving very high temperatures. Ryu and Sonoda studied this particular vinylcyclopropane-cyclopentene rearrangement using different transition metal complexes as catalysts.[35] While Pd and Pt complexes resulted ineffective for the transformation, and Rh complexes only afforded traces of the desired products, Ni(0) catalysts showed a high selectivity for the reaction under refluxing toluene or xylene (Scheme 2.21).



Scheme 2. 21. Ni(0)/PPh_3-catalyzed rearrangement of 1-silyloxy-1-vinylcyclopropane

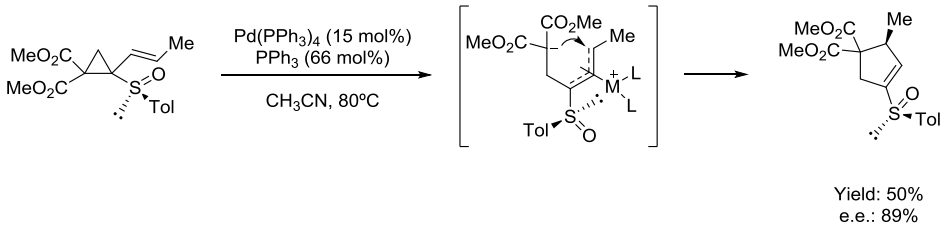
Palladium-mediated vinylcyclopropane-cyclopentene rearrangement requires activated vinylcyclopropanes to take place, usually requiring two electron-withdrawing groups at the cyclopropane moiety. In this field, the Pd(0)-catalyzed rearrangement of dienyl substituted cyclopropane-1,1-dicarboxylates was reported by Oshima and coworkers.[36] The authors suggested that the presence of both electron-withdrawing groups and the dienyl substituent were crucial for the rearrangement to take place. After the nucleophilic attack of the Pd(0) to the dienyl moiety, a π-pentadienyl palladium zwitterionic intermediate was generated. The W type conformation acquired by this pentadienyl group resulted to be crucial for the process to proceed with a high regioselectivity, observing the exclusive formation of cyclopentene derivatives (Scheme 2.22).

[35] Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, *11*, 941.
[36] Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1982**, *23*, 2871.



Scheme 2. 22. Pd(0)-catalyzed VCP-CP rearrangement of dienyl-substituted cyclopropanes

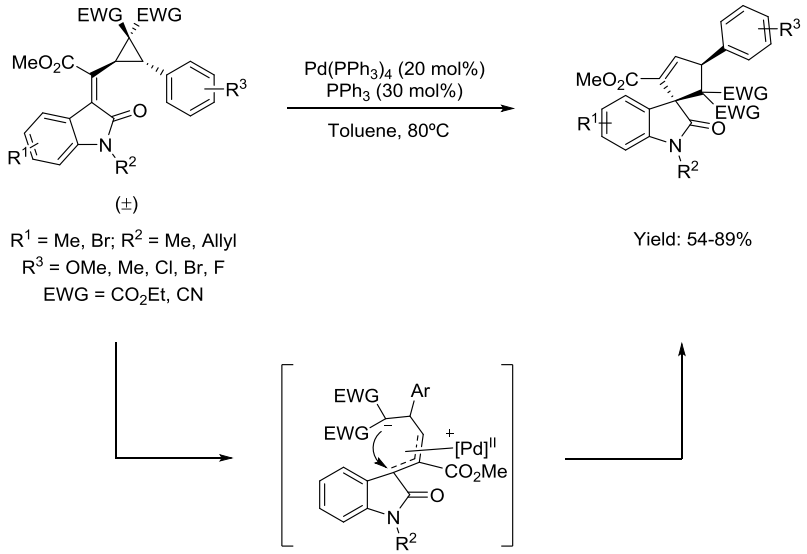
In the same line, the group of Hiroi studied the possibility of developing the first transition metal-catalyzed asymmetric rearrangement of chiral vinylcyclopropanes into cyclopentene derivatives.[37] Despite the use of a chiral sulfonyl group as auxiliary, it did not influence in the stereochemical control observed in the cyclopentene formation, being this determined by the chirality of starting cyclopropyl sulfoxides. The transformation was performed with high levels of stereospecificity being the nucleophilic attack of the carbanion from the back side of the transition metal catalyst in the π-allylic transition metal complex (Scheme 2.23).



Scheme 2. 23. Pd(0)-catalyzed VCP-CP rearrangement of chiral vinylcyclopropanes

More recently, the group of Shanmugan described a Pd-catalyzed synthesis of 3-spirocyclopentene-2-oxindoles in good yields from 3-vinylcyclopropane-2-oxindoles.[38] As in the previous cases, the presence of two electron-withdrawing groups and an aromatic substituent in the cyclopropane structure were found to be necessary to stabilize the zwitterionic enolate/π-allyllpalladium complex formed during the progress of the reaction. The stabilization of the π-allylpalladium complex led to the exclusive formation of a single diastereoisomer as reaction product (Scheme 2.24).

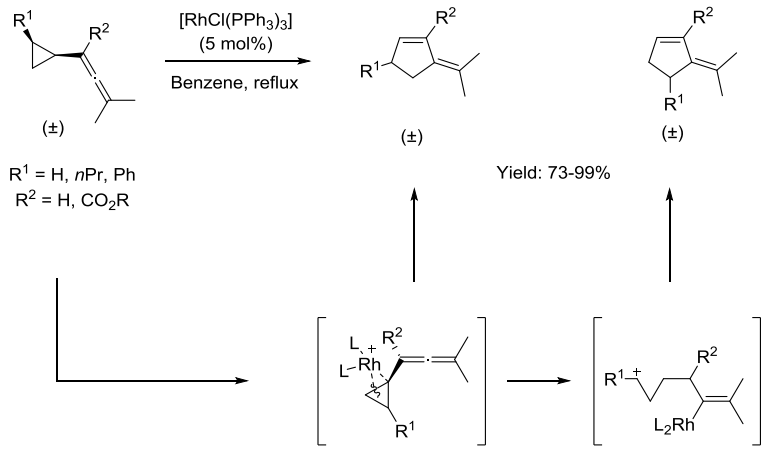
[37] Hiroi, K.; Arinaga, Y. *Tetrahedron Lett*. **1994**, *35*, 153.
[38] Lingam, K. A. P.; Shanmugan, P. *Tetrahedron Lett*. **2013**, *54*, 4202.



Scheme 2. 24. Pd-catalyzed VCP-CP rearrangement of indole-derived vinylcyclopropanes

Saigo and coworkers extended the methodology and reported for the first time the selective rearrangement of allenylcyclopropanes to methylenecyclopentenes under Rh catalysis.[39] The reaction was proposed to provide two isomeric cyclopentenes depending on the substitution pattern of the allenylcyclopropane. When an alkyl substituent was placed in the cyclopropane, a 4-substituted 1-alkylidene-2-cyclopentene product was formed through the oxidative addition of Rh across the C-CH_2 bond of the cyclopropane. On the other hand, aryl substituents in the cyclopropane moiety contributed to an ionic ring-opening process through the oxidative insertion of the metal center across the C-CHAr bond forming an acyclic stabilized cation (Scheme 2.25).

[39] Hayashi, M.; Ohmatsu, T.; Meng, Y.-P.; Saigo, K. *Angew. Chem. Int. Ed*. **1998**, *37*, 837.

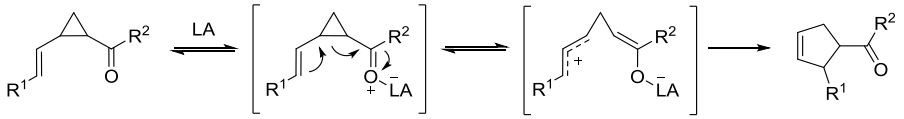


Scheme 2. 25. Rh-catalyzed rearrangement of allenylcyclopropanes

1.4. Acid mediated VCP-CP rearrangement

1.4.1. Mechanism

Lewis acids enable carrying out the vinylcyclopropane-cyclopentene rearrangement under mild conditions, provided that some functionalities in the cyclopropane ring are able to interact with the Lewis acid. For instance, carbonyl functionalities placed at the adjacent position to the vinyl moiety enable the coordination with the Lewis acid increasing the C-C bond polarization and facilitating the formation of the acidic zwitterionic intermediate which undergoes the final ring-closing process. Hence, the Lewis acid-mediated vinylcyclopropane-cyclopentene rearrangement is not a stereoespecific transformation (Scheme 2.26).[40,41]

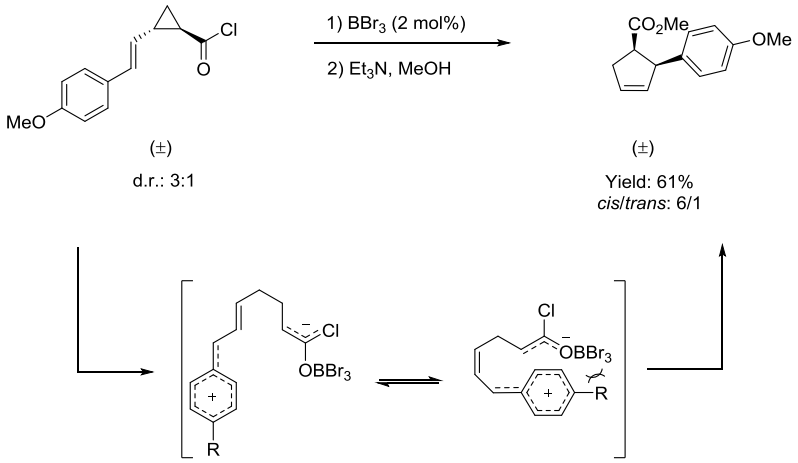


Scheme 2. 26. Mechanism for the Lewis acid-promoted rearrangement of donor-acceptor VCPs

[40] Trost, B. *Comprehensive Organic Synthesis II:* Combining C-C π-bonds*,* Pergamon, Oxford, 1991.
[41] Satyanarayana, J.; Rao, M. V. B.; Ila, H.; Junjappa, H. *Tetrahedron Lett*. **1996**, *37*, 3565.

1.4.2. Scope of the reaction

The first Lewis acid-promoted VCP-CP rearrangement was reported by Suzukamo.[42] They synthesized 2-arylcyclopent-3-enecarboxylates from racemic 2-styrylcyclopropanecarbonyl chlorides in good yields but with limitations regarding the substrate scope. Electron-withdrawing groups in the aromatic ring made the cyclopropane not reactive enough to undergo the rearrangement, being electron-donating groups necessary since they favored the stability of the zwitterionic carbocation/enolate intermediate. The interaction between the cationic phenyl moiety and the anionic carbonyl moiety in the opened intermediate resulted in the major formation of the *cis* diastereosisomer over the *trans* during the cyclization step. Moreover, the starting material could be used as a mixture of diastereoisomers, leading to a single diastereoisomer of the final product because of the formation of this achiral intermediate (Scheme 2.27).

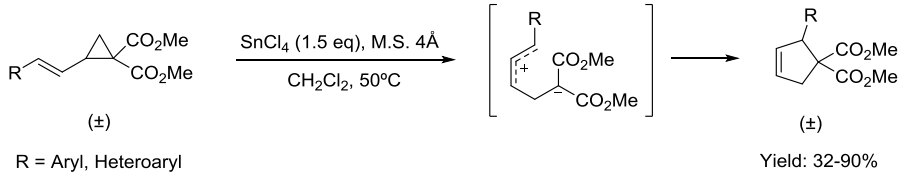


Scheme 2. 27. First VCP-CP rearrangement promoted by Lewis acids

The incorporation of two electron-withdrawing groups in the structure of the vinylcyclopropane makes them more reactive towards the rearrangement. For example, Ivanova and coworkers developed in 2018 a Lewis acid-mediated isomerization of donor-acceptor cyclopropanes into substituted cyclopentenes.[43] The reaction allowed the

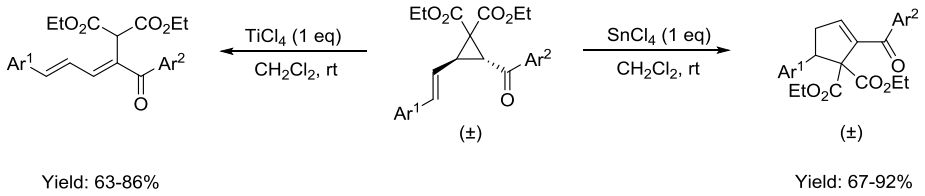
[42] Sakito, Y.; Suzukamo, G. *Chem. Lett*. **1986**, 621.
[43] Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnobrov, V. D.; Levina, I. I.; Trushkov, I. V. *J. Org. Chem.* **2018**, *83*, 543.

incorporation of aryl and heteroaryl substituents as electron-donor groups at the vinyl unit (Scheme 2.28).



Scheme 2. 28. $SnCl_4$-promoted VCP-CP rearrangement of vinylcyclopropanecarboxylates

The group of Srinivasan studied the ring-opening reaction of substrates with different EWG in vicinal positions. Thus, *trans*-2-aroyl-3-styrylcyclopropane-1,1-dicarboxylates react in the presence of different Lewis acids observing different reactivity modes depending on the catalyst.[44] When tin (IV) chloride was employed, the vinylcyclopropane-cyclopentene rearrangement took place smoothly, isolating differently substituted cyclopentenes in moderate to good yields and as a single regioisomer. However, when titanium tetrachloride was employed, a ring-opening process followed by an E2-like elimination of a proton took place affording 1,3-dienes (Scheme 2.29).

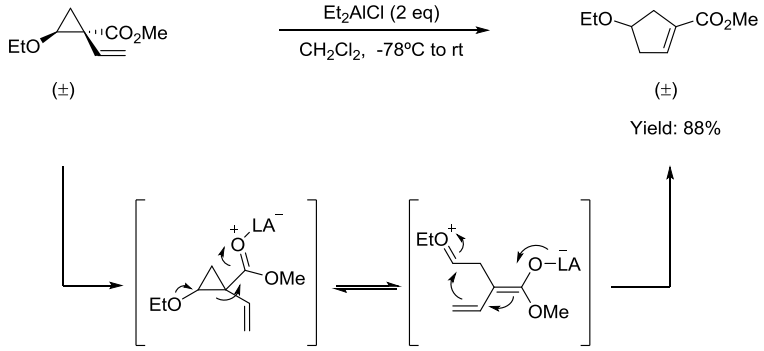


Scheme 2. 29. $SnCl_4$-promoted vinylcyclopropane-cyclopentene rearrangement of vinylcyclopropyl ketones

1-vinylcyclopropanecarboxylates, this case with an alkoxy donor group at C2 can also undergo the vinylcyclopropane-cyclopentene rearrangement efficiently. In this field, the group of Davies developed a vinylcyclopropane-cyclopentene rearrangement catalyzed by diethylaluminium chloride.[45] The mechanism involving these substrates consists on the coordination of the Lewis acid to the acceptor group (normally carbonyl group of the ester), followed by a ring-opening process which is facilitated by the donor group. Then, a zwitterionic species is generated as consequence of the cleavage of the cyclopropane bond between the

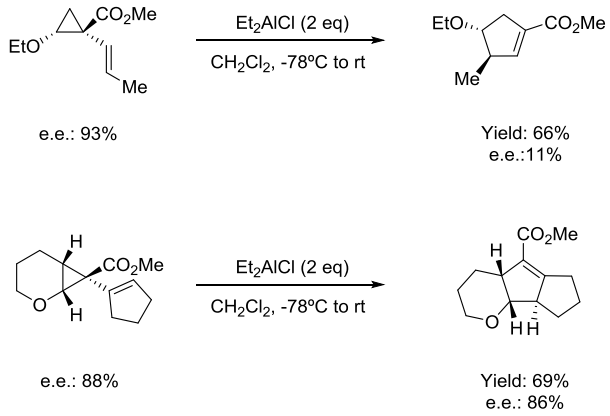
[44] Thangamani, M.; Srinivasan, K. *J. Org. Chem*. **2018**, *83*, 571.
[45] (a) Davies, H. M. L.; Hu, B. *J. Org. Chem*. **1992**, *57*, 4309. (b) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett*. **1991**, *32*, 2871.

ester and the donor group, which suffer from a ring-closing event affording the final cyclopentenes (Scheme 2.30).



Scheme 2. 30. Et_2AlCl-promoted vinylcyclopropane-cyclopentene rearrangement

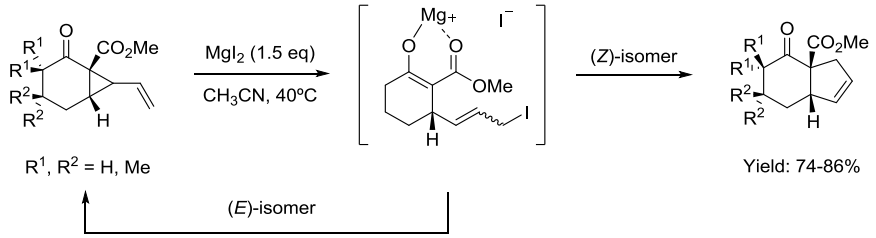
The same group published years later the asymmetric synthesis of cyclopentenes through the VCP-CP rearrangement starting from enantioenriched vinylcyclopropanes.[46] From the studied examples, it can be concluded that fused cyclopropanes were needed to avoid the loss of enantioenrichment as it happened in enantioenriched cyclopropanes containing two or three stereogenic centers. The explanation given by the authors justify the presence of an extra stereogenic center present in fused systems as the one preserving the enantioenrichment (Scheme 2.31).



Scheme 2. 31. Et_2AlCl-promoted rearrangement of chiral cyclic and bicyclic VCPs

[46] Davies, H. M. L.; Konog, N.; Churchill, M. M. *J. Org. Chem*. **1998**, *63*, 6586.

On the other hand, Lewis acids containing a highly nucleophilic counterion, such iodide in MgI_2 and LiI, can promote the rearrangement proceeding by another reaction mechanism. That is the particular case of the vinylcyclopropane-cyclopentene rearrangement developed by the group of Lambert in 2009.[47] The key VCP-CP rearrangement was promoted by MgI_2 which acted as a coordinating Lewis base (Mg^{2+}) and as a nucleophile (I^-) in a homoconjugate addition to the vinyl moiety of the cyclopropane, thus forming an allyl iodide enolate intermediate which cyclized to fused cyclopentenes in high yields. The stereochemistry of the olefin intermediate played an important role in this reaction: while the (*Z*)-isomer leads to the final cyclopentene through an intramolecular S_N2 alkylation, (*E*)-isomer undergoes S_N2' reaction reverting back to the starting cyclopropane.



Scheme 2. 32. MgI_2-promoted rearrangement of vinylcyclopropanes

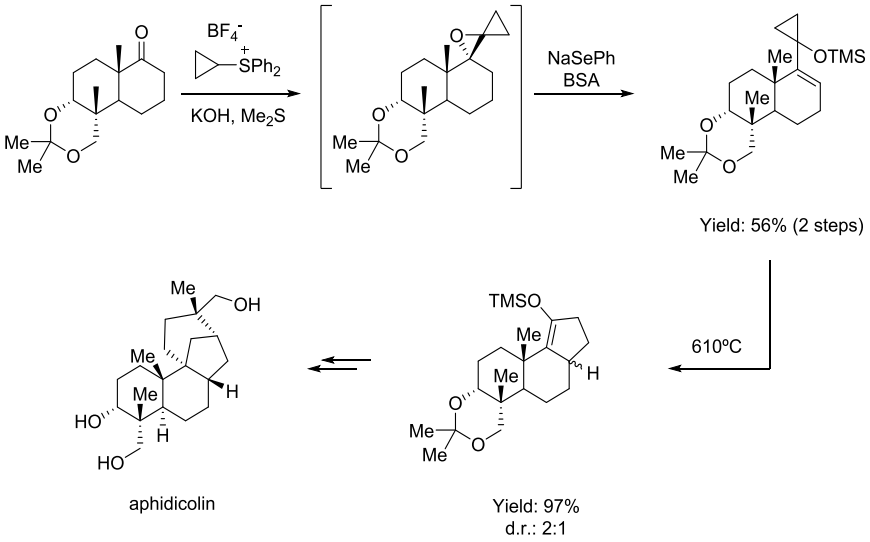
1.5. Application to the synthesis of natural products

Over the years many synthetic methodologies have been applied to the synthesis of natural products. Likewise, the vinylcyclopropane-cyclopentene rearrangement has also been employed as key step in the synthesis of a wide range of them. Although several examples of the synthesis of natural products involving rearrangements under photochemical and acidic conditions have been reported in literature, the majority of them involved thermal conditions.

The ability of vinylcyclopropanes to undergo easy rearrangements under thermal conditions has been used by Trost and coworkers for the synthesis of aphidicolin, a terpenoid tetraol which shows *in vitro* activity against herpes virus.[48] They faced the synthesis of vinyl cyclopropane through a condensation of a cyclohexanone with diphenylsulfonium

[47] Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc*. **2009**, *131*, 2496.
[48] Trost, B. M.; Nishimura, Y.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc*. **1979**, *101*, 1328.

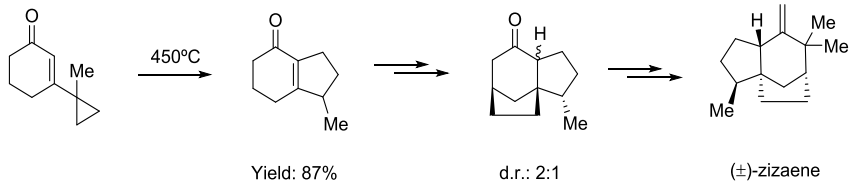
cyclopropylide affording oxaspiropentane followed by a substitution-elimination process employing sodium phenylselenide which rendered the key 1-vinylcyclopropanol quantitatively silylated. VCP-CP rearrangement under thermal conditions *via* flash vacuum pyrolysis furnished the desired cyclopentene as a 2:1 mixture of epimers. Aphidicolin was next obtained after a 6-step sequence (Scheme 2.33).



Scheme 2. 33. Synthesis of Aphidicolin

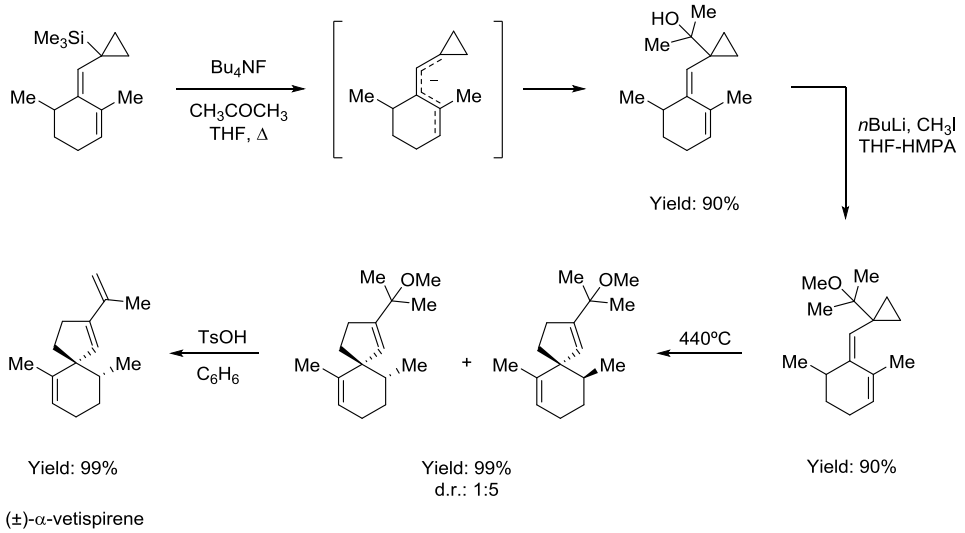
Piers reported an 11-step total synthesis of (±)-zizaene, the parent hydrocarbon of the zizaene family of interesting sesquiterpenoids isolated from vetiver oil.[49] They started the synthesis with a five-membered ring annelation process based on the thermal rearrangement of 3-(1-methylcyclopropyl)cyclohex-2-enone, which furnished the annelated ketone in 87% yield at 450ºC. After 10-step sequence they isolated the 2:1 mixture of epimers of a tricyclic compound previously described as an intermediate in the synthesis of (±)-zizaene[50] (Scheme 2.34).

[49] Piers, E.; Banville, J. *J. Chem. Soc. Chem*. **1979**, 1138.
[50] Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc*. **1972**, *94*, 5386.



Scheme 2. 34. Total synthesis of (±)-zizaene

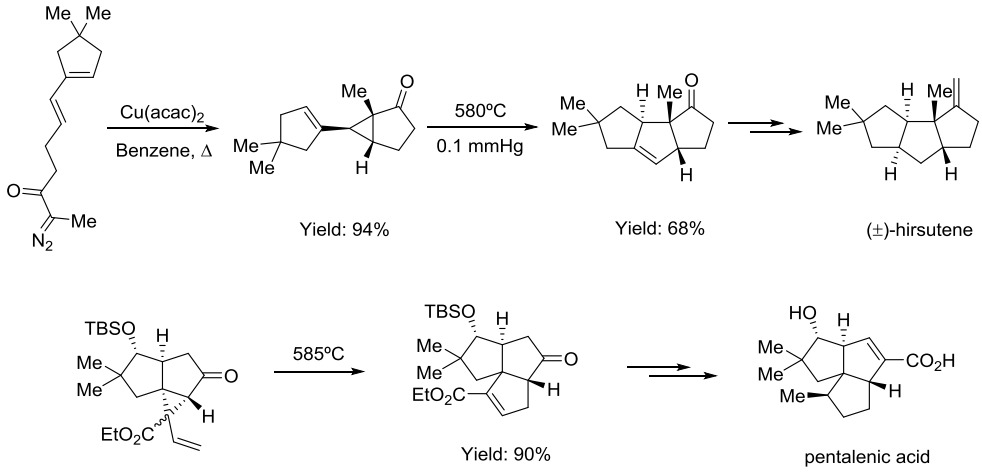
Vetispirene, a spirocyclo[4.5]decane sesquiterpene, was also synthesized by the group of Paquette using a thermal vinylcyclopropane-cyclopentene rearrangement as key step of the synthesis in five steps with an overall yield of 38%.[51] The synthesis started from a silylated dienylcyclopropane which upon heating at 65°C in anhydrous tetra-*n*-butylammonium fluoride and acetone generated a pentadienyl anion that reacted with acetone to produce the required vinylcyclopropane. Thermal rearrangement at 440°C produced a quantitative 1:5 mixture of diastereomeric cyclopentenes. A final treatment of the major diastereoisomer with *p*-toluenesulfonic acid in benzene rendered (±)-α-vetispirene in quantitative yield (Scheme 2.35).



Scheme 2. 35. Total synthesis of (±)-α-vetispirene

[51] Yan, T.-H.; Paquette, L. A. *Tetrahedron Lett*. **1982**, *23*, 3227.

Bicyclic systems containing a vinylcyclopropane subunit have also been studied in the vinylcyclopropane-cyclopentene rearrangement directed to the synthesis of triquinane sesquiterpenes natural products. In this field, Hudlicky and coworkers carried out the total synthesis of (±)-hirsutene, a coriolin class of sesquiterpenes containing a tricyclo[6.3.0.0^{2,6}]undecane ring system in its structure in 38% global yield.[52] The key steps of the synthesis involved an intramolecular cyclopropanation step previously reported by the group followed by a VCP-CP rearrangement. The aforementioned rearrangement was performed under thermal conditions evaporating vinylcyclopropane through a lead carbonate tube at 0.1 mmHg (Scheme 2.36). The same group reported years later a versatile strategy for the construction of triquinane sesquiterpenes, involving an intramolecular cyclopentene annulation under conditions of pyrolysis. The obtained product was directly subjected to the synthesis of pentalenic acid, pentalenene and derived compounds (Scheme 2.36).[53]

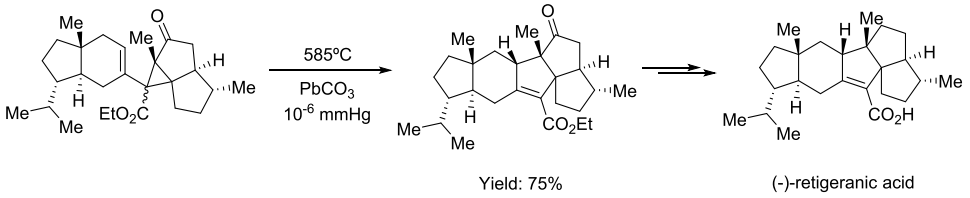


Scheme 2. 36. Total synthesis of (±)-hirsutene and pentalenic acid

The synthesis of retigeranic acid, a sesterterpene monocarboxylic acid with a tricyclo[6.3.0.0^{2,6}]undecane skeleton, was also carried out through the vinylcyclopropane-cyclopentene rearrangement under thermal conditions by Hudlicky and coworkers after

[52] Hudlicky, T.; Kutsan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc*. **1980**, *102*, 6351.
[53] Hudlicky, T.; Sinai-Zingde, G.; Papadopoulos, P. *Tetrahedron* **1987**, *43*, 5685.

obtaining the necessary cyclopentene in 75% yield by evaporation of the *endo*/*exo* mixture of isomers of vinylcyclopropanes through a Vycour tube conditioned with $PbCO_3$ (Scheme 2.37).[54a]



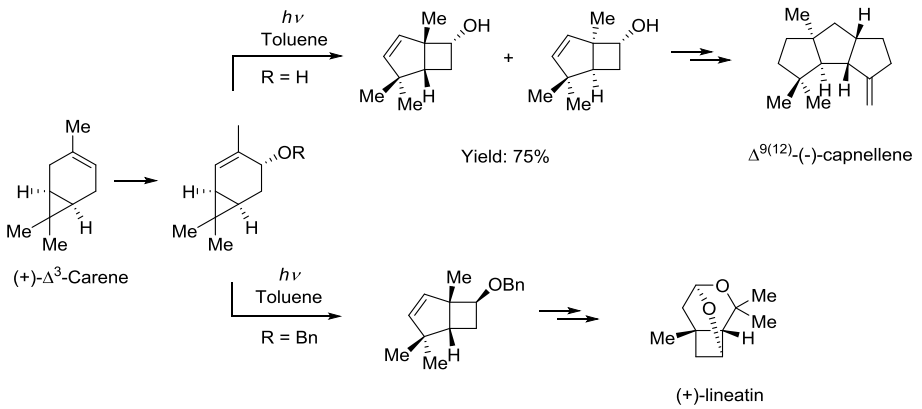
Scheme 2. 37. Total synthesis of (-)-retigeranic acid

Application of photochemical vinylcyclopropane-cyclopentene rearrangements in the synthesis of natural products has been less developed over the years. However, it is possible to find some interesting examples of natural products in the literature, such as the previously mentioned total synthesis of grandisol reported by Sonowane and coworkers (Scheme 2.13).[55] Some years later, the same group reported the total synthesis of enantiomerically pure (-)-$\Delta^{9(12)}$-capnellene and (+)-lineatin employing the same methodology.[56] Thus, starting from Δ^3-carene, a key optically pure secondary alcohol was obtained by an epoxidation step followed by base-induced isomerization and ring-opening reaction. This was next used as the common starting intermediate for the synthesis of both natural products. When R group was H, a diastereomeric mixture of allylic alcohols was obtained in 75% yield after a toluene-sensitized photolysis which was converted in (-)-capnellene after some chemical manipulations. On the other hand, if the hydroxyl group was protected as benzylic ether, the photochemical VCP-CP rearrangement led to a single product which was submitted to different transformations rendering (+)-lineatin, an aggregation pheromone of the bark beetle tryptodendron lineatum (Scheme 2.38).

[54] (a) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc*. **1985**, *107*, 4339. (b) Hudlicky, T.; Radesca-Kwart, L.; Li, L.; Bryant, T. *Tetrahedron Lett*. **1988**, *29*, 3283.

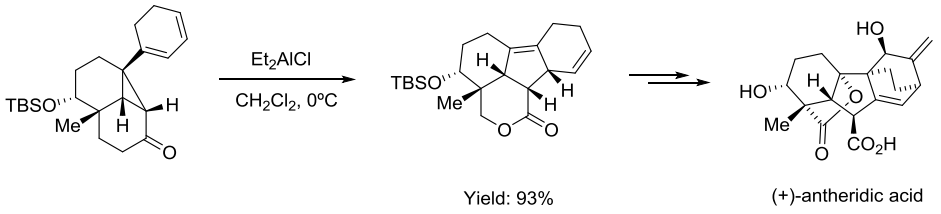
[55] Sonowane, H. R.; Nanjundiah, B. S.; Kumar, M. U. *Tetrahedron Lett*. **1984**, *25*, 2245.

[56] (a) Sonawane, H. R.; Naik, V. G.; Bellur, N. S.; Shah, V. G.; Purohit, P. C.; Kumar, M. U.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron* **1991**, *47*, 8259. (b) Sonawane, H. R.; Bellur, N. S.; Shah, V. G.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron Lett.* **1991**, *32*, 1107. (c) Sonawane, H. R.; Nandjundiah, S. B.; Kulkarni, D. G.; Ahuja, J. R. *Synlett*, **1993**, 875.



Scheme 2. 38. Total synthesis of $\Delta^{9(12)}$-(-)-capnellene and (+)-lineatin

Although the predominance of thermal conditions, some natural products have been prepared employing acid catalysis. One example was described by the group of Corey, which reported the total synthesis of (+)-antheridic acid, the major antheridiogen from *Anemia phyllitidis*, using a 10-step sequence.[57] The key step of the synthetic route involved the Et_2AlCl-promoted vinylcyclopropane-cyclopentene rearrangement which afforded the desired cyclopentene in 93% yield, easily transformed after some chemical manipulations into (+)-antheridic acid (Scheme 2.39).

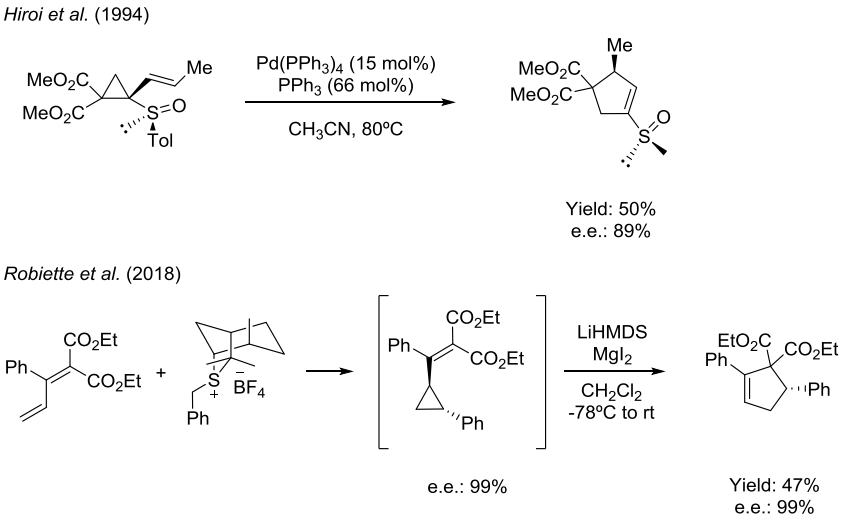


Scheme 2. 39. Enantioselective total synthesis of (+)-antheridic acid

[57] Corey, E. J.; Kigoshi, H. *Tetrahedron Lett*. **1991**, *32*, 5025.

2. SPECIFIC OBJECTIVES AND WORK PLAN

As it has been outlined in previous section, donor-acceptor cyclopropanes take part in numerous reactions described in literature. Specifically, vinylcyclopropanes and their rearrangements are appealing strategies to synthesize a wide range of interesting compounds in nature. Remarkably, when a final chiral cyclopentene product is required in an enantioenriched form, all the examples of vinylcyclopropane-cyclopentene rearrangements described in the literature rely on enantiospecific versions (Scheme 2.40).[37,58] However, there is no example in the literature of an enantioselective version of the vinylcyclopropane-cyclopentene rearrangement that converts racemic vinylcyclopropane substrates into enantioenriched cyclopentenes.

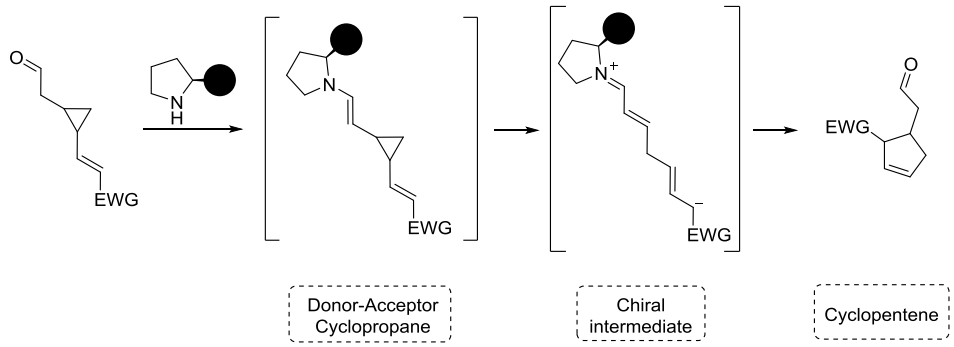


Scheme 2. 40. Enantiospecific VCP-CP rearrangements

Hence, and in view of the lack of enantioselective VCP-CP rearrangements hitherto reported, we turned our attention to develop an enantioselective organocatalyzed vinylcyclopropane-cyclopentene rearrangement. For this reason, we envisaged the possibility of employing a cyclopropylacetaldehyde with a 2-vinyl electron-withdrawing group substituent

[58] Clergue, S.; Rousseau, O.; Delaunay, T.; Dequirez, G.; Tran, T.-V.; El Aakchioui, S.; Barozzino-Consiglio, G.; Robiette, R. *Chem. Eur. J.* **2018**, *24*, 11417.

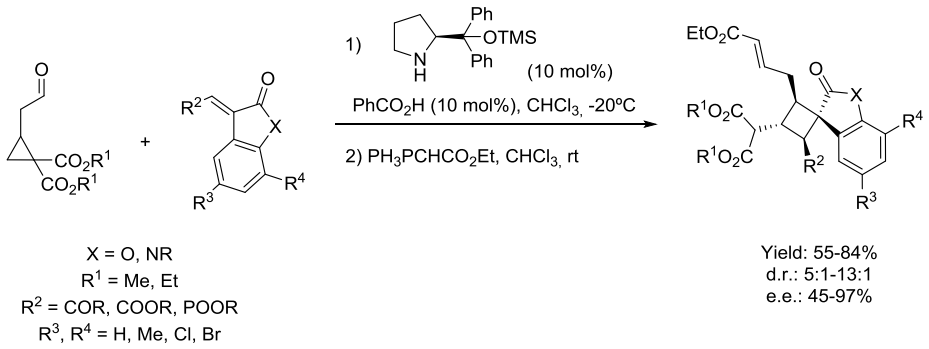
as suitable substrate for the reaction and the use of a chiral secondary amine as catalyst. In particular, we expected that a chiral secondary amine should condense with the aldehyde generating an enamine moiety which converts the substrate *in situ* into a donor-acceptor cyclopropane with potential to undergo a ring-opening reaction furnishing a chiral intermediate that would undergo a ring-closing process yielding the desired enantioenriched cyclopentene (Scheme 2.41). Thus, starting from a racemic substrate and operating through the mechanism depicted in the scheme it would be possible to obtain enantioselectively cyclopentene adducts.



Scheme 2. 41. Our hipothesis

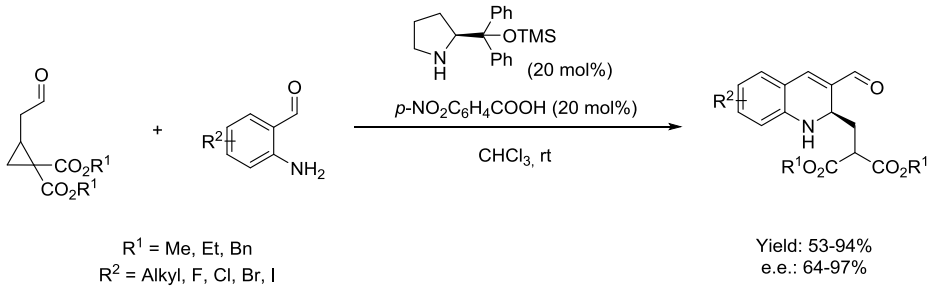
There are two examples in the literature where the opening process in a cyclopropane is carried out through this type of activation with a chiral amine. Prof. Jørgensen and coworkers were the pioneers in developing a novel organocatalytic enamine-based activation of cyclopropanes.[59] In the reported study, an asymmetric [2+2] cycloaddition between cyclopropylacetaldehydes and 3-alkyliden oxindoles was developed giving access to spirocyclobutaneoxindoles in good to excellent yields and enantioselectivitites (Scheme 2.42).

[59] Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2015**, *137*, 1685.



Scheme 2. 42. Organocatalytic cycloaddition between cyclopropylacetaldehydes and 3-olefinic oxindoles

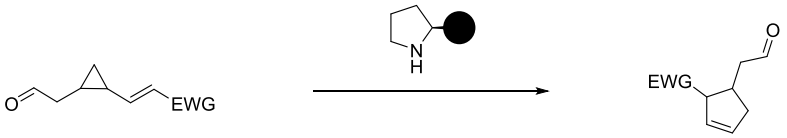
Later on, our group presented an easy and straightforward procedure for the synthesis of highly enantioenriched quinolines in which the ring-opening mechanism was identical. In this particular case, the organocatalytically generated donor-acceptor cyclopropane would undergo a *one-pot* process that comprised the aforementioned cyclopropane ring-opening reaction and a domino aza-Michael/aldol reaction (Scheme 2.43).[60]



Scheme 2. 43. Synthesis of dihydroquinolines by the *in situ* generation of a donor-acceptor cyclopropane

In view of these precedents, our general objective is **developing an aminocatalytic enantioselective vinylcyclopropane-cyclopentene rearrangement**, for which the ring-opening reaction will take place by the formation of a donor-acceptor cyclopropane (Scheme 2.44).

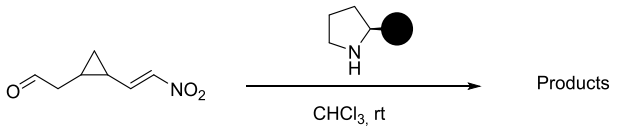
[60] Sanchez-Diez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrilllo, L.; Vicario, J. L. *Org. Lett*. **2016**, *18*, 1270.



Scheme 2. 44. General objective

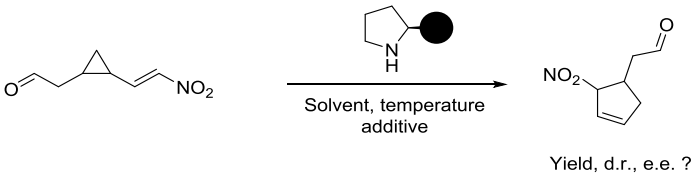
To accomplish the aforementioned objective, the subsequent work plan was outlined:

- *Proof of concept:* the viability of the envisioned reaction will be tested using the 2-nitrovinyl substituted cyclopropylacetaldehyde shown in Scheme 2.45. Using this model substrate, the standard conditions for the reaction to take place towards the formation of the product will be examined.



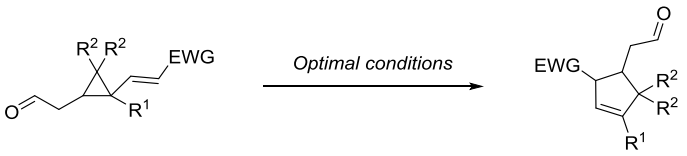
Scheme 2. 45. Envisioned model reaction

- *Optimization of the reaction conditions:* once the target rearrangement product have been found, a variety of chiral catalysts will be evaluated in the enantioselective version of the reaction trying to obtain the highest enantioselectivity in this model reaction. In the same way, different experimental parameters like solvents, temperature and additives will be modified in order to find optimal conditions to obtain the desired product in high yield and high diastereo- and enantioselectivities (Scheme 2.46).



Scheme 2. 46. VCP-CP rearrangement reaction: optimization of the reaction conditions

- *Scope of the reaction:* the scope and limitations of the developed method will be examined for structurally different substrates. Alkyl substituents will be introduced in the cyclopropane structure as well as different electron-withdrawing groups on the vinyl moiety (Scheme 2.47).

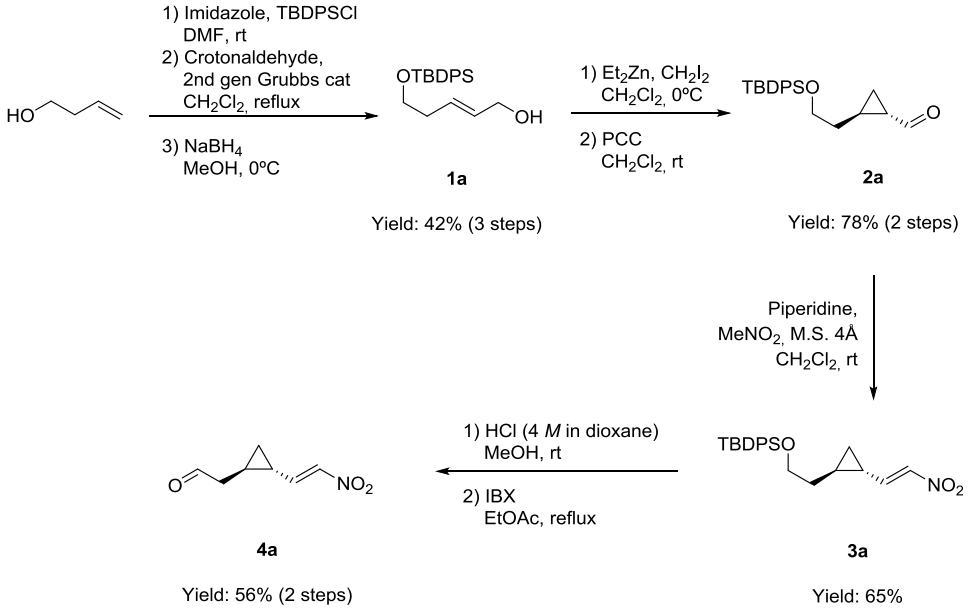


Scheme 2. 47. Scope of the reaction

3. RESULTS AND DISCUSSION

3.1. Proof of concept

We started our work evaluating the ability of cyclopropane **4a** to undergo vinylcyclopropane-cyclopentene rearrangement under chiral secondary amine catalysis. In order to accomplish this research, we first started synthesizing the necessary starting material, which was carried out in an eight-step sequence as shown in Scheme 2.48.



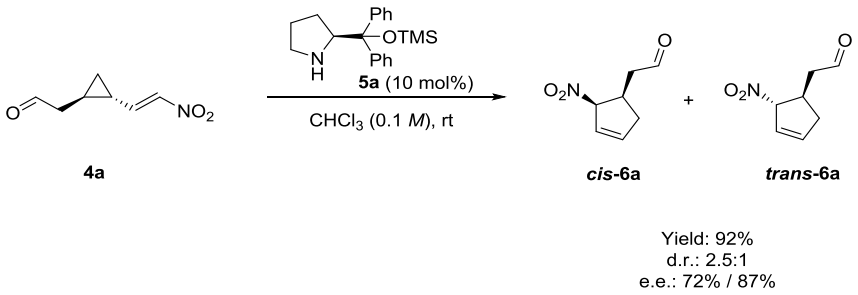
Scheme 2. 48. Synthesis of cyclopropane **4a**

The synthesis started with the preparation of allylic alcohol **1a** through a three-step sequence starting from commercially available 3-buten-1-ol. The reactions consisted in a protection step of the alcohol as *tert*-butyldiphenylsilyl ether affording (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane in 99% yield, a cross-metathesis employing crotonaldehyde as the coupling partner and second generation Grubbs catalyst leading to the corresponding α,β-unsaturated aldehyde in 65% yield and a sodium borohydride-mediated reduction which rendered the allylic alcohol **1a** in 68% yield. The formation of the cyclopropane moiety was performed through the Furukawa modification of the Simmons-Smith cyclopropanation, in

which Et_2Zn is employed instead of metallic zinc obtaining (2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)methanol in 90% yield. Next step consisted on the oxidation of the alcohol to the corresponding aldehyde employing pyridinium chlorochromate, furnishing **2a** in an 87% yield. Then, incorporation of nitrovinyl group in the cyclopropane moiety was faced. For that purpose, it was decided to perform a Henry condensation with nitromethane under Knoevenagel conditions yielding **3a** in 65% yield. Finally, a deprotection and IBX-promoted oxidation steps afforded the target substrate **4a**.

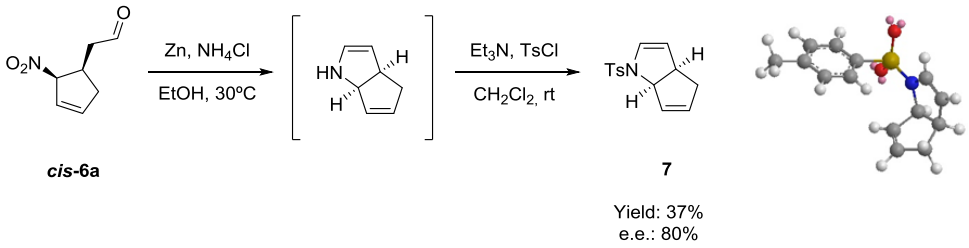
Once the starting material was synthesized, we started studying the viability of the projected VCP-CP rearrangement using (*S*)-diphenylprolinol trimethylsilyl ether **5a** (also known as Jørgensen-Hayashi catalyst) as catalyst, which is an archetypical chiral secondary amine catalyst used in the literature for reactions under enamine activation.[61] We also chose chloroform as solvent and worked at room temperature as standard reaction conditions previously used by our group in the ring-opening of related cyclopropylacetaldehyde substrates.[60] An immediate change of color was observed when the substrate was added to a solution of the catalyst and the complete disappearance of the starting material was observed by thin layer chromatography. Afterwards, the reaction was set up adding a solution of the catalyst over a solution of the aldehyde observing the exclusive formation of two products after short reaction time (one minute), which were identified as the diastereomeric cyclopentenes ***cis*-6a** and ***trans*-6a** after flash column chromatography. The structural assignment of *cis* and *trans* relative configuration was made through the analysis of ^{1}H-NMR coupling constants. Those products, *cis* and *trans* cyclopentenes, were obtained in excellent combined yield, and promising enantioselectivity (Scheme 2.49).

[61] (a) Mukherjee, S.; Yag, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471. (b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632. (c) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 7876.



Scheme 2. 49. Preliminary study of the reaction

As these cyclopentenes ***cis*-6a** and ***trans*-6a** were not crystalline compounds, both were independently subjected to further chemical manipulation in order to obtain a crystalline material which would help us assign the absolute stereochemistry. We faced the challenge of reducing the nitro group of cyclopentenes ***cis*-6a** and ***trans*-6a** independently. Thus, the Zn-mediated reduction of nitro to amino group in the presence of ammonium chloride in EtOH at 30°C was carried out separately over *cis* and *trans* diastereoisomers. While the reaction did not work for the diastereoisomer ***trans*-6a**, when diastereoisomer ***cis*-6a** was employed, it could be observed the total disappearance of starting material by ^{1}H-NMR analysis and the formation of a new bicyclic compound identified as the dihydropyrrolocyclopentane adduct, which could not be isolated. Subsequent tosylation of the enamine with *p*-toluenesulfonyl chloride led to the formation of **7** in a 37% global yield (Scheme 2.50). Taking advantage of its solid nature, bicyclic **7** could be crystallized, and hence, the absolute stereostructure of the product could be determined at this point by single crystal X-Ray analysis showing a (*R*,*R*) configuration which led to a (*S*,*R*) configuration in ***cis*-6a**.



Scheme 2. 50. Zn-mediated reduction/cyclization of **cis-6a** and X-ray structure of **7**

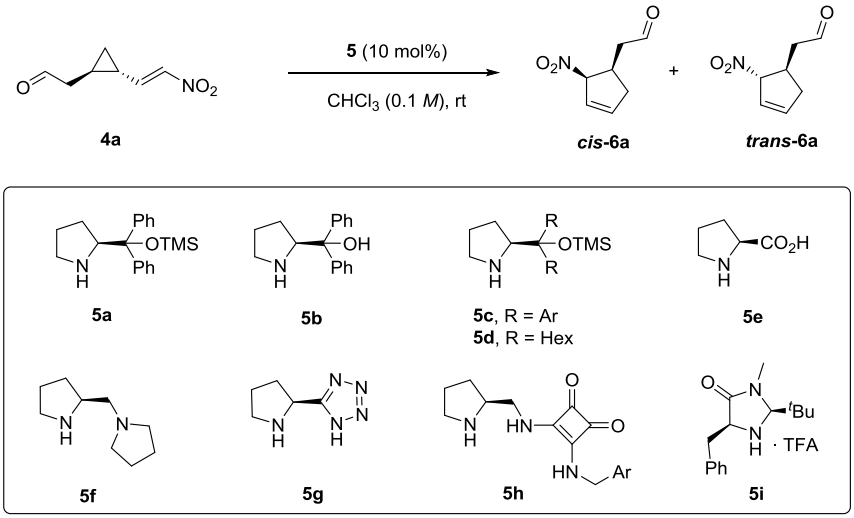
With these initial experiments, it was demonstrated the feasibility of carrying out the vinylcyclopropane-cyclopentene rearrangement under mild conditions, using a chiral

secondary amine as Lewis base catalyst. However, the reaction conditions needed to be further optimized in order to obtain the cyclopentene adducts in the highest possible yield and enantiomeric excess.

3.2. Optimization of the reaction conditions

Considering previous results as evidence of the feasibility of the reaction, next efforts were directed to the optimization of the reaction conditions. In this sense, we initially focused on the identification of the best catalyst in terms of both the yield and diastereo- and enantioselectivity. In view that the reaction proceeded well employing Jørgensen-Hayashi catalyst **5a** we started testing other structurally related diarylprolinol-based chiral secondary amines (Table 2.1).

Table 2. 1. Evaluation of secondary amine catalysts



Entry[a]	Catalyst	time	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	**5a**	1 min	92	2.5:1	72	87
2	**5b**	24 h[f]	32	1.5:1	5	22
3	**5c**[e]	30 min	90	1.7:1	73	94
4	**5d**	30 min	80	1:1	73	77
5	**5e**	24 h[f]	57	2.5:1	3	30
6	**5f**	1 h	32	1:5.5	50	34
7	**5g**	24 h[f]	55	1.9:1	16	27
8	**5h**[e]	5 days[f]	18	1.5:1	4	7
9	**5i**	5 days[f]	24	3.8:1	n.d.[g]	n.d.[g]

[a]Reactions were carried out at 0.06 mmol scale of **4a**, using 10 mol% of catalyst in 0.6 mL of solvent at rt. [b]Yields refer to isolated pure products ***cis*-6a** and ***trans*-6a**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase. [e]Ar = 3,5-$(CF_3)_2C_6H_3$. [f]Not full conversion observed. [g]n.d.: not determined.

The non-protected diphenylprolinol catalyst **5b** rendered cyclopentenes ***cis*-6a** and ***trans*-6a** in 32% yield and very low enantioselectivities (Table 2.1, entry 2) in comparison with Jørgensen-Hayashi catalyst **5a**, previously tested (Table 2.1, entry 1). The lower yield could be attributed to the possibility of the aminoalcohol to interact with the formyl group and leading to an unreactive hemiaminal intermediate also deactivating the catalyst. In addition, the low enantiomeric excess could be due to the lower steric bulk that the side chain of the catalyst presents which is not able to effectively block one of the faces of the substrate. Hence, we

continued working with *O*-protected diarylprolinoles increasing the steric bulk of the catalyst. For that purpose, we selected bis-[3,5-bis(trifluoromethyl)phenyl]prolinol (catalyst **5c**) and dihexylprolinol (catalyst **5d**) analogues, in which steric rather than electronic properties of the substituent can influence in the enantioselectivity of the process.[62] We could observe in both cases a notable decrease in the diastereomeric ratio (Table 2.1, entries 3-4). However, in spite of the low value of diastereomeric ratio, both catalysts rendered the reaction products in excellent yields and moderate enantioselectivities. In view of these results, we next moved to other structurally different pyrrolidine-containing catalysts. L-proline **5e** was able to render adducts ***cis*-6a** and ***trans*-6a** in moderate yield after 24 hours of reaction, although the enantioselectivity was low (Table 2.1, entry 5). (*S*)-(+)-2-(1-pyrrolidinylmethyl)pyrrolidine catalyst **5f** turned not to be efficient enough to perform the reaction with good results (Table 2.1, entry 6). Next, other catalysts with architectures that could show other secondary interactions apart from the steric shielding were surveyed. However, all these catalysts did not provide full conversion being the yields and the enantioselectivities lower than in the previous cases. For instance, Ley catalyst[63] **5g** was tested affording moderate yield and low enantiomeric excess for both diastereoisomeric products of the reaction (Table 2.1, entry 7). The reaction was also surveyed with bifunctional pyrrolidine-squaramide catalyst **5h** developed by Jørgensen[64] which could afford a dual activation approach for both the aldehyde and nitroalkene by using the combination of the amine and the thiourea which was expected to engage in selective hydrogen bonding with nitroalkene. However, this catalyst resulted not to be especially active in this transformation, observing low conversion and very low enantioselectivity after 5 days of reaction (Table 2.1, entry 8). Finally, MacMillan imidazolidinone **5i** was also tested affording the cyclopentenes ***cis*-6a** and ***trans*-6a** with very low yield and enantiomeric excess (Table 2.1, entry 9).

In view that the best results were obtained when the reaction was carried out employing Jørgensen-Hayashi catalyst **5a**, some analogues with different silyl groups were tested

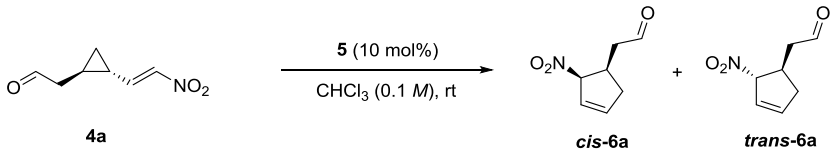
[62] Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2015**, *54*, 13860.

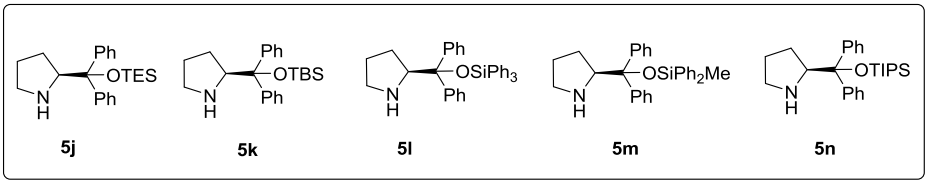
[63] (a) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun*. **2004**, 1808. (b) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett*, **2004**, 558.

[64] (a) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543. (b) Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L.; Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 884. See also: Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int*. *Ed.* **2015**, *54*, 3043.

(catalysts **5j**-**5n**) since the steric bulk of the side chain seemed to play a crucial role in the enantioselectivity (Table 2.2). Whatever the nature of the silyl substituents was, the obtained enantioselectivities were higher than those obtained with the other catalysts tested before. In addition, it was also found that in all cases the minor *trans* diastereoisomer ***trans*-6a** was obtained with higher value of enantiomeric excess than the major *cis* diastereoisomer ***cis*-6a**. It is noteworthy to highlight that in all the cases the reaction took place in much shorter times than when other catalysts were employed. Yields from moderate to high were observed with all these catalysts, being **5k** and **5l** which afforded the highest yields and similar e.e. values (Table 2.2, entries 2-3). We could conclude that when bulkier silyl substituents were placed in the diphenylprolinol structure, better were the results in terms of both yield and diastereo- and enantioselectivities.

Table 2. 2. Evaluation of pyrrolidinemethanol-derived catalysts



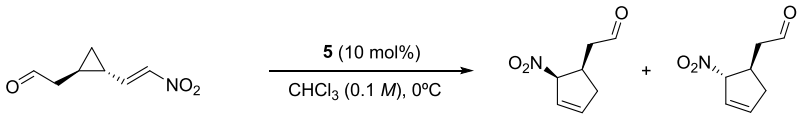


Entry[a]	Catalyst	time	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	**5j**	15 min	73	4:1	79	95
2	**5k**	1 min	85	3:1	71	91
3	**5l**	1 min	83	5:1	79	94
4	**5m**	1 min	62	3.7:1	79	94
5	**5n**	1 min	64	2.8:1	76	91

[a]Reactions were carried out at 0.06 mmol scale of **4a**, using 10 mol% of catalyst in 0.6 mL of solvent at rt. [b]Yields refer to isolated pure products ***cis*-6a** and ***trans*-6a**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase.

Encouraged by the promising results obtained with catalysts **5a, 5j-n** in both yield and diastero- and enantioselectivities, and not observing a clear tendency of the three parameters under study with any catalyst, we next decided to continue working with all of those five catalysts. Their performance at lower temperatures was evaluated to check whether the hitherto obtained results could be improved (Table 2.3). Decreasing the temperature from 25°C to 0°C led to a remarkably improvement in both the diastereomeric ratio and the enantiomeric excess in all cases (Table 2.3, entries 1-6). Furthermore, to our delight, the yield of the reaction was not affected by the temperature. From all the catalysts tested, catalyst **5l** provided the best results in overall, considering yield, diastereomeric ratio and enantiomeric excess (Table 2.3, entry 4). Finally, this catalyst was tested at a lower temperature but, unfortunately, at -30°C the reaction stopped and only a 56% of conversion was obtained after three days of reaction time (Table 2.3, entry 7).

Table 2. 3. Evaluation of best catalysts at low temperatures



4a ***cis*-6a** ***trans*-6a**

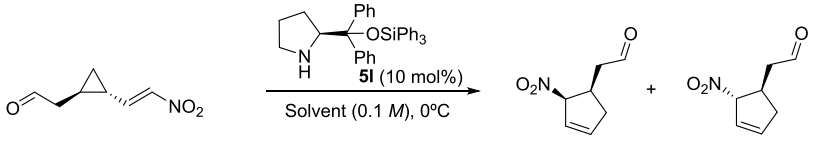
Entry[a]	Catalyst	time	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	**5a**	1 h	50	4.3:1	73	93
2	**5j**	1 min	73	4.3:1	81	95
3	**5k**	1 h	85	4.7:1	79	97
4	**5l**	1 min	83	7:1	81	92
5	**5m**	30 min	68	4.2:1	81	95
6	**5n**	15 min	77	1.9:1	80	97
7[e]	**5l**	24 h[f]	56	n.d.[g]	80	92

[a]Reactions were carried out at 0.06 mmol scale of **4a**, using 10 mol% of catalyst in 0.6 mL of solvent at 0ºC. [b]Yields refer to isolated pure products ***cis*-6a** and ***trans*-6a**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase. [e]The reaction was carried out at -30°C, [f]Not full conversion observed. [g]n.d.: not determined

At this point, catalyst **5l** and a temperature of 0°C were selected for evaluating other experimental parameters of the reaction. In this sense, we moved to study the effect of the solvent in order to achieve the products ***cis*-6a** and ***trans*-6a** with the highest possible yield and diastereo- and enantioselectivities (Table 2.4). When the reaction was performed employing

polar aprotic solvents like THF, cyclopentenes ***cis*-6a** and ***trans*-6a** were obtained in excellent yields with moderate to good enantiocontrol, but the diastereomeric ratio remained being moderate (Table 2.4, entry 2). On the other hand, solvents like diethyl ether and toluene were tested providing low to moderate yields in both cases and moderate enantioselectivities (Table 2.4, entries 3-4). Ethyl acetate did not result to be an appropriate solvent to carry out the reaction due to the moderate yield obtained (Table 2.4, entry 5). Protic solvents like MeOH, although increased the diastereomeric ratio notably, did not provide full conversion, furnishing the desired products ***cis*-6a** and ***trans*-6a** in only 20% yield (Table 2.4, entry 6). Finally, the highly polar acetonitrile or acetone afforded the reaction products with moderate to excellent yields and excellent diastereo- and enantioselectivities (Table 2.4, entries 7-8).

Table 2. 4. Evaluation of different solvents



4a ***cis*-6a** ***trans*-6a**

Entry[a]	Solvent	time	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	$CHCl_3$	1 min	83	7:1	81	92
2	THF	24 h	97	3.5:1	79	96
3	Et_2O	24 h[e]	49	2.5:1	76	84
4	Toluene	24 h[e]	42	5.0:1	68	n.d.[f]
5	EtOAc	24 h[e]	59	4.6:1	74	87
6	MeOH	24 h[e]	20	13:1	63	n.d.[f]
7	MeCN	24 h[e]	75	7.2:1	84	88
8	Acetone	24 h	97	6.4:1	81	95
9	CH_2Cl_2	1 min	78	8.3:1	84	96
10	1,2-dichloroethane	1 min	95	6:1	87	97
11	1,1,2-trichloroethane	1 min	99	7:1	87	96
12	CCl_4	1 min	35	3:1	68	79

[a]Reactions were carried out at 0.06 mmol scale of **4a**, using 10 mol% of catalyst in 0.6 mL of solvent at 0ºC. [b]Yields refer to isolated pure product ***cis*-6a** and ***trans*-6a**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase. [e]Not full conversion observed [f]n.d.: not determined

As employing chloroform as solvent the best results up to date had been obtained (Table 2.4, entry 1), other chlorinated solvents were tested rendering excellent results in all cases unless when carbon tetrachloride was used (Table 2.4, entry 12) probably due to its apolar

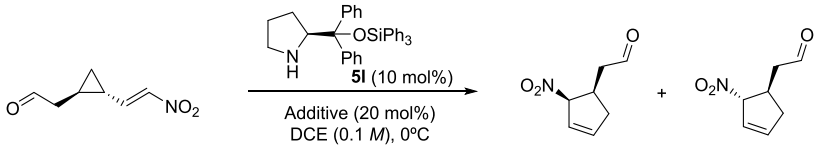
character. A more polar solvent such as dichloromethane furnished the products with a higher 78% yield, being the enantiomeric excess very similar (Table 2.4, entry 9). Employing 1,2-dichloroethane and 1,1,2-trichloroethane, the reaction products ***cis*-6a** and ***trans*-6a** were obtained quantitatively and the enantiomeric excess of both diastereoisomers was very high (Table 2.4, entries 10-11). To sum up, we could conclude that the reaction proceeded in shorter reaction times when chlorinated solvents were employed. Other polar solvents rendered also good results in terms of the yield and enantioselectivities but the reaction times were longer. Moreover, it could be observed that diastereomeric ratios were higher when chlorinated solvents were employed. Thus, the best results in terms of the yield and diastereo- and enantioselectivities were obtained with chlorinated solvents, selecting 1,2-dichloroethane as the optimal one for further screening.

Finally, with the best catalyst, temperature and solvent in hand, we examined if any additive would be able to improve the results obtained so far. Many aminocatalyzed reactions in the literature are performed in the presence of Brønsted acids as cocatalyst, due to their ability to favor the condensation of the aldehyde with the catalyst increasing the amount of active species present in the reaction.[65] For this reason, we decided to evaluate the performance of the reaction by incorporating a variety of benzoic acids in 20 mol% loading (Table 2.5). Therefore, the addition of benzoic acid resulted in a high improvement of the diastereomeric ratio but a notably decrease of the reaction yield was observed (Table 2.5, entry 3). With this result in hand, we selected a variety of benzoic acids of different pk_a to check if the acidity of the acids could affect to the reaction outcome. In general, the less acidic benzoic acids bearing electron-donating groups in their structure made the reaction to proceed in shorter times (Table 2.5, entries 2, 4-5). In particular, when *para*-methoxybenzoic acid was employed the yield was moderate but the enantioselectivity remained high (Table 2.5, entry 2). *Ortho*-methoxybenzoic acid furnished cyclopropanes in 84% yield, being the diastereomeric ratio and the enantiomeric excess the same than when *para*-methoxybenzoic acid was used (Table 2.5, entry 4). When methoxyl group was incorporated in both *ortho* positions of the aromatic ring, a remarkably increase of the diastereomeric ratio was observed, although the yield decreased together with the enantiomeric excess of the major *cis* diastereoisomer (Table 2.5, entry 5). On the other hand, when the acidity of benzoic acids was increased by the use of electron-withdrawing group-substituted benzoic acids, we could not observe a clear tendency.

[65] Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. *Chem. Rev*. **2016**, *116*, 4006.

The use of *ortho*- and *ortho*,*para*-substituted dinitrobenzoic acids as additives, provided rearrangement product ***cis*-6a** in a completely diastereoselective manner, obtaining the *cis* diastereoisomer as a single product (Table 2.5, entries 7-8). However it was obtained in a very low yield and moderate enantioselectivity. Otherwise, the incorporation of 20 mol% loading of *para*-nitrobenzoic acid provided the mixture of diastereoisomers in high yields and high enantioselectivities (Table 2.5, entry 6). Finally, other acids like trifluoroacetic acid, acetic acid and *p*-toluensulfonic acid monohydrate were tested (Table 2.5, entries 9-11), but none of these additives were able to improve our best results.

Table 2. 5. Evaluation of different additives



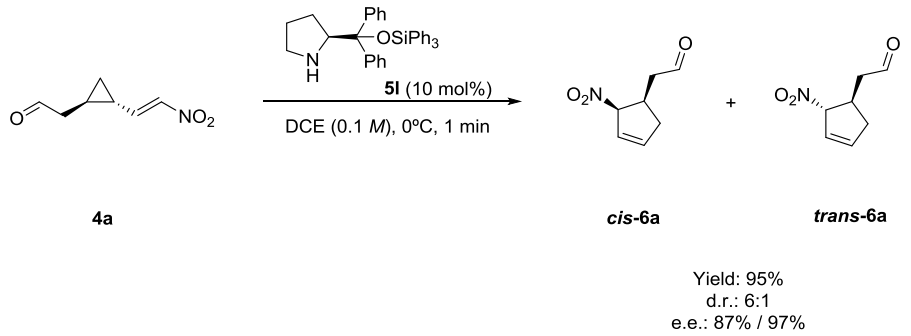
4a ***cis*-6a** ***trans*-6a**

Entry[a]	Additive	pk_a (H_2O)	time	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	None	-	1 min	95	6:1	87	97
2	4-$MeOC_6H_4COOH$	4.47	1 min	58	6.5:1	87	96
3	C_6H_5COOH	4.2	30 min	68	13:1	82	96
4	2-$MeOC_6H_4COOH$	4.09	30 min	84	6.7:1	88	97
5	2,6-$(MeO)_2C_6H_3COOH$	3.98	1 min	65	14:1	79	94
6	4-$NO_2C_6H_4COOH$	3.44	15 min	82	9:1	85	97
7	2-$NO_2C_6H_4COOH$	2.17	24 h	14	>20:1	74	n.d.[e]
8	2,4-$(NO_2)_2C_6H_3COOH$	1.43	24 h	38	>20:1	76	n.d.[e]
9	TFA	0.23	24 h	13	n.d.[e]	72	n.d.[e]
10	CH_3COOH	4.75	1 h	78	11:1	82	95
11	$TsOH{\cdot}H_2O$	-2.8	24 h	42	4.5:1	67	60

[a]Reactions were carried out at 0.06 mmol scale of **4a**, using 10 mol% of catalyst and 20 mol% of additive in 0.6 mL of solvent at 0ºC [b]Yields refer to isolated pure products ***cis*-6a** and ***trans*-6a**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase. [e]n.d.: Not determined.

Once the most important reaction parameters had been evaluated, it was concluded that the optimal reaction conditions for performing the vinylcyclopropane-cyclopentene rearrangement reaction implied the use of 10 mol% of (*S*)-2-{diphenyl[(triphenylsilyl)oxy]methyl}pyrrolidine catalyst **5l** in 1,2-dichloroethane (0.1 *M*) as solvent at 0ºC performing the reaction for one minute, obtaining under these conditions a 6:1

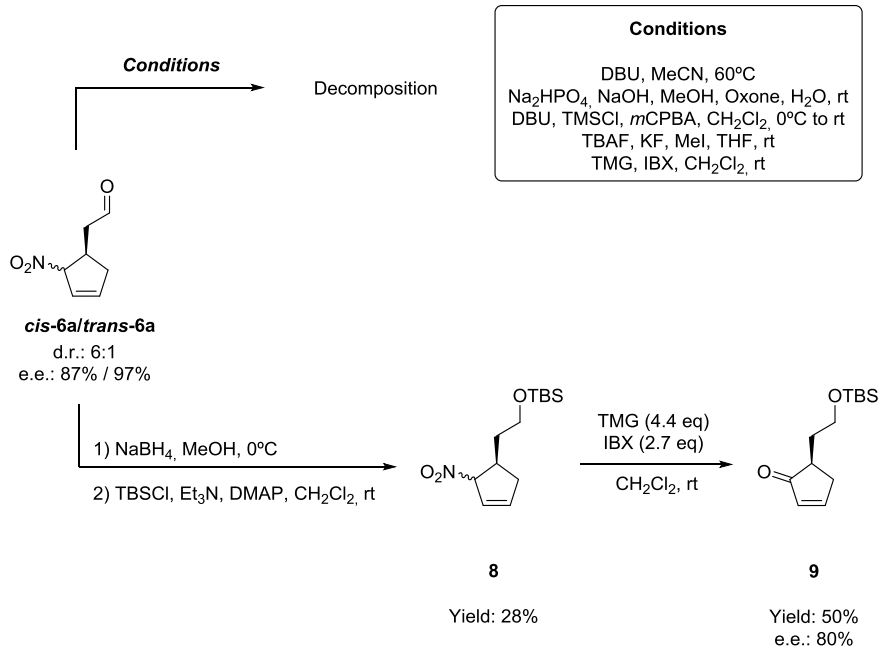
mixture of diastereomeric cyclopentenes ***cis*-6a** and ***trans*-6a** in 95% yield, with an enantiomeric excess of 87% and 97%, respectively (Scheme 2.51).



Scheme 2. 51. Optimized conditions for enantioselective vinylcyclopropane-cyclopentene rearrangement

In view of the results regarding the diastereomeric ratios, we next evaluated the possibility of converging the two diastereoisomers in a single product. For that purpose, we thought to perform a Nef reaction, which would allow the conversion of the nitro group into a ketone moiety removing one stereocenter. It should be noted that ***cis*-** and ***trans*-6a** are epimers at C2 as it will be shown thereafter. After first unfruitful attempts reproducing some standard Nef reaction conditions over a mixture of ***cis*-6a** and ***trans*-6a**,[66] we decided to reduce the formyl group and then protect it with a robust silyl group such as TBS. With the new substrate **8** in hand, after performing the Nef reaction with 1,1,4,4-tetramethylguanidine (TMG) and 2-iodoxybenzoic acid (IBX) in dichloromethane as solvent,[66a] we were able to isolate the α,β-unsaturated cyclopentenone **9** in a promising 50% yield and a 80% enantiomeric excess (Scheme 2.52).

[66] (a) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1983**, *24*, 5227. (b) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett*. **1987**, *28*, 5361. (c) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synth. Comm*. **1998**, *28*, 3057. (d) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett*. **2002**, *43*, 5233. (e) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 717. (f) VanGelder, K. F.; Kozlowski, M. C. *Org. Lett*. **2015**, *17*, 5748.

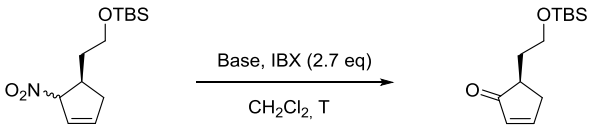


Scheme 2. 52. Preliminary results of Nef reaction

In view of this encouraging result, we turned to evaluate diverse reaction conditions with different bases and changing the molar ratio of the reagents in order to get best reaction performance (Table 2.6). First of all, the same conditions were tested both at lower and higher temperatures. Performing the reaction at 0°C did not provide full conversion even after running the reaction for seven days (Table 2.6, entry 2). Increasing the temperature up to 40°C did not improve the yield of the reaction (Table 2.6, entry 3) being the enantiomeric excess in both cases lower than when the reaction was performed at room temperature. By decreasing the equivalents of both the base and the oxidant employed in the reaction, the α,β-unsaturated ketone **9** was obtained in 26% yield (Table 2.6, entry 4). Other tertiary amine bases were evaluated observing that triethylamine was the best one, rendering **9** in a high 89% yield (Table 2.6, entry 8). When DIPEA, DBU or piperidine were used the yield of the reaction turned to be from low to moderate (Table 2.6, entries 5-7), observing a noteworthy decrease in the enantioselectivity when DBU was employed (Table 2.6, entry 6). With triethylamine as the best base to carry out the transformation, we reevaluated whether lowering the temperature the enantiomeric excess could be improved but an important decrease of the yield was

observed (Table 2.6, entry 9). The reaction was also performed with less equivalents of both the base and the oxidant, but the reaction product was isolated in lower yield (Table 2.6, entry 10). After all these experiments, we could conclude that 4.4 equivalents of triethylamine and 2.7 equivalents of IBX in dichloromethane at room temperature were the optimal conditions for performing the Nef reaction, obtaining the α,β-unsaturated cyclopentenone **9** in 89% yield and 81% enantiomeric excess.

Table 2. 6. Evaluation of the Nef reaction conditions



8 **9**

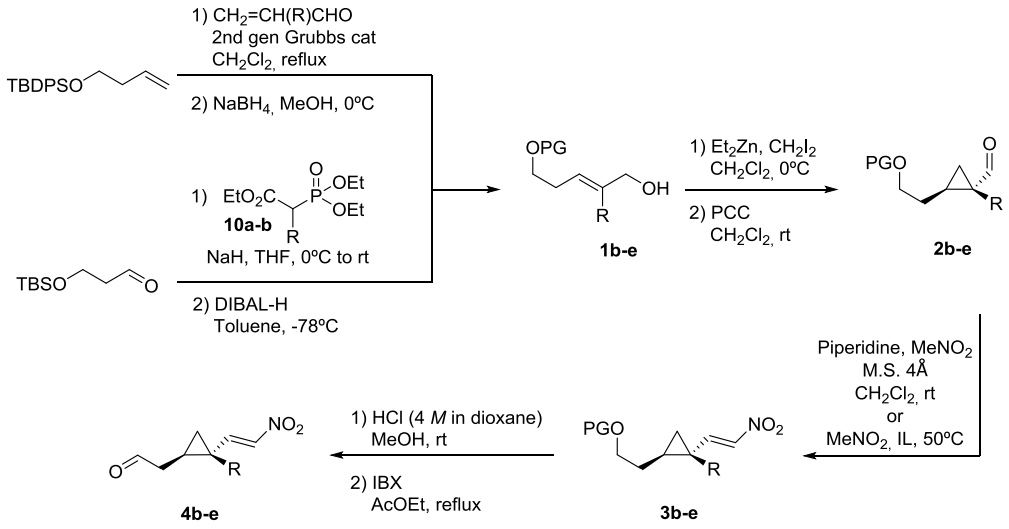
Entry[a]	Base (eq)[b]	T (°C)	Time	Yield (%)[c]	e.e. (%)[d]
1	TMG (4.4)	rt	2.5 h	50	80
2	TMG (4.4)	0	168 h[f]	38	72
3	TMG (4.4)	40	2.5 h	29	65
4[e]	TMG (2.2)	rt	3 h	26	75
5	DIPEA (4.4)	rt	4.5 h	37	82
6	DBU (4.4)	rt	0.5 h	55	7
7	Piperidine (4.4)	rt	4.5 h	14	74
8	Et_3N (4.4)	rt	4.5 h	89	81
9	Et_3N (4.4)	0	4 h	56	78
10[e]	Et_3N (2.2)	rt	2.5 h	40	82

[a]Reactions were carried out at 0.04 mmol scale of **8** in 0.6 mL of solvent (0.075 *M*). [b]pk_a (TMG) = 15.2; pk_a (DIPEA) = 10.7; pk_a (DBU) = 13.5; pk_a (piperidine) = 11.2; pk_a (Et_3N) = 10.8 (All the pk_a values in H_2O) [c]Yields refer to isolated pure product **9**. [d]Calculated by HPLC on chiral stationary phase. [e]IBX 1.35 eq [f]No full conversion observed.

3.3. Scope of the reaction

Once the optimal experimental conditions for the reaction were found, we proceeded to explore other cyclopropylacetaldehydes with different substitution patterns in the cyclopropane moiety in order to get further insight into the scope of the organocatalytic reaction. We proceeded to synthesize a variety of cyclopropylacetaldehydes with different alkyl substituents at the same carbon atom in which the nitrovinyl substituent was placed (C2 at cyclopropane). The synthetic route is depicted in Table 2.7 and is closely related to the synthetic approach used for the synthesis of the model compound **4a**.

Table 2. 7. Synthesis of substituted cyclopropylacetaldehydes



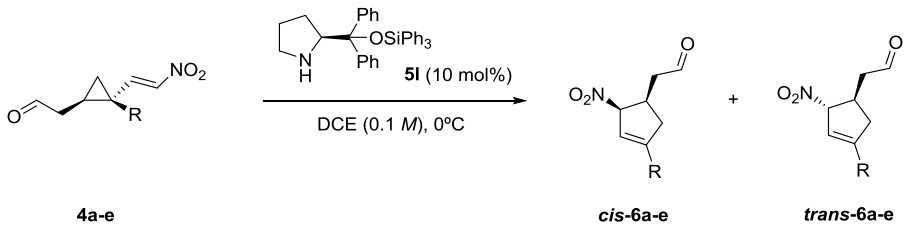
	Metathesis Reduction	HWE Reduction	Cyclopropanation Oxidation	Henry	Deprotection Oxidation
R	**Yield (%)**	**Yield (%)**	**Yield (%)**	**Yield (%)**	**Yield (%)**
CH_3	**1b** (55%)	-	**2b** (63%)	**3b** (35%)	**4b** (37%)
CH_2CH_3	**1c** (31%)	-	**2c** (82%)	**3c** (23%)	**4c** (46%)
$CH_2CH_2CH_3$	-	**1d** (39%)	**2d** (39%)	**3d** (77%)	**4d** (63%)
$CH_2CH_2CH=CH_2$	-	**1e** (17%)	**2e** (37%)	**3e** (40%)	**4e** (30%)

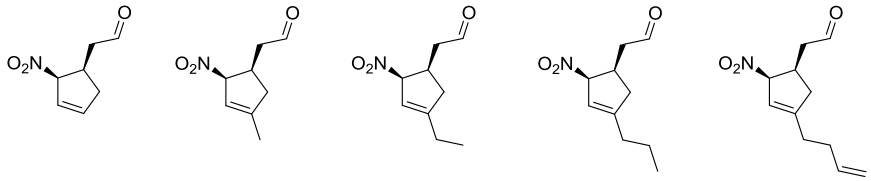
The synthesis started from the same starting material (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane which was subjected first to cross-metathesis reaction with methacrolein or 2-ethylacrolein as coupling partners, and second, to a sodium borohydride-mediated reduction obtaining the corresponding allylic alcohols **1b-c** in 55% and 31% yield, respectively. For the incorporation of larger R substituents, the approach to **1d-e** had to be changed, using 3-[(*tert*-butyl)dimethylsilyloxy]propanal as starting material and carrying out a Horner-Wadsworth-Emmons reaction with the corresponding propyl and but-3-enyl substituted phosphonates **10a-b**. The corresponding α,β-unsaturated esters were obtained, which after a DIBAL-H-promoted reduction furnished propyl- and but-3-enyl-substituted allylic alcohols **1d-e**. The cyclopropanation and the following oxidation steps were performed using the reaction conditions employed with the model substrate, obtaining **2a-e** in moderate yields. The incorporation of the nitrovinyl moiety was achieved by a Henry condensation with nitromethane. For compounds **3d-e**, the Henry reaction had to be performed using a modified procedure: methoxyl propylamine acetate ionic liquid was employed as it is described to be used for Henry reactions under solvent-free conditions.[67] Finally, after deprotection and IBX-mediated oxidation steps differently substituted cyclopropylacetaldehydes **4b-e** were obtained (Table 2.7).

Once cyclopropanes **4b-e** were synthesized, these were submitted to the vinylcyclopropane-cyclopentene rearrangement under previously optimized conditions (Table 2.8). When a methyl group was introduced in the cyclopropane, the corresponding cyclopentenes ***cis*-6b** and ***trans*-6b** were obtained with a slightly decrease in the yield (Table 2.8, substrate **4b**). The yield was not affected when increasing the size of the substituent from methyl to ethyl group, obtaining adducts ***cis*-6c** and ***trans*-6c** in 83% yield in a 76% and 86% enantiomeric excess, respectively. Nevertheless, when we further increased the length of the alkyl chain introducing a propyl substituent, the yield fell up to 64%. Unfortunately, the enantiomeric excess was also affected and a notable decrease was observed (Table 2.8, products ***cis*-6d** and ***trans*-6d**). Finally, in the case of but-3-enyl substituent nor the yield nor the enantiomeric excess were good observing a remarkably fall of both experimental parameters (Table 2.8, products ***cis*-6e** and ***trans*-6e**).

[67] Wang, W.; Cheng, W.; Shao, L.; Liu, C. H.; Yang, J. *Kinet Catal*, **2009**, *2*, 186.

Table 2. 8. Scope of the reaction: substituted nitrocyclopentenylacetaldehydes.[a]



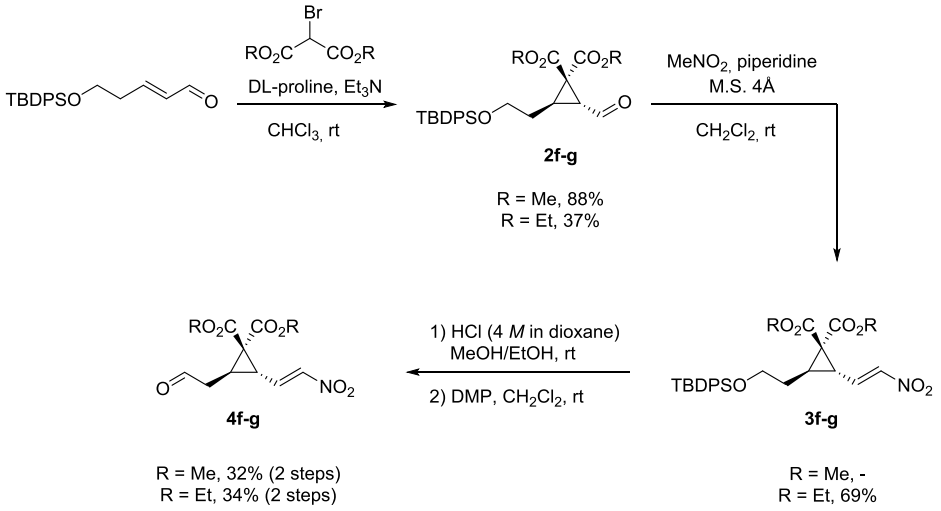


6a	**6b**	**6c**	**6d**	**6e**
Yield: 95% d.r.: 6:1 e.e.: 87% / 97%	Yield: 78% d.r.: 3:1 e.e.: 76% / 90%	Yield: 83% d.r.: 2.5:1 e.e.: 76% / 86%	Yield: 64% d.r.: 3.4:1 e.e.: 44% / 79%	Yield: 53% d.r.: n.d. e.e.: 32% / 47%

[a]Reactions were carried out at 0.1 mmol scale of substrates **4a-e**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6a-e** and ***trans*-6a-e**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase. n.d.: not determined.

Next, we decided to explore the effect of introducing two substituents in the methylene moiety of the model cyclopropylacetaldehyde. We envisaged a simple route such as the one shown in Scheme 2.53 in which the cyclopropane with two geminal alkoxycarbonyl substituents can be easily accessed through a Michael-initiated intramolecular alkylation between (*E*)-5-[(*tert*-butyldiphenylsilyl)oxy]pent-2-enal and dialkyl bromomalonate. This reaction was carried out using the iminium activation approach, this case employing DL-proline as catalyst.[68] Under these conditions, *gem*-disubstituted formylcyclopropanes **2f-g** were obtained in 88% and 37% yield. The nitrovinyl group was incorporated by using same Henry reaction methodology as before rendering the corresponding products **3f-g** which after deprotection and oxidation steps furnished cyclopropanes **4f-g**.

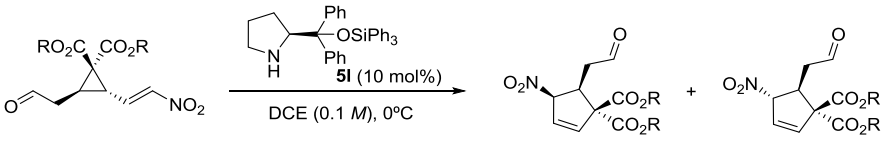
[68] (a) Mansen, H. N.; Longbottom, D. A.; Ley, S. V. *Chem. Commun*. **2006**, 4838. (b) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc*. **2007**, *129*, 10886. (c) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 7867. (d) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701.



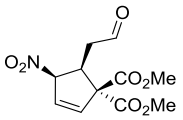
Scheme 2. 53. Synthesis of *gem*-disubstituted cyclopropylacetaldehydes

These two new cyclopropanes **4f-g** were submitted to the catalytic enantioselective VCP-CP rearrangement reaction under the optimal conditions, isolating the corresponding cyclopentenes **6f-g** in good yields as a mixture of diastereoisomers but with excellent enantioselectivities (Table 2.9) as the only products of the reaction. *Cis* diastereoisomer was again the major diastereoisomer formed during the reaction, although now the two diastereoisomers were isolated with the same excellent enantiomeric excesses.

Table 2. 9. Scope of the reaction: *gem*-disubstituted nitrocyclopentenylacetaldehydes.[a]

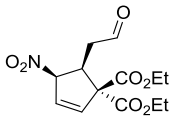


4f-g | ***cis*-6f-g** | ***trans*-6f-g**



6f

Yield: 62%
d.r.: 4.2:1
e.e.: 90% / 97%



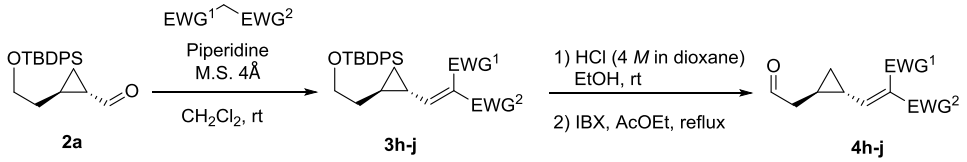
6g

Yield: 68%
d.r.: 2.2:1
e.e.: 90% / 92%

[a]Reactions were carried out at 0.1 mmol scale of substrates **4f-g**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6f-g** and ***trans*-6f-g**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase.

Finally, we explored the possibility of extending the methodology to vinylcyclopropanes with other electron-withdrawing groups at the vinyl moiety. The incorporation of different electron-withdrawing groups was carried out from compound **2a** through a Knoevenagel condensation with diethyl malonate, malononitrile or ethyl cyanoacetate obtaining **3h** in 60% yield, **3i** in 32% yield and **3j** in the highest 78% yield. Then, after a deprotection and a final oxidation steps, cyclopropanes **4h-j** were isolated (Table 2.10).

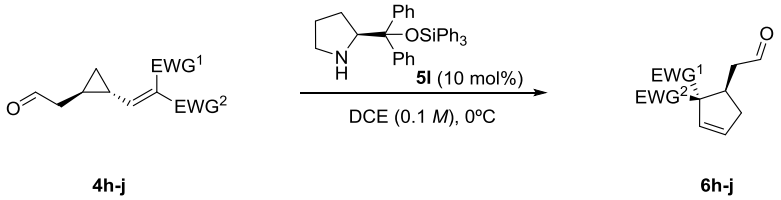
Table 2. 10. Synthesis of cyclopropylacetaldehydes with two EWG

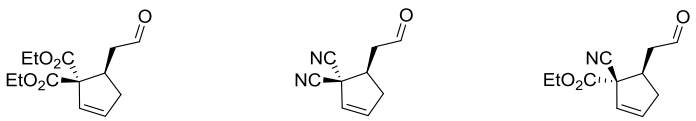


		Knoevenagel	Deprotection/Oxidation
EWG[1]	**EWG[2]**	**Yield (%)**	**Yield (%)**
CO_2Et	CO_2Et	**3h** (60%)	**4i** (45%)
CN	CN	**3i** (32%)	**4i** (14%)
CN	CO_2Et	**3j** (78%)	**4j** (67%)

In general, none of these substrates were found to be suitable materials for the reaction (Table 2.11). Substrate **4h**, with two ethoxycarbonyl substituents, rendered the cyclopentene **6h** in 34% yield and a low 43% enantiomeric excess. The incorporation of two nitrile groups as electron-withdrawing groups yielded a racemic cyclopentene **6i** in 56% yield. Finally, the combination of both substituents only furnished cyclopentene **6j** in moderate yield and enantioselectivity.

Table 2. 11. Scope of the reaction: disubstituted cyclopentenylacetaldehydes.[a]





Yield: 34%
e.e.: 43%

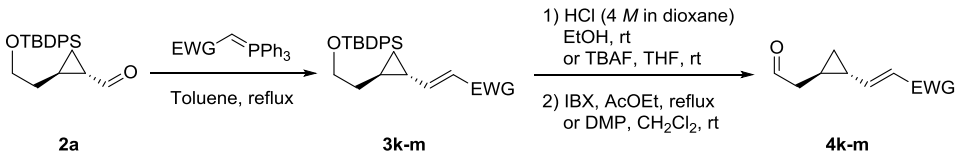
Yield: 56%
e.e.: 6%

Yield: 54%
d.r.: > 20:1
e.e.: 39%

[a] Reactions were carried out at 0.1 mmol scale of substrates **4h-j**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products **6h-j** and e.e. was calculated by HPLC on chiral stationary phase.

In view that these results were not as good as we expected we faced the incorporation of one electron-withdrawing group in the vinyl moiety of the cyclopropane. On the one hand, an ethoxycarbonyl substituent was introduced through a Wittig reaction employing ethyl (triphenylphosphoranylidene)acetate as wittig ylide obtaining **3k** in 92% yield. On the other hand, two different ketones were synthesized following the same methodology. Phenyl ketone and *para*-chlorophenyl ketone were synthesized by a Wittig reaction with the corresponding ylide obtaining **3l** and **3m** in 78% and 85% yield, respectively. Once again, a deprotection and a final oxidation steps were carried out obtaining cyclopropanes **4k-m** (Table 2.12).

Table 2. 12. Synthesis of cyclopropylacetaldehydes with one EWG

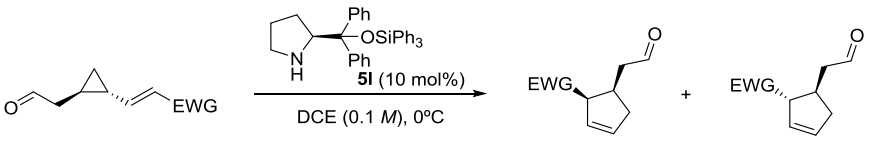


2a **3k-m** **4k-m**

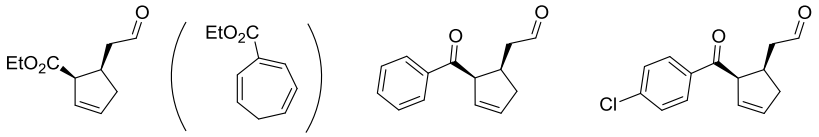
	Wittig	**Deprotection/Oxidation**
EWG	**Yield (%)**	**Yield (%)**
CO_2Et	**3k** (92%)	**4k** (44%)
PhCO	**3l** (78%)	**4l** (62%)
4-ClC_6H_4-CO	**3m** (85%)	**4m** (44%)

Cyclopropane **4k** was not reactive towards the vinylcyclopropane-cyclopentene rearrangement but it resulted in the formation of ethyl cyclohepta-1,3,6-triene-1-carboxylate **11** as a result of a 7-*exo*-cyclization of the ring-opening intermediate (Table 2.13). On the other hand, substrates **4l** and **4m** that incorporated a α,β-unsaturated ketone moiety in their structure, were capable of undergoing the rearrangement reaction in moderate yields and good enantiocontrol (Table 2.13, products ***cis*-6l-m** and ***trans*-6l-m**).

Table 2. 13. Scope of the reaction: monosubstituted cyclopentenylacetaldehydes.[a]



4k-m ***cis*-6k-m** ***trans*-6k-m**



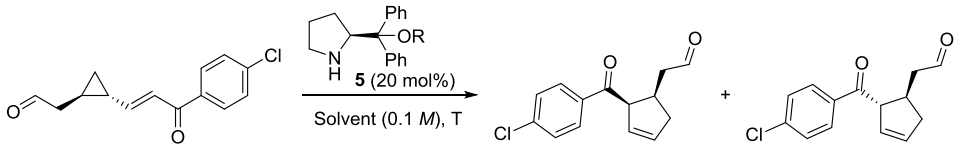
11 **6l** **6m**

Yield < 5%	Yield: 24%	Yield: 55% d.r.: 1.8:1 e.e.: 80% / 98%	Yield: 56% d.r.: 2.5:1 e.e.: 85% / 96%

[a] Reactions were carried out at 0.1 mmol scale of substrates **4k-m**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6k-m** and ***trans*-6k-m**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase.

This fact gave us the possibility of extending the scope of the reaction to ketones of different stereoelectronic properties. However, notwithstanding the excellent enantomeric excesses which *cis* and *trans* cyclopentenes were obtained with, the yield of the reaction remained being moderate. For this reason, we decided to reevaluate the reaction conditions employing **4m** as a model substrate trying to improve the performance of the reaction. As it can be appreciated in Table 2.14, a short screening of catalysts, solvents and temperatures was performed.

Table 2. 14. Reevaluation of reaction conditions over compound **4m**



4m ***cis*-6m** ***trans*-6m**

Entry[a]	Catalyst	Solvent	T (°C)	Yield (%)[b]	d.r.[c]	e.e. *cis* (%)[d]	e.e. *trans* (%)[d]
1	**5a**	1,2-dichloroethane	0	44	1.4:1	58	92
2	**5l**	1,2-dichloroethane	0	56	2.5:1	84	96
3	**5m**	1,2-dichloroethane	0	70	2.6:1	85	96
4	**5m**	1,2-dichloroethane	rt	81	2.2:1	63	95
5	**5m**	$CHCl_3$	0	51	2.5:1	81	96
6	**5m**	Toluene	0	53	3.1:1	70	94
7	**5m**	1,2,3-trichloroethane	0	54	2.6:1	80	94
8	**5m**	CH_2Cl_2	rt	61	2.7:1	77	95

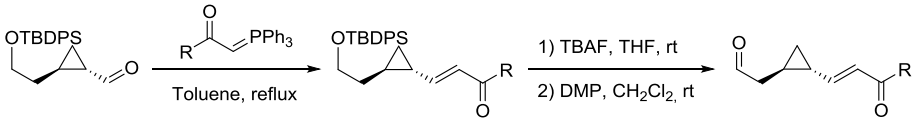
[a]Reactions were carried out at 0.06 mmol scale of **4m**, using 20 mol% of catalyst in 0.6 mL of solvent. [b]Yields refer to isolated pure products ***cis*-6m** and ***trans*-6m**. [c]Diastereomeric ratios values were determined in the reaction mixture by ^{1}H-NMR analysis [d]Calculated by HPLC on chiral stationary phase.

First of all, three catalysts with different silyl groups were reevaluated performing the reaction in 1,2-dichloroethane at 0°C (Table 2.14, entries 1-3), observing that catalyst **5m** furnished cyclopentenes ***cis*-6m** and ***trans*-6m** with better yield and similar levels of diastereo- and enantioselectivity (Table 2.14, entry 3). Next, the reaction was performed at room temperature; although the final rearrangement products were obtained in 81% yield, the enantiomeric excess dropped significantly (Table 2.14, entry 4). Thereby, we decided to perform the reaction in other solvents (Table 2.14, entries 5-8). Although the enantiocontrol was good in all the cases, the yield remained being moderate when chloroform, toluene or 1,2,3-trichloroethane were employed (Table 2.14, entries 5-7). However, when dichloromethane was employed the yield resulted slightly improved with only a minor decrease in the e.e. for the *cis* diastereoisomer ***cis*-6m** (Table 2.14, entry 8). It was concluded that **5m** was the most suitable catalyst for carrying out the rearrangement in 1,2-dichloroethane at 0°C.

In view of these results and taking into account that the scope of the reaction can be further increased by using enones as acceptor groups, we next proceeded to synthesize a

family of cyclopropylacetaldehydes incorporating α,β-unsaturated ketone lateral chains which could be evaluated in the VCP-CP rearrangement using these new optimized conditions. These substrates were synthesized as described before starting from **2a** through a sequential Wittig olefination followed by deprotection and oxidations steps (Table 2.15).

Table 2. 15. Synthesis of cyclopropylacetaldehydes incorporating α,β-unsaturated ketone lateral chain



2a **3n-z** **4n-z**

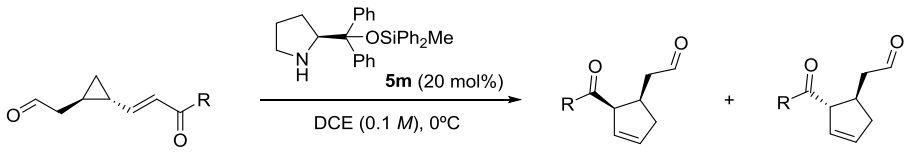
	Wittig	**Deprotection/Oxidation**
R	**Yield (%)**	**Yield (%)**
p-$CF_3C_6H_4$	**3n** (48%)	**4n** (46%)
p-FC_6H_4	**3o** (80%)	**4o** (46%)
p-BrC_6H_4	**3p** (71%)	**4p** (46%)
m,*p*-diClC_6H_3	**3q** (56%)	**4q** (51%)
p-CNC_6H_4	**3r** (59%)	**4r** (39%)
o-BrC_6H_4	**3s** (52%)	**4s** (13%)
m-$OMeC_6H_4$	**3t** (88%)	**4t** (51%)
p-PhC_6H_4	**3u** (87%)	**4u** (22%)
2-Naphtyl	**3v** (93%)	**4v** (54%)
p-MeC_6H_4	**3w** (88%)	**4w** (47%)
p-$OMeC_6H_4$	**3x** (76%)	**4x** (59%)
Me	**3y** (61%)	**4y** (71%)
^{t}Bu	**3z** (48%)	**4z** (26%)

With the new family of cyclopropylacetaldehydes in hand, we performed the vinylcyclopropane-cyclopentene rearrangement reaction. First of all, aromatic ketones with substituents in *para* position were tested (Table 2.16). By the incorporation of *para*-substituted aromatic α,β-unsaturated ketone lateral chain we could not observe a clear tendency. Cyclopropanes **4m,o-p** with a halogen in *para*-position of the aromatic ring lead to rearrangement cycloadducts ***cis*-6m,o-p and *trans*-6m,o-p** in moderate yields observing the highest yield with the most electron-withdrawing fluorine halogen (Table 2.16, products ***cis*-6o** and ***trans*-6o**). However, both the diastereomeric ratio and enantiomeric excess were very similar. When other electron-withdrawing groups were placed in the *para* position of the α,β-unsaturated aromatic ketone, different results were observed. Both trifluoromethyl and

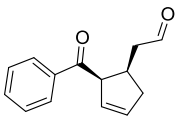
nitrile substituents were not suitable substituents for the efficient performance of the rearrangement. The corresponding cyclopentenes ***cis*/*trans*-6n** and ***cis*/*trans*-6r** were obtained in very low 32% and 24% yields, although the enantioselectivity was good for both diastereoisomers (Table 2.16, products **6n**, **6r**). On the other hand, when electron-donating substituents were located in the *para*-position of the α,β-unsaturated aromatic ketone, cyclopentene adducts were isolated in lower yield. **4w** and **4x** rendered the corresponding cyclopentenes in moderate 57% and 48% yield and moderate to good enantiocontrol (Table 2.16, products ***cis*/*trans*-6w** and ***cis*/*trans*-6x**). Finally, when *para*-phenyl-substituted α,β-unsaturated aromatic ketone moiety was incorporated to the cyclopropane a remarkably increase of the yield was observed isolating the cyclopentenes ***cis*-6u** and ***trans*-6u** in an overall 63% yield, being the enantioselectivity of the reaction also good, similar to other substrates (Table 2.16, substrate **4u**). A very similar result was observed when the reaction was carried out over no substituted aromatic α,β-unsaturated ketone **4l**. The corresponding cyclopentenes ***cis*-6l** and ***trans*-6l** were isolated in a 68% yield with good enantiocontrol (Table 2.16). However, cyclopropane **4v** yielded the corresponding cyclopentenes ***cis*-6v** and ***trans*-6v** in slightly lower yield and an enantiomeric excess of 78% and 97% for *cis* and *trans* diastereoisomers, respectively (Table 2.16).

A remarkably improvement of the reaction outcome was appreciated when two electron-withdrawing groups were incorporated in the aromatic ring of the α,β-unsaturated ketone. This is the case of cyclopropane **4q** which furnished the corresponding cyclopentenes ***cis*-6q** and ***trans*-6q** in a good 72% yield and 76% and 94% enantiomeric excess for the *cis* and *trans* cycloadducts respectively, when the reaction was performed in dichloromethane as solvent at room temperature (Table 2.16). When the electron-withdrawing group was incorporated in *ortho* position of the aromatic ring, the reaction did not take place, probably due to the steric hindrance between the *ortho* substituent and the catalyst (Table 2.16, substrate **4s**). On the other hand, the incorporation of an electron-donor substituent in *metha* position of the aromatic α,β-unsaturated aromatic ketone, such as methoxyl group, provided the cyclopentenes ***cis*-6t** and ***trans*-6t** in moderate yield, although the enantiomeric excess remained being good (Table 2.16).

Table 2. 16. Scope of the reaction: aryloylcyclopentenylacetaldehydes.[a]

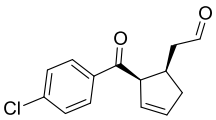


4l-z | ***cis*-6l-z** | ***trans*-6l-z**



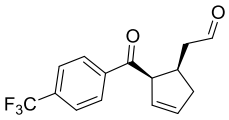
6l

Yield: 68%
d.r.: 2.6:1
e.e.: 79% / 98%



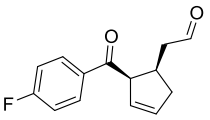
6m

Yield: 70%
d.r.: 2.6:1
e.e.: 85% / 96%



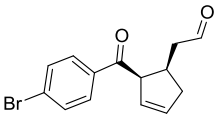
6n

Yield: 32%
d.r.: 5.3:1
e.e.: 88% / 93%



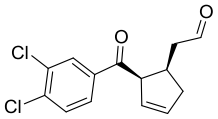
6o

Yield: 71%
d.r.: 2.8:1
e.e.: 75% / 98%



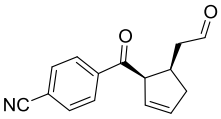
6p

Yield: 60%
d.r.: 2.5:1
e.e.: 80% / 97%



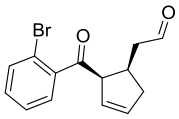
6q

Yield: 51% (72%)[b]
d.r.: 2.3:1 (3.7:1)[b]
e.e.: 76% / 94% (76% / 94%)[b]



6r

Yield: 24%
d.r.: 3.7:1
e.e.: 68% / 95%

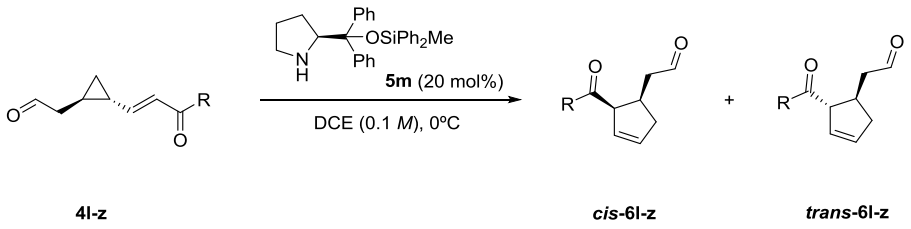


6s

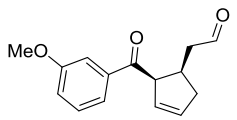
Yield < 5%

[a] Reactions were carried out at 0.1 mmol scale of substrates **4l-z**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6l-z** and ***trans*-6l-z**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase. [b] Catalyst **5m** (20 mol%), CH_2Cl_2 (0.1 *M*), rt.

Table 2. 16. Scope of the reaction: aryloylcyclopentenylacetaldehydes.[a] (continued)

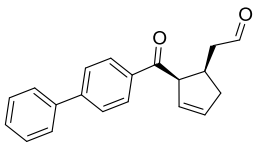


4l-z ***cis*-6l-z** ***trans*-6l-z**



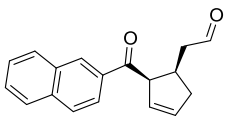
6t

Yield: 29% (57%)[b]
d.r.: 2.3:1 (2.2:1)[b]
e.e.: 74% / 75% (81% / 72%)[b]



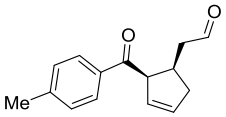
6u

Yield: 63%
d.r.: 3.1:1
e.e.: 89% / 64%



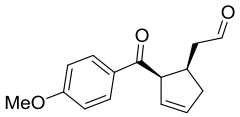
6v

Yield: 56%
d.r.: 2.7:1
e.e.: 78% / 97%



6w

Yield: 32% (57%)[b]
d.r.: 2.6:1 (2.4:1)[b]
e.e.: 81% / 95% (79% / 77%)[b]



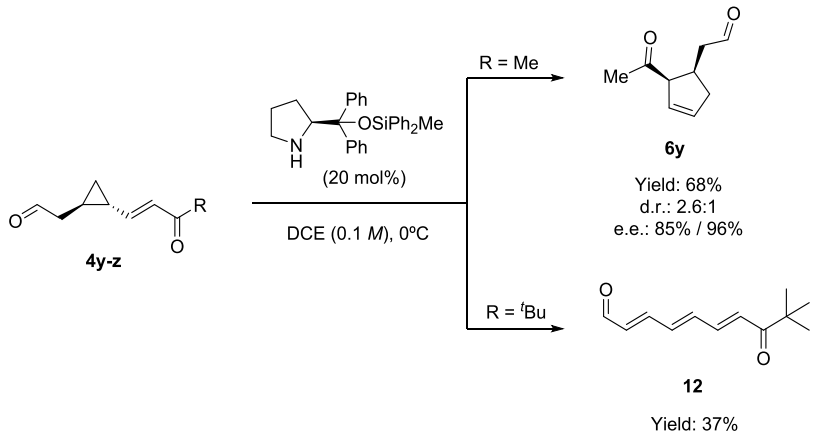
6x

Yield: 48%
d.r.: 2.3:1
e.e.: 80% / 94%

[a] Reactions were carried out at 0.1 mmol scale of substrate **4l-z**, using 10 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6l-z** and ***trans*-6l-z**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase. [b] Catalyst **5m** (20 mol%), CH_2Cl_2 (0.1 *M*), rt.

Finally, we also surveyed the performance of cyclopropanes **4y** and **4z** that presented an alkyl group as the R substituent of the enone moiety. Substrate **4y** provided cyclopentenes ***cis*-6y** and ***trans*-6y** in an excellent 79% yield and excellent enantioselectivity with a diastereomeric ratio of 3:1 (Scheme 2.54). When *tert*-butyl group was incorporated in the α,β-unsaturated ketone, the cyclopropane turned to be not efficient for the rearrangement (Scheme 2.54). In

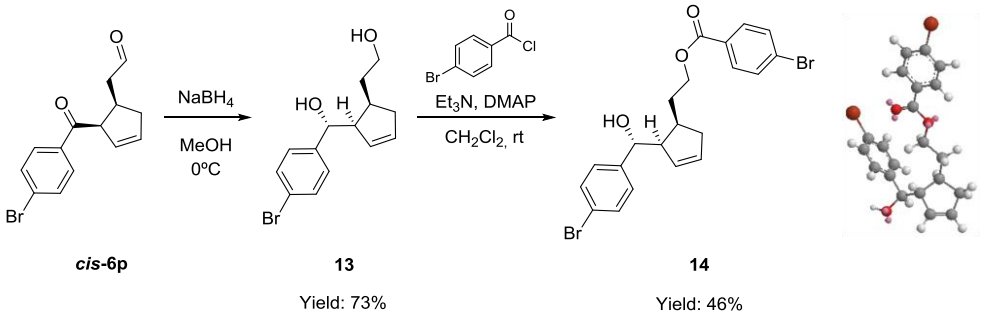
this case, the starting material **4z** led to the polyunsaturated aldehyde product **12** which could be isolated. This by-product was not able to undergo closing reaction to provide the corresponding cyclopentenes under several conditions tested.



Scheme 2. 54. Scope of the reaction: acylcyclopentenylacetaldehydes [69]

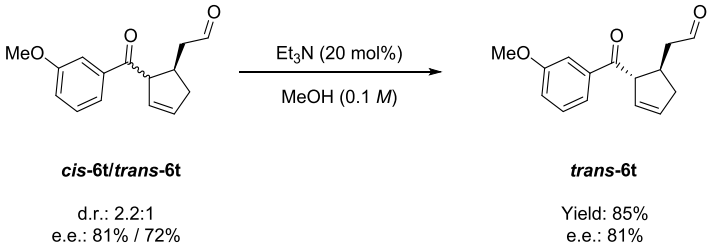
All these products **6l-z** were found to be oils and therefore their absolute configuration could not be determined at this stage. For this reason, we selected cyclopentene ***cis*-6p**, which presented a heavy atom in its structure as suitable compound to undergo chemical modification with the aim of obtaining a crystalline derivative in order to determine the absolute configuration by X-ray analysis. For this reason, compound ***cis*-6p** was reacted with $NaBH_4$, leading to the formation of compound **13** in which both carbonyl moieties had been reduced, being isolated as a single diastereoisomer. This compound was also found to be an oil, so we performed an esterification reaction in order to obtain **14** as a solid sample an so, after a crystallization process, its fully characterization by means of single-crystal X ray diffraction could be performed (Scheme 2.55).

[69] Reactions were carried out at 0.06 mmol scale of **4y-z**, using 20 mol% of catalyst in 0.6 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*/*trans*-6y** and **12**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase.



Scheme 2. 55. Transformation of aldehyde ***cis*-6p** and X-ray analysis of **14**

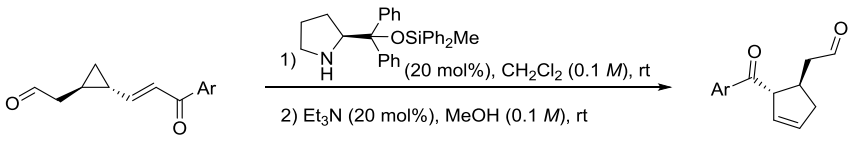
Finally, in view of the low diastereomeric ratios that have been obtained with almost all the tested substrates, we faced the challenge of converting the *cis* diastereoisomer ***cis*-6t** into the thermodynamically more stable *trans* adduct ***trans*-6t** through the epimerization of the acidic center at the α-position to the ketone moiety. After several experiments, we were able to isolate pure *trans* diastereoisomer ***trans*-6t** in 85% yield and an enantiomeric excess of 81% from the mixture of diastereoisomers after being stirring two days at room temperature in MeOH with a 20 mol% of triethylamine (Scheme 2.56).



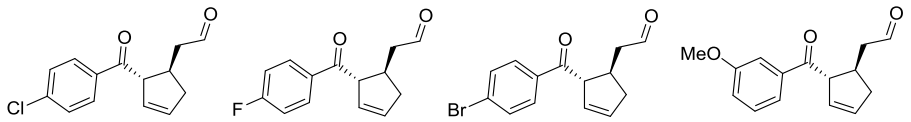
Scheme 2. 56. Base-mediated isomerization of diastereoisomers ***cis*-6t**/***trans*-6t**

With this successful result in hand, we decided to carry out the vinylcyclopropane-cyclopentene rearrangement followed by epimerization using some selected substrates (Table 2.17). *Trans* diastereoisomers could be isolated in a very similar yield that those obtained in the rearrangement step due to the isomerization process took place in a quantitative manner. Thus, this methodology allowed us to isolate *trans* diastereoisomers as a single reaction product with the same efficiency as before. Furthermore, we could not appreciate any racemization event during this sequence.

Table 2. 17. Scope of reaction: VCP-CP rearrangement/isomerization of aryloylcyclopentenylacetaldehydes.[a]



4m, o-p, t, v-x **trans-6m, o-p, t, v-x**

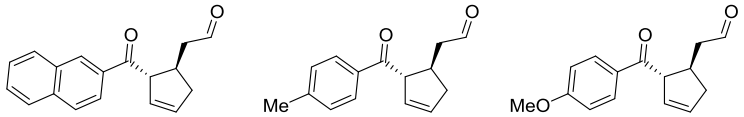


***trans*-6m**
Yield: 56%
e.e.: 76%

***trans*-6o**
Yield: 63%
e.e.: 66%

***trans*-6p**
Yield: 34%
e.e.: 77%

***trans*-6t**
Yield: 49%
e.e.: 81%



***trans*-6v**
Yield: 49%
e.e.: 83%

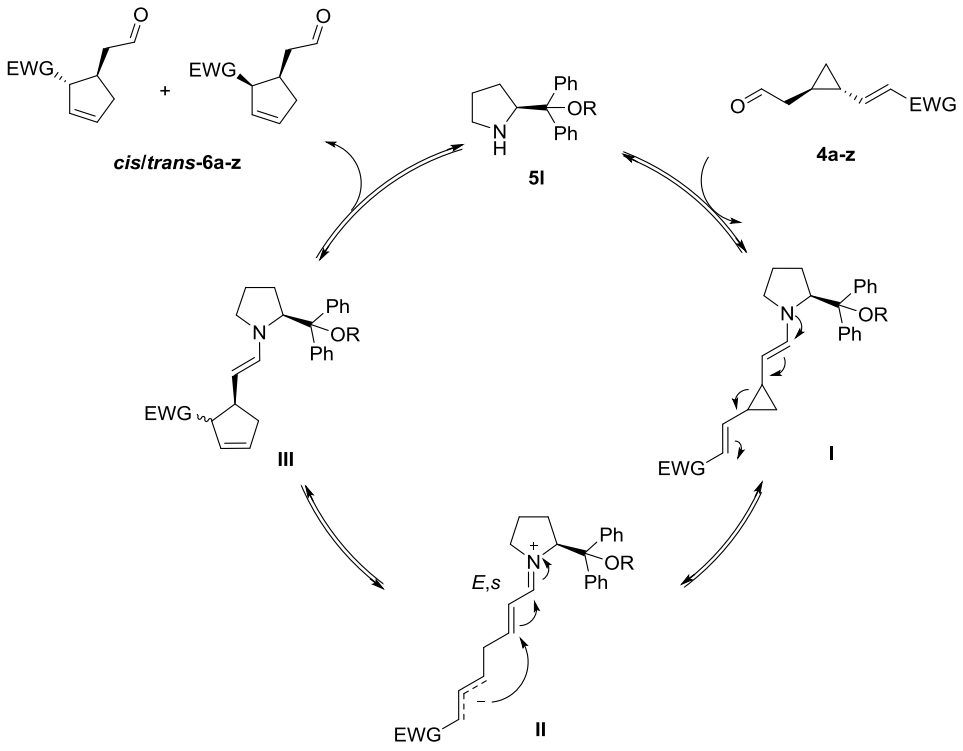
***trans*-6w**
Yield: 48%
e.e.: 83%

***trans*-6x**
Yield: 26%
e.e.: 83%

[a] Reactions were carried out at 0.1 mmol scale of substrates **4m, o-p, t, v-x**, using 20 mol% of catalyst in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). After isolation by FC chromatography, 20 mol% Et_3N was added in 1.0 mL of MeOH. Yields refer to isolated pure products ***trans*-6m, o-p, t, v-x** after an aqueous work-up and e.e. was calculated by HPLC on chiral stationary phase.

3.4. Mechanistic insights

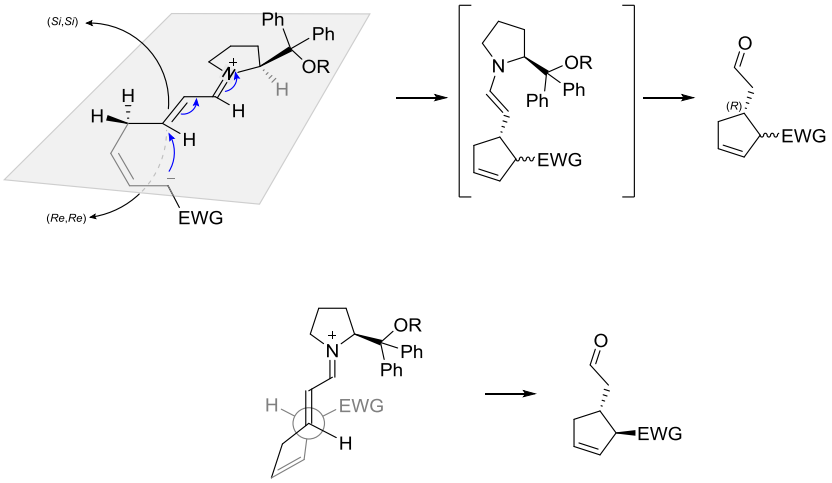
In view of all the experimental data, the catalytic cycle shown in the Scheme 2.57 can be proposed. First, the chiral amine would condense with the cyclopropylacetaldehydes **4a-z** to *in situ* generate the donor-acceptor cyclopropane **I**. The enamine counterpart would promote the ring-opening step that leads to the formation of zwitterionic iminium ion **II**, where the negative charge is stabilized by the electron-withdrawing group. Next, the system would undergo a subsequent 5-exo-trig cyclization between the nucleophilic dienolate moiety as the electrophilic α,β-unsaturated iminium ion that leads to the final cyclopentene product. Finally, the catalyst is released, furnishing *cis* and *trans* diastereoisomers of the corresponding cyclopentenes **6a-z**.



Scheme 2. 57. Catalytic cycle of the vinylcyclopropane-cyclopentene rearrangement

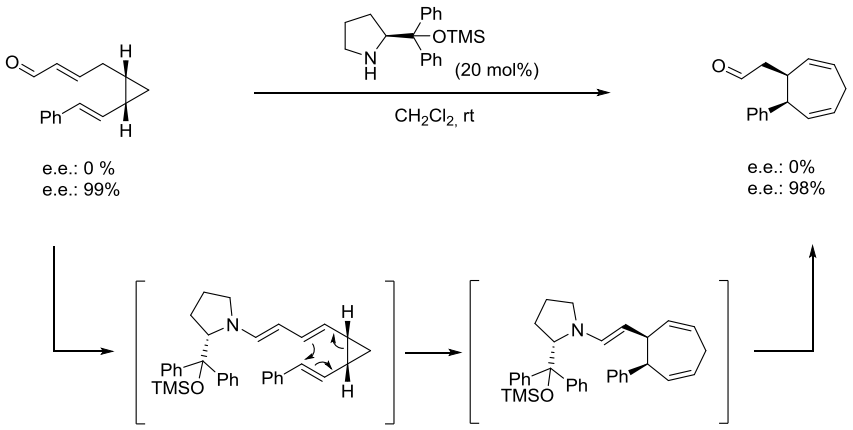
The absolute configuration of the C1 stereocenter in the cyclopentenylacetaldehyde adduct is in good agreement with the formation of a *E*,*E* iminium ion and the reaction of the

nucleophile through the less hindered face of this α,β-unsaturated iminium ion in a *s-trans* conformation, which is also in line with the stereochemical outcome of other similar reactions using the same type of intermediates.[61b] Finally, stereochemistry at C2 results from the thermodynamic *cis*/*trans* mixture because of the acidic nature of the proton present at this stereogenic center (Scheme 2.58).



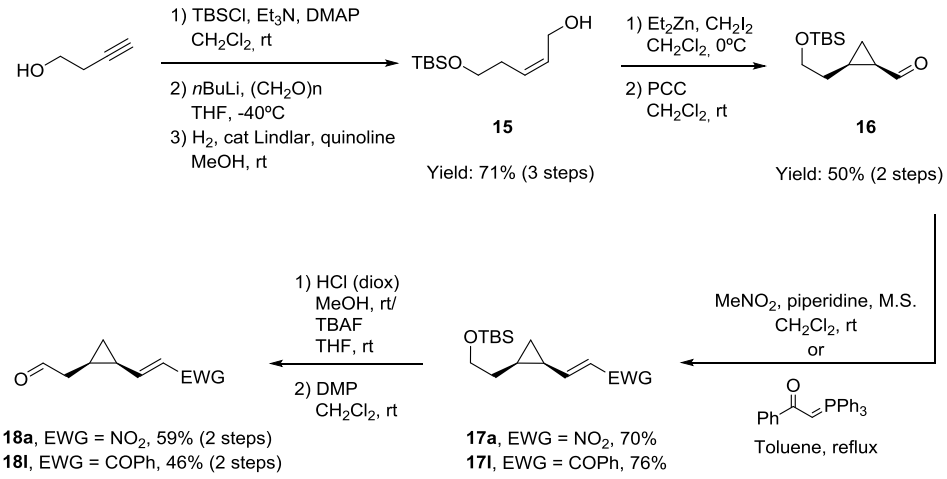
Scheme 2. 58. Stereochemical model

In addition, while this project was ongoing, Christmann and coworkers published a dienamine-induced divinylcyclopropane-cycloheptadiene rearrangement which can be considered as a vinilogous version of that presented in this research.[13e] In their reaction, a donor-acceptor cyclopropane with a *cis* relationship between the substituents was employed as substrate. The generation of 1,5-diene was proposed to take place through dienamine formation followed by a [3,3]-sigmatropic rearrangement. In this case the presence of a chiral catalyst did not have any influence on the stereochemical outcome of the reaction, this proceeding under complete substrate control. In fact, starting from an enantiopure substrate, chirality transfer from the cyclopropane to cycloheptadiene was observed (Scheme 2.59).



Scheme 2. 59. [3,3]-sigmatropic rearrangement of *in situ* generated donor-acceptor cyclopropanes

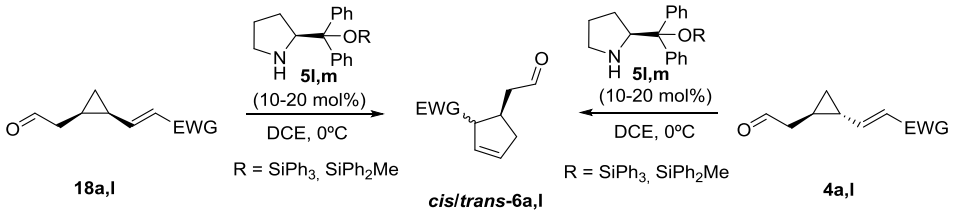
With this precedent in mind, and in view of the similarity with our system, we turned our efforts to synthesize some examples of a vinylcyclopropylacetaldehyde substrate with a *cis* relative configuration to be evaluated in the VCP-CP rearrangement. For the synthesis of the *cis*-vinylcyclopropylacetaldehydes, we followed the methodology described by Christmann and coworkers with some modifications. The route started with the protection of commercially available 3-butyn-1-ol as a silyl ether followed by a chain elogation reaction employing paraformaldehyde and a Lindlar catalyst-mediated hydrogenation affording allylic alcohol **15**. **15** was submitted to a Simons-Smith cyclopropanation and a PCC-mediated oxidation furnishing cyclopropanecarbaldehyde **16**. Next, both nitrovinyl and α,β-unsaturated phenyl ketone moieties were introduced in the cyclopropane structure through a Henry and a Wittig reaction in 70% and 76% yield, respectively. Finally, after a deprotection and a final oxidation steps, *cis*-cyclopropylacetaldehydes **18a** and **18l** were obtained (Scheme 2.60).



Scheme 2. 60. Synthesis of *cis*-vinylcyclopropylacetaldehydes

These newly synthesized *cis*-vinylcyclopropylacetaldehydes were evaluated in the vinylcyclopropane-cyclopentene rearrangement under the optimized conditions and their results were compared with those obtained with *trans* derivatives **4a,l** (Table 2.18). As it can be observed, for *cis*-cyclopropylacetaldehyde **18a** with a nitrovinyl moiety, the rearrangement provided cyclopentenes ***cis*-6a** and ***trans*-6a** in a slightly lower 62% yield. However, the diastereomeric ratio increased remarkably, being *cis* diastereoisomer again the major one. The enantioselectivity of the transformation resulted to be similar for ***trans*-6a** and slightly slower for ***cis*-6a**. On the other hand, *cis*-cyclopropylacetaldehyde **18l** with a α,β-unsaturated ketone moiety led to cyclopentenes ***cis*-6l** and ***trans*-6l** in similar yield, and the same diastereomeric ratio and enantiomeric excess than the corresponding *trans*-cyclopropylacetaldehyde **4l**. Hence, we can conclude that cyclopentenes obtained from racemic *cis* and/or *trans* cyclopropylacetaldehydes were not obtained as racemates, such as in the research developed by Christmann, which would indicate that the developed vinylcyclopropane-cyclopentene rearrangement is not a [3,3]-sigmatropic process. The stereochemistry of the overall process may be controlled in this case by the chiral catalyst, and not by the substrate, as it is observed in the rearrangement developed by Christmann and coworkers.

Table 2. 18. Vinylcyclopropane-cyclopentene rearrangement over *cis* and *trans* cyclopropylacetaldehydes.[a]



	From **18a,l**			From **4a,l**		
EWG	**Yield**	**d.r.**	**e.e.**	**Yield**	**d.r.**	**e.e.**
NO_2	62%	12:1	69% / 92%	95%	6:1	87% / 97%
PhCO	60%	2.7:1	73% / 97%	68%	2.6:1	72% / 95%

[a] Reactions were carried out at 0.1 mmol scale of substrates **18a,l** or **4a,l**, using 10 mol% of catalyst **5l** (for **4a** and **18a**) and 20 mol% of catalyst **5m** (for **4l** and **18l**) in 1.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products ***cis*-6a,l** and ***trans*-6a,l**, d.r. values were determined in the reaction mixture by ^{1}H-NMR analysis and e.e. was calculated by HPLC on chiral stationary phase.

4. CONCLUSIONS

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

- We have been able to design a suitable methodology for carrying out a catalytic enantioselective vinylcyclopropane-cyclopentene (VCP-CP) rearrangement under enamine activation, providing enantioenriched cyclopentenes.

- Vinylcyclopropylacetaldehydes have demonstrated to be suitable substrates for this rearrangement, converting the substrate into donor-acceptor cyclopropanes and undergoing a ring-opening reaction yielding a chiral intermediate which is able to undergo a ring-closing process in an enantioselective fashion.

- The methodology has demonstrated to have a wide scope regarding the electron-withdrawing group in the cyclopropane. Incorporation of substituents in the cyclopropane skeleton turns to be limited.

- Experimental studies support that the reaction takes place stepwise. Starting from racemic vinylcyclopropylacetaldehydes enantiopure cyclopentenes are obtained through an intermediate in which the stereogenic centers present in the starting material have disappeared.

Chapter 3

3

Transition metal-free stereoselective borylation of allenylamides

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1. INTRODUCTION

1.1. Diboron compounds

Organoboranes are essential compounds in organic chemistry due to their versatility and their high value as reagents in synthetic chemistry.[1a] In the last decades a lot of efforts have been made in the area of organoborane chemistry due to their possibility of easy-transforming the C-B bond into other valuable functionalities.[1b] Apart from their versatility, organoboranes can be also considered ideal candidates for green chemistry since they are typically not toxic and easy to handle. Moreover, these reagents present an excellent functional group tolerance allowing carrying out a wide range of synthetic transformations.[2] Different types of diboron compounds are summarized in Table 3.1 which will be explained in detail in the following paragraphs.

Table 3. 1. Diboron compounds: structure and applicability

Diboron compound	Structure	Applications
Diboron tetrahalide	B_2X_4	Diborylation of alkenes/alkynes
Tetraaminodiboron	$B_2(NR_2)_4$	Diborylation of alkenes
Tetraalkoxydiboron	$B_2(OR)_4$	Hydroborylation reactions Diborylation reactions
Gem-diborylalkanes	RB-C-BR	Cross-coupling reactions Functional group transformations Asymmetric synthesis

The synthesis of a diboron compound was first reported in 1925. Stock, Brandt and Fischer prepared for the first time the boron subhalide B_2Cl_4, using an electric discharge between zinc electrodes immersed in liquid boron trichloride.[3] However, this diboron tetrachloride was obtained in a very low yield, which made this methodology not efficient enough for the synthesis of these compounds. Later on, other methodologies such as performing the reaction in gas phase using a mercury arc[4] or employing microwave excitation of gaseous boron

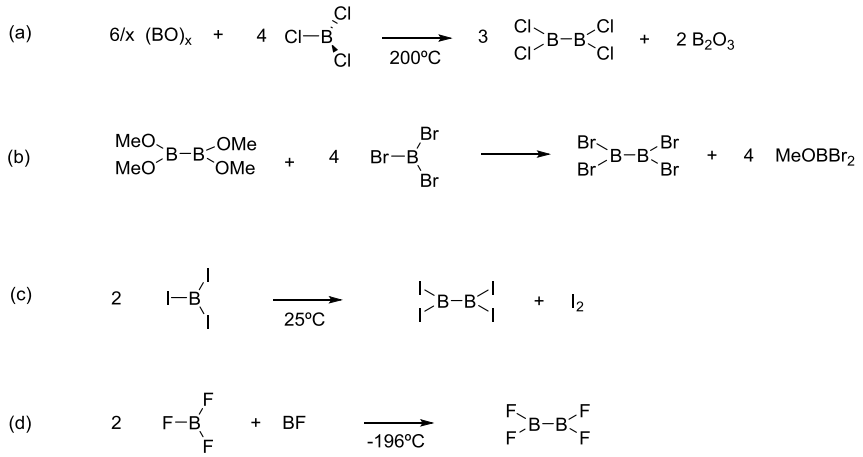
[1] (a) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11700. (b) Sandford, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 5481.

[2] Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev*. **2016**, *116*, 9091.

[3] Stock, A.; Brandt, A.; Fischer, H. *Ber. Dtsch. Chem. Ges. B*, **1925**, *58*, 643.

[4] (a) Holiday, A.; Massey, A. G. *J. Am. Chem. Soc*. **1958**, *80*, 4744. (b) Holliday, A.; Massey, A. G. *Chem. Rev*. **1962**, *62*, 303.

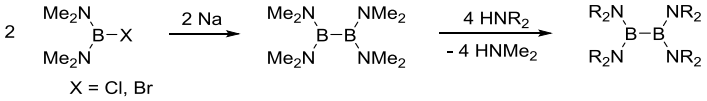
trichloride[5] were developed but all of them provided low yields or involved harsh reaction conditions. It was not until 1961 when diboron tetrachloride was synthesized in an efficient manner by reaction of boron trichloride with boron monoxide at 200°C (Scheme 3.1 a).[6] The other product obtained in the reaction was probably boron trioxide or a mixed compound of boric oxide and boron trichloride, but it was not isolated. Once diboron tetrachloride was synthesized, its analogues were prepared employing similar methodologies. For example, diboron tetrabromide species was isolated by reaction of tetramethoxydiboron and boron tribromide (Scheme 3.1 b),[7] while diboron tetraiodide was synthesized by reduction of BI_3 using electrodeless radiofrecuency discharge (Scheme 3.1 c).[8] However, these species are rarely used in synthesis. Diboron tetrafluoride was not prepared until the late 50s, when diboron tetrachloride was reacted with SbF_3.[9] Years later, Timms reported that co-condensation of BF with BF_3 at -196°C afforded B_2F_4 (Scheme 3.1 d).[10]



Scheme 3. 1. Synthesis of tetrahalodiboranes (B_2Cl_4, B_2Br_4, B_2I_4 and B_2F_4)

[5] Frazer, J. W.; Holzmann, R. T. *J. Am. Chem. Soc*. **1958**, *80*, 2907.
[6] McCloskey, A. L.; Brotherton, R. J.; Boone, J. L. *J. Am. Chem. Soc*. **1961**, *83*, 4750.
[7] Dembitsky, V. M.; Ali, H. A.; Srabnik, M. Recent Chemistry of Diboron Compounds. *Advances in Organometallic Chemistry*, Academic Press, pp 193-250, Cambridge, 2004.
[8] Schumb, W. C.; Gamble, E. L.; Banus, M. D. *J. Am. Chem. Soc*. **1949**, *71*, 3225.
[9] Finch, A.; Schlesinger, H. I. *J. Am. Chem. Soc*. **1958**, *80*, 3573.
[10] Timms, P. L. *Acc. Chem. Res*. **1973**, *6*, 118.

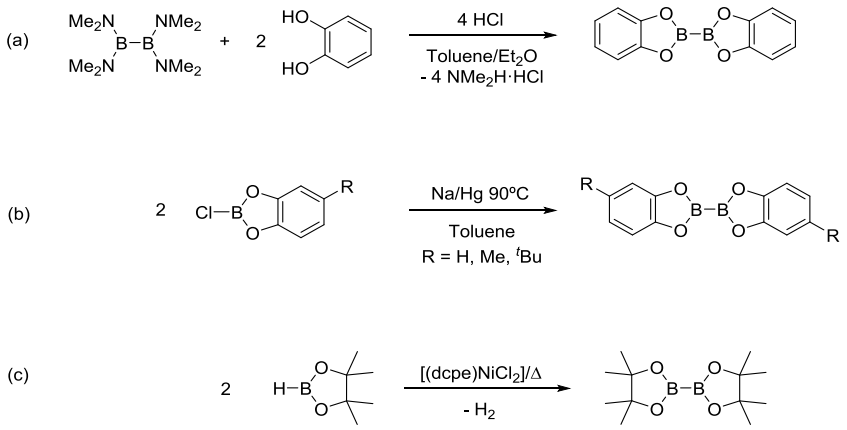
The discovery of tetrakis(dimethylamino)diboron $B_2(NMe_2)_4$ represented an important breakthrough in diboron chemistry.[11] This species, although moisture sensitive, resulted to be chemically stable under air. Its stability can be attributed to extensive N-B π-bonding and the steric crowding provided by the dimethylamino groups. The first synthesis of $B_2(NMe_2)_4$ was carried out by Urry and coworkers after replacing diboron tetrachloride by dimethylamino groups.[12] Later on, Brotherton and coworkers developed an improved methodology for the preparation of these diboron species by the addition of halobis(dimethylamino)boranes to dispersed liquid sodium.[11] They also reported the transamination with a number of secondary amines, providing the corresponding aminodiboron species (Scheme 3.2).



Scheme 3. 2. Synthesis of tetrakis(dimethylamino)diboron

Tetraalkoxydiboron compounds are relatively easy to prepare, air-stable and easy to manipulate. Brotherton and coworkers developed a general route to the synthesis of these diboron compounds based on the addition of alcohols to $B_2(NMe_2)_4$ (Scheme 3.3 a).[13] Decades later, Hartwig published a synthetic route for the preparation of substituted bis(catecholato)diboron by the reaction of a sodium/mercury amalgam with the corresponding halocatecholborane (Scheme 3.3 b).[14] More recently, some publications from the group of Braunschweig and Guethlein showed that bis(pinacolato)diboron B_2pin_2 and bis(cathecolato)diboron B_2cat_2 could be synthesized by the metal-catalyzed dehydrogenative coupling of the starting boranes HBpin and HBcat, respectively (Scheme 3.3 c).[15]

[11] Brotherton, R. J.; McCloskey, A. L.; Petterson, L. L.; Steinberg, H. *J. Am. Chem. Soc.* **1960**, *82*, 6242.
[12] Urry, G.; Wartik, T.; Moore, R. E.; Schlesinger, H. I. *J. Am. Chem. Soc*. **1954**, *76*, 5293.
[13] Brotherton, R. J.; McCloskey, A. L.; Boone, J. L.; Manasevit, H. M. *J. Am. Chem. Soc*. **1960**, *82*, 6245.
[14] Anastasi, N. R.; Waltz, K. M.; Weerakon, W. L.; Hartwig, J. F. *Organometallics* **2003**, *22*, 365.
[15] (a) Braunschweig, H.; Guethlein, F. *Angew. Chem. Int. Ed*. **2011**, *50*, 12613. (b) Braunschweig, H.; Claes, C.; Guethlein, F. *J. Organomet. Chem*. **2012**, *706-707*, 144. (c) Braunschweig, H.; Brenner, P.; Dewhurst, R. D.; Guethlein, F.; Jimenez-Halla, J. O. C.; Radacki, K.; Wolf, J.; Zöllner, L. *Chem. Eur. J*. **2012**, *18*, 8605.



Scheme 3. 3. Synthesis of tetraalkoxydiboron compounds

In the development of new tetraalkoxydiboron species, bis(pinacolato)diboron B_2pin_2, bis(neopentylglycolato)diboron B_2neop_2 and bis(hexyleneglycolato)diboron B_2hex_2 have resulted to be powerful tools in borylation reactions. Moreover, non-symmetrical diboron reagents such as BpinBdan (dan = 1,8-diaminonaphtalene)[16], $BpinBMes_2$, BpinBdab (dab = 1,2-diaminobenzene)[17] or PDIPA (pinacolato diisopropanolaminato diboron) are being used as well in recent years (Figure 3.1).

[16] Iwadate, N.; Suginome, M. *J. Am. Chem. Soc*. **2010**, *132*, 2548.
[17] Borner, C.; Keeberg, C. *Eur*. *J. Inorg. Chem*. **2014**, *15*, 2486.

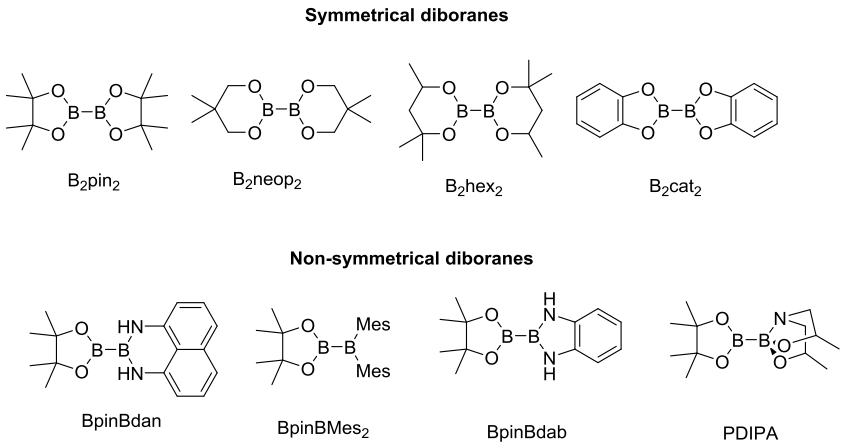


Figure 3. 1. Common di- and tetraalkoxydiboron compounds

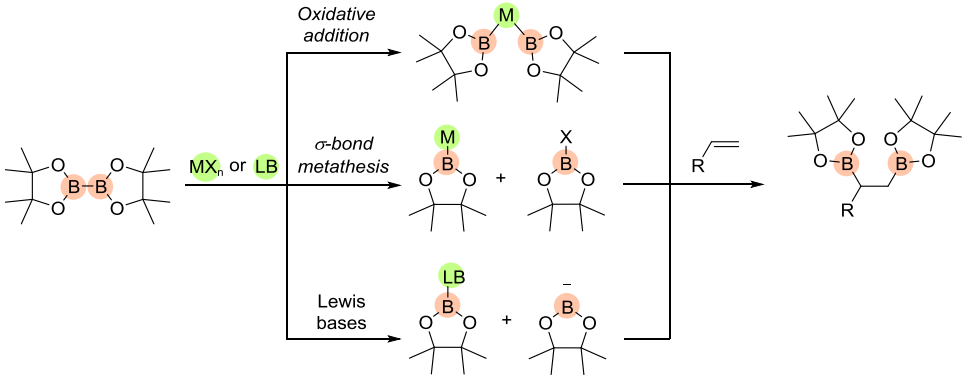
Nonetheless, alkoxydiboron compounds are not able themselves to be added to an unsaturated system needing to be activated by an external catalyst. This could be attributed to the strong and covalent nature of the C-B bond, which will be polarized in the presence of a catalyst inducing its cleavage and the following addition to the unsaturated system.

1.2. Activation of diboron compounds

Alkoxydiboron compounds have been used as useful new reagents for the diborylation of alkenes and alkynes over the years. However, these diboron compounds generally present a high stability due to the π-type overlap with the oxygen atoms which make these compounds specially air and water stable. As consequence of the less acidic B-B system and due to their high B-B bond energy (104 kcal/mol), they show a low reactivity towards the addition to unsaturated systems. Hence, an activation step is required to achieve the addition of tetraalkoxydiboron compounds to double or triple bonds.

The activation of these reagents can be performed in the presence of metals or in a transition metal-free environment. Transition metals can activate organoboranes *via* oxidative addition or *via* transmetallation, while Lewis bases are also suitable to activate

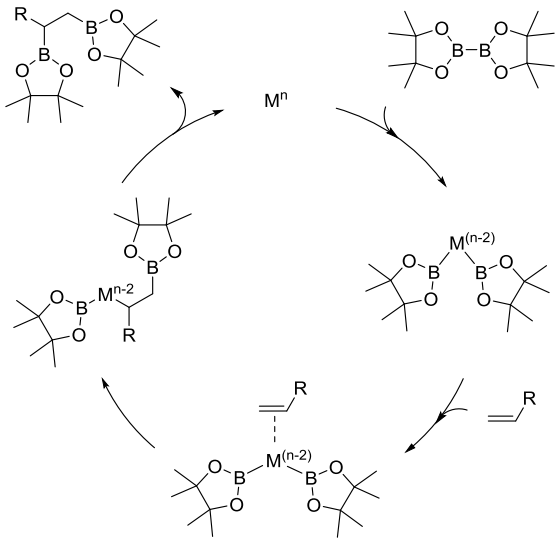
tetraalkoxydiboronates through their addition to the B centre that triggers the formation of a trialkylborate-Lewis base complex with a nucleophilic dialkoxyboron anion (Scheme 3.4).[18]



Scheme 3. 4. Activation modes for B_2pin_2

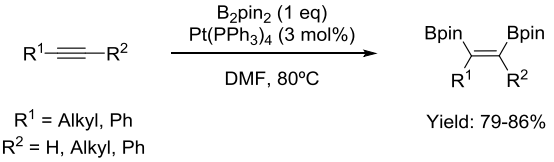
The oxidative addition of diboranes to transition metals such as Pd, Pt or Rh allows the catalytic transfer of organoboranes to unsaturated systems due to the formation of boryl-metal complexes.[19] When this type of transition metal complex, characterized by a low-valent metal, interacts with the tetraalkoxydiboron species, an intramolecular homolytic B-B bond cleavage takes in an oxidative addition process. After the oxidative addition, coordination of the unsaturated substrate with the boryl-metal complex occurs. The dialkoxyboron metal moiety will be *syn* selectively inserted in the unsaturated system which will furnish the diborylated product after a reductive elimination step regenerating the active catalytic species (Scheme 3.5).

[18] (a) Westcott, S. W.; Fernández, E. Singular Metal Activation of Diboron Compounds. *Advances in Organometallic Chemistry*, Elsevier, pp 39-89, 2015. (b) Fernández, E. *An. Quím.* **2017**, *113*, 170.
[19] Ishiyama, T.; Miyaura, N. *J. Organomet. Chem*. **2000**, *611*, 392.



Scheme 3. 5. Activation of B_2pin_2 *via* oxidative addition

The first catalytic diborylation of alkynes was performed by Miyaura and coworkers in 1993.[20] The addition of bis(pinacolato)diboron to terminal and internal alkynes catalyzed by tetrakis(triphenylphosphine)platinum (0) was developed. In fact, the authors were the first ones to propose a mechanism involving oxidative addition of B_2pin_2 to Pt as the initial step, followed by the coordination of the alkyne to the metal complex. Differently substituted *cis*-1,2-bis(boryl)alkenes were obtained in excellent yields and a complete *syn* selectivity during the addition was observed (Scheme 3.6).

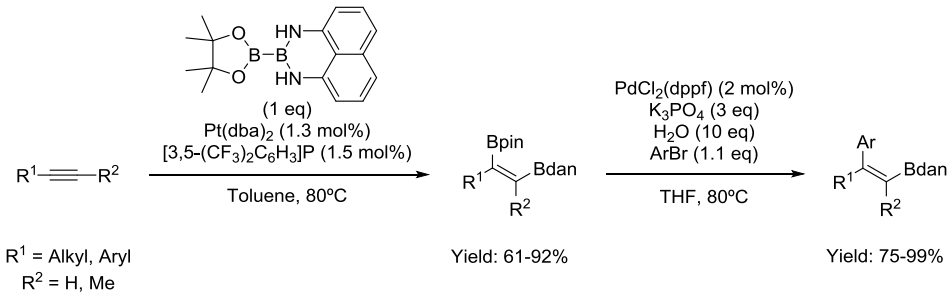


Scheme 3. 6. Platinum-catalyzed diborylation reaction of alkynes employing B_2pin_2

Non-symmetric diboron compounds can also be used to borylate unsaturated systems, allowing to carry out regioselective transformations of the diborylated adducts successfully. Thus, the regioselective diborylation of alkynes with BpinBdan affording 1,2-diborylated

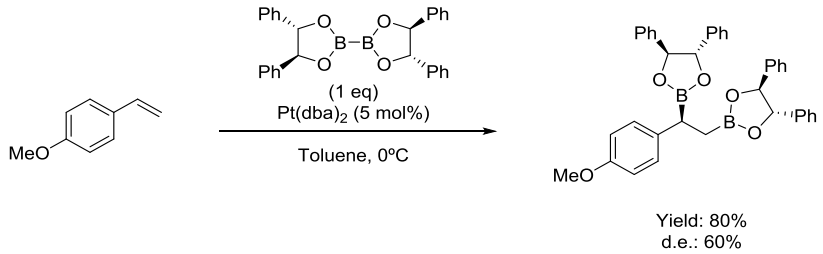
[20] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc*. **1993**, *115*, 11018.

alkenes was reported by Suginome.[16] The reaction proceeded well when a platinum or iridium catalyst was employed, rendering diborylated products with high yields and high regioselectivities. The diborylated products were subjected to different chemoselective transformations involving the more reactive Bpin moiety, such as Suzuki-Miyaura cross-coupling (Scheme 3.7).



Scheme 3. 7. Platinum-catalyzed diborylation reaction of alkynes employing BpinBdan

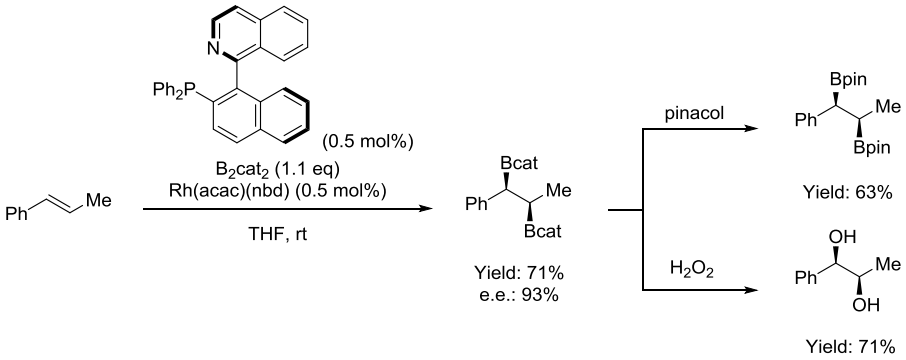
Stereocontrolled borylation of alkenes can also be carried out using chiral ligands at the diboron reagents in order to achieve enantiocontrol. This leads to the formation of enantioenriched organoboranes which can be subsequently employed in further stereospecific transformations for the construction of enantioenriched complex molecules. In this field, Marder and coworkers developed the first platinum-catalyzed diastereoselective diborylation of styrenes by the use of chiral diboron reagents derived from (*S*,*S*)-diphenylethane-1,2-diol.[21] Substituted vinylarenes were synthesized in high yields and moderate diastereoselectivities (Scheme 3.8).



Scheme 3. 8. Platinum-catalyzed diborylation reaction of styrenes employing chiral diboron reagents

[21] Marder, T. B.; Norman, N. C.; Rice, R. *Tetrahedron Lett*. **1998**, *39*, 155.

However, the use of metal complexes with chiral ligands in a catalytic fashion directed to generate enantioenriched organoboranes has been a breakthrough in the chemistry of boron allowing carrying out a wide range of transformations.[22] Morken and coworkers opened a new era in this field by modifying rhodium complexes with (*R*)-QUINAP, describing the first example of a catalytic enantioselective diborylation reaction of alkenes.[23] The methodology was valid for *trans* alkenes observing high enantiocontrol when both alkyl and aryl substituents were placed in the alkene. Furthermore, they were able to transform differently substituted olefins into optically active synthetic building blocks. On the one hand, a transesterification reaction was performed employing pinacol furnishing bis(pinacol)boronates in moderate yield, and on the other hand, enantiopure diols were synthesized by an oxidation step using hydrogen peroxide (Scheme 3.9).



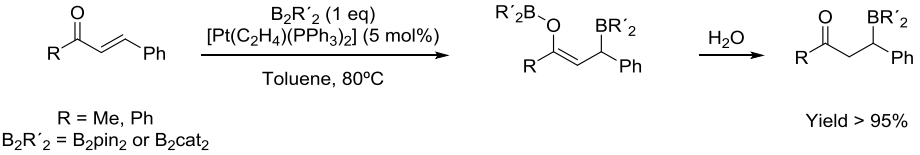
Scheme 3. 9. Rhodium-catalyzed enantioselective diborylation reaction of alkenes employing B_2cat_2

On the other hand, many examples have been described involving the addition of diboron compounds to α,β-unsaturated carbonyl substrates. One example of the conjugate addition of B_2pin_2 to a Michael acceptor was described by Marder and coworkers, in which it was reported for the first time the diborylation reaction of α,β-unsaturated ketones employing platinum

[22] For recent literature in the use of chiral ligands, see: (a) Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. *Beilstein J. Org. Chem*. **2015**, *11*, 2007. (b) Reyes, R. L.; Harada, T.; Taniguchi, T.; Monde, K.; Iwai, T.; Sawamura, M. *Chem. Lett*. **2017**, *46*, 1747. (c) Su, B.; Zhou, T.-G.; Xu, P.-L.; Shi, Z.-J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2017**, *129*, 7311. (d) Miwa, Y.; Kamimura, T.; Satu, K.; Shishido, D.; Yoshido, D.; Yoshida, K. *J. Org. Chem*. **2019**, *84*, 14291. (e) Shen, C.; Zeidan, N.; Wu, Q.; Breuers, C. B. J.; Liu, R.-R.; Jia, Y.-X.; Lautens, M. *Chem. Sci*. **2019**, *10*, 3118. (f) Shi, Y.; Gao, Q.; Xu, S. *J. Am. Chem. Soc*. **2019**, *141*, 10599. (g) Iwamoto, H.; Endo, K.; Ozawa, Y.; Watanabe, Y.; Kubota, K.; Imamoto, T.; Ito, H. *Angew. Chem. Int. Ed*. **2019**, *58*, 11112.

[23] Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc*. **2003**, *125*, 8702.

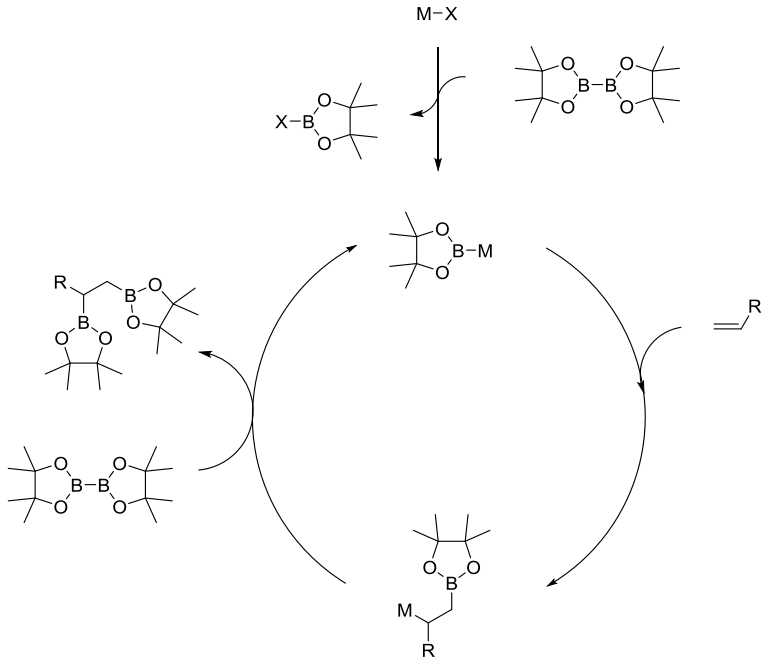
complexes.[24] The catalyzed diborylation reaction was believed to proceed by the oxidative addition of diboron compounds to the metal by a 1,4-addition affording a boron enolate intermediate, which after an aqueous work-up afforded the corresponding β-borylated carbonyl compound (Scheme 3.10).



Scheme 3. 10. Platinum-catalyzed diborylation reaction of α,β-unsaturated ketones employing $B_2R´_2$

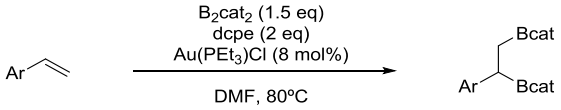
Other metals such as Cu, Ag and Au can be also used to activate diboron reagents. This methodology implies the reaction of these metals with tetraalkoxydiboranes through a σ-bond metathesis between the diboron reagent and the metal complex including a M-X bond (X being OR group, generally), promoting the heterolytic cleavage of the B-B bond with the formation of a M-boryl species and the resulting X-$B(OR)_2$. Next, the metal-boron complex interacts with the olefin promoting the formation of a β-boryl organometallic intermediate that after a second transmetallation step provides the final diborylated product with the regeneration of the active catalytic species (Scheme 3.11).

[24] Lawson, Y. G.; Gerald Lesley, M. J.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun*. **1997**, 2051.



Scheme 3. 11. Activation of B_2pin_2 *via* σ-bond metathesis

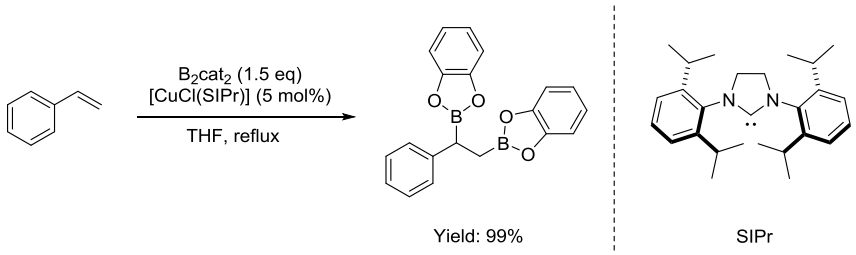
Following the previously explained mechanism, Marder and coworkers were the pioneers in developing catalytic diborylation methods of alkenes with metal complexes based on metals of group 11. They developed a gold-catalyzed diborylation reaction of terminal alkenes using the catalytic system [Au(PEt_3)Cl]/1,2-bis(diciclohexylphosphino)ethane (dcpe) observing the exclusive formation of the 1,2-diborylated product.[25] It should be mentioned that an electron-rich phosphane additive was needed for the reversible B-B bond activation by the monovalent gold center and to start the catalytic cycle (Scheme 3.12).



Scheme 3. 12. Gold-catalyzed diborylation reaction of alkenes employing B_2cat_2

[25] Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1336.

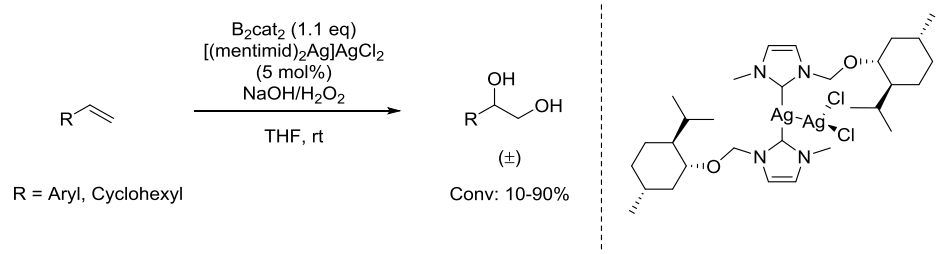
Using a more earth-abundant metal, Fernández and coworkers described the first copper-mediated diborylation reaction of alkynes and alkenes.[26] It should be mentioned that copper resulted to be a cheaper metal in comparison with gold and silver which provided an evident advantage of this methodology compared to others. They demonstrated that a catalytic system formed by a Cu(I) complex modified with *N*-heterocyclic carbenes was able to carry out hydroborylation and diborylation reactions. The reaction between styrene and bis(cathecolato)diboron furnished the corresponding diborylated adduct in excellent yield, being the only limitation the use of other diboranes such as B_2pin_2 which was not tolerated (Scheme 3.13).



Scheme 3. 13. Copper-catalyzed diborylation reaction of alkenes employing B_2cat_2

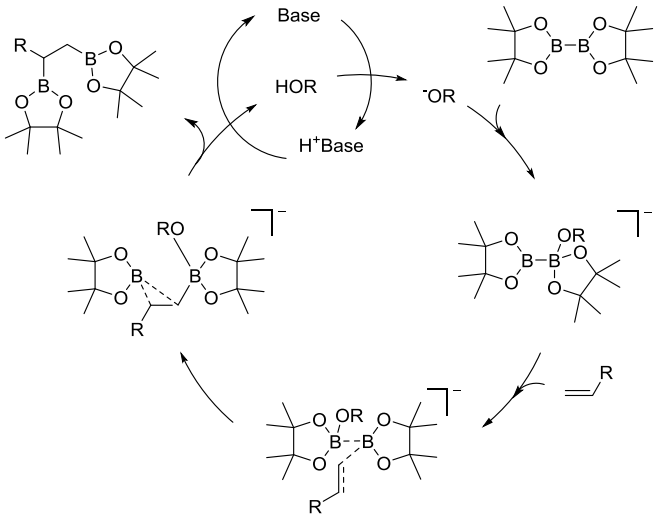
Ag(I) salts have been also employed as catalysts for diborylation of alkenes in a very limited number of examples in the literature.[27] A common aspect of these methodologies is that strong σ-donor ligands such as *N*-heterocyclic carbenes are needed, as it can be seen in the example reported by Fernández and coworkers. This methodology used Ag(I)-NHC complexes for the catalytic diborylation reaction of styrenes proceeding with moderate conversions.[28] Notwithstanding the use of a chiral catalyst, no asymmetric induction was observed in the final diols which were obtained as racemates (Scheme 3.14).

[26] Lillo, V.; Fructos, M. R.; Ramirez, J.; Braga, A. A. C.; Maseras, F.; Diaz-Requejo, M. M.; Perez, P. J.; Fernández, E. *Chem. Eur. J*. **2007**, *13*, 2614.
[27] (a) Corberán, R.; Ramírez, J.; Poyatos, M.; Peris, M.; Fernández, E. *Tetrahedron: Asymmetry* **2006**, *17*, 1759. (b) Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett*. **2014**, *16*, 3512.
[28] Ramirez, J.; Corberán, R.; Sanaú, M.; Peris, E.; Fernández, E. *Chem. Commun*. **2005**, 3056.



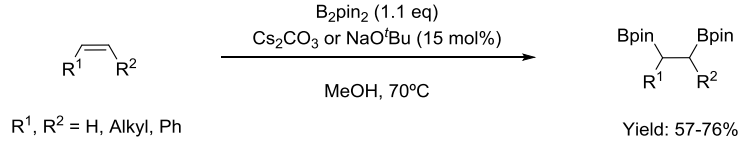
Scheme 3. 14. Silver-catalyzed enantioselective diborylation reaction of alkenes employing B_2cat_2

The concept behind the nucleophilic diborylation of non-activated alkenes in a metal-free environment consists on a combination of a base and an alcohol. It provides an alkoxide anion which is generated *in situ* from an alcohol (generally, methanol) and a catalytic amount of base, being the responsible of activating the diboron reagent. A Lewis acid-base adduct is formed (MeO^-→Bpin-Bpin) where the initially acidic sp^2 boron is now quaternized, becoming a σ-nucleophile that reacts with an olefin acting as an electrophile. While the sp^3 boron atom loses negative charge density after interacting with the Lewis base, the sp^2 boron atom gains electron density. These structural changes polarize the B-B bond, weakening it and making the sp^2 boron become nucleophile. The boron atom of the activated diboron reagent interacts with the double bond of the unsaturated system. After the nucleophilic attack, there will be an interaction between the strongly polarized B-B σ bond (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the alkene (Scheme 3.15).



Scheme 3. 15. Activation of B_2pin_2 by Lewis bases

The first diborylation reaction in the absence of transition metal complexes was again reported by Fernández and coworkers in 2011.[29] The addition of B_2pin_2 over a wide range of differently substituted olefins, such as terminal cyclic and acyclic alkenes, *cis* and *trans* internal alkenes and vinylarenes, was performed (Scheme 3.16).

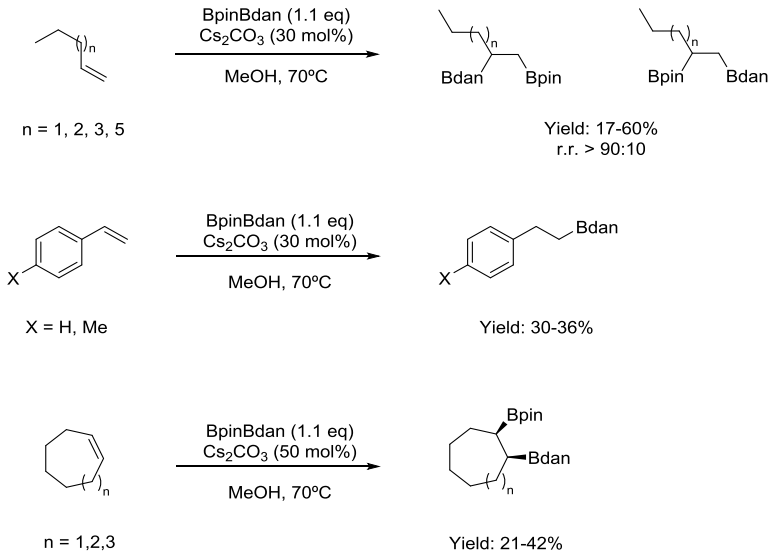


Scheme 3. 16. Lewis base-catalyzed diborylation reaction of alkenes employing B_2pin_2

Metal-free diborylation reaction can be also carried out employing non-symmetrical organoborane compounds, being important the control of the regioselectivity of the process. This is what happened in the example published by Fernández and coworkers in 2015 where the diborylation reaction of alkenes in a metal-free context was performed using Bpin-Bdan as borylating agent.[30] In this case, the methoxide anion interacts selectively with the Bpin moiety due to its more Lewis acidic character (the π-donation from the lone pair of nitrogen to the

[29] Bonet, A.; Pubill-Ulldemolins, C; Bo, C.; Gulyás, G.; Fernández, E. *Angew. Chem. Int. Ed*. **2011**, *50*, 7158.
[30] Miralles, N.; Cid, J.; Cuenca, A. B.; Carbó, J. J.; Fernández, E. *Chem. Commun*. **2015**, *51*, 1693.

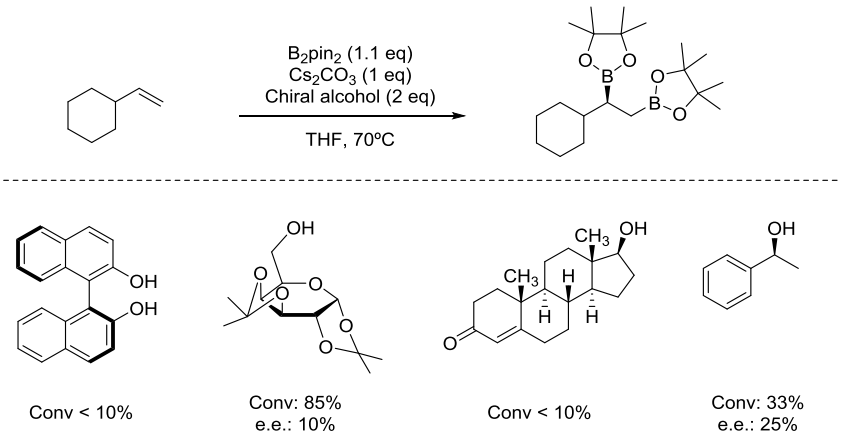
empty orbital of boron made the Bdan moiety not susceptible to alkoxide attack). The reaction was fully regioselective, observing the addition of the activated Bpin moiety to the less hindered carbon of the olefin. On the other hand, when vinylarenes were employed only the hydroborylated product with Bdan moiety in the terminal position was observed. Cyclic olefins were also tested observing the *syn* addition of BpinBdan to cyclic systems (Scheme 3.17).



Scheme 3. 17. Base-catalyzed diborylation reaction of alkenes employing BpinBdan

An important breakthrough in metal-free activation of diboron compounds was the possibility of synthesizing enantiomerically pure products. Fernández and coworkers developed in 2012 an organocatalytic asymmetric diborylation reaction of alkenes by the use of chiral alcohols as reaction promoters.[31] Despite the wide range of tested chiral alcohols such as BINOL, pyranose and furanose derivatives, very low enantioselectivities were achieved in all cases (Scheme 3.18).

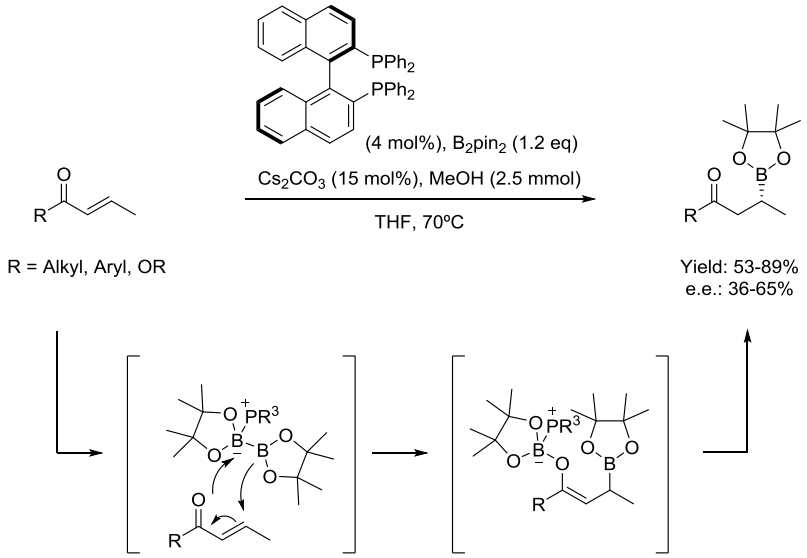
[31] Bonet, A.; Sole, C.; Gulyás, H.; Fernández, E. *Org. Biomol. Chem*. **2012**, *10*, 6621.



Scheme 3. 18. Base-promoted diborylation reaction of alkenes employing B_2pin_2 and chiral alcohols

An alternative for overcoming this poor enantioselectivity and in order to obtain enantioenriched organoboranes, the same group designed the conjugate addition to α,β-unsaturated esters and ketones.[32] By the use of chiral phosphanes the synthesis of enantiopure β-borylated carbonyl compounds was achieved in moderate yields and enantioselectivities. They proposed that the heterolytic cleavage of the B-B bond took place due to the interaction of the phosphane with the empty orbital of one of the boron atoms, converting, as presented before, the boron moiety in a nucleophile. The observed asymmetric induction could be explained in terms of the proximity of the formed chiral phosphane-boryl intermediate to the carbonyl compound in the 1,4-addition reaction (Scheme 3.19).

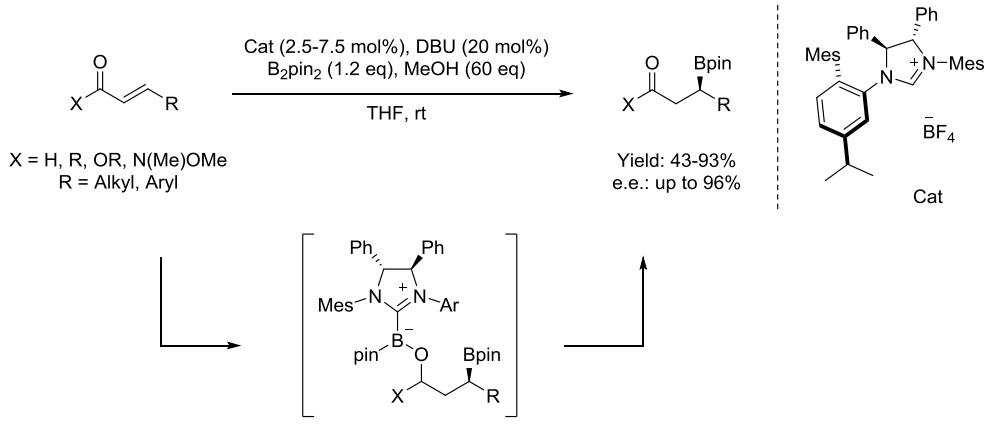
[32] Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed*. **2010**, *49*, 5130.



Scheme 3. 19. BINAP-catalyzed asymmetric borylation reaction of α,β-unsaturated substrates employing B_2pin_2

A closely related methodology to obtain enantioenriched organoboranes was reported by the group of Hoveyda and consisted on the use of enantiomerically pure *N*-heterocyclic carbenes as Lewis base catalysts for performing the conjugate borylation reaction of α,β-unsaturated carbonyls.[33] This methodology accepted a broad scope regarding the substrate and allowed carrying out the reaction with acyclic and cyclic ketones, acyclic esters, aldehydes and Weinreb amides. β-boryl carbonyl compounds were isolated in high yields and enantioselectivities (Scheme 3.20).

[33] Wu, H.; Radomkit, S.; O´Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2012**, *134*, 8277.

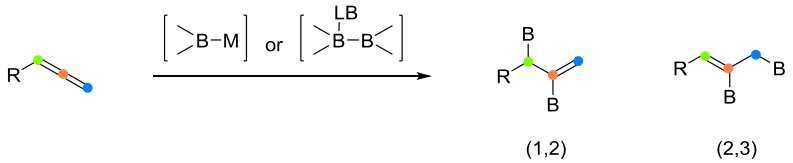


Scheme 3. 20. NHC-catalyzed asymmetric borylation reaction of α,β-unsaturated compounds employing B_2pin_2

Thus, it can be concluded that diboron compounds play nowadays an important role in organic chemistry towards the synthesis of complex molecules. However, they generally take part in reactions involving simple unsaturated systems such as not functionalized olefins or simple alkynes. Their participation in more complex systems has been less studied and few examples have been hitherto reported. As an example of more complex systems, there are allenes, whose role in borylation reactions will be reported in the following section.

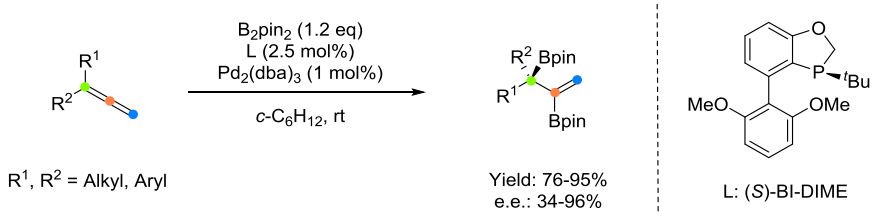
1.3. Borylation of allenes

With regard to the borylation of allenes, a variety of examples have been reported in the last decades, involving these methodologies the use of a metal catalyst as reaction promoter. Allenes present different reactive points towards the activated boryl reagent, since one of the boron atoms can be added to the proximal, central or distal positions, being the other function attached to another position (Scheme 3.21). The regioselectivity of the reaction could be determined by steric effects of both the substituents on the allene and the ligands employed during the reaction.



Scheme 3. 21. Regioselection in the diborylation reactions of allenes

With regard to diborylation reactions of allenes, examples involving different regioselectivities have been described.[34] A representative example of a diborylation reaction of allenes at the proximal and central positions reported by Ding and coworkers is shown in Scheme 3.22.[35] Products containing a chiral tertiary boronic ester were synthesized in excellent yields and high enantioselectivities by the use of phosphorous chiral ligands. DFT studies proposed a concerted mechanism for the oxidative addition of B_2pin_2 and allene insertion which would explain the observed regioselectivity.



Scheme 3. 22. Palladium-catalyzed proximal and central diborylation reaction of allenes employing B_2pin_2

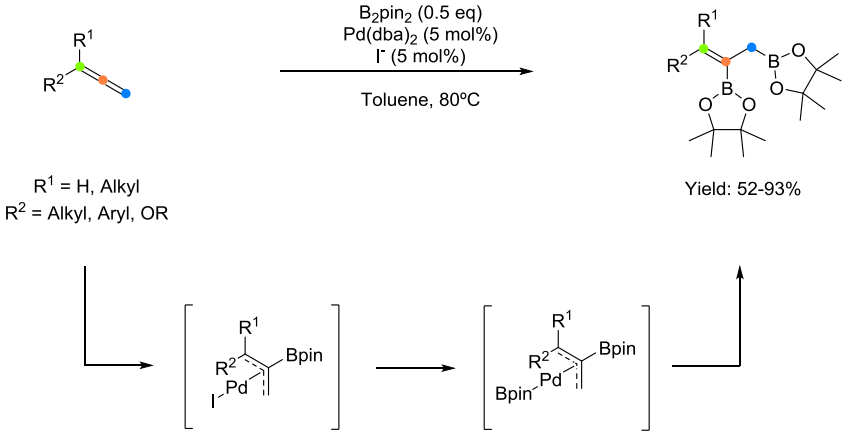
There can be also found examples of diborylation reactions involving the central and distal positions of allenes. For example, in 2001 the palladium-catalyzed diborylation reaction of allenes employing organic iodides such 3-iodo-2-methylcyclohex-2-en-1-one as cocatalyst was published by the group of Cheng.[36] (2,3)-Diborylated *Z* olefins were obtained in a regioselective and high stereoselective manner. The key of this transformation was the oxidative addition of the I-B bond to the Pd center being a palladium iodide the catalytic active species, in contrast

[34] Some examples of diborylation reactions involving central and distal positions: (a) Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L. *ACS Catal*. **2015**, *5*, 2172. (b) Zhao, W.; Montgomery, J. *J. Am. Chem. Soc.* **2016**, *138*, 9763. (c) Kidonakis, M.; Stratakis, M. *ACS Catal.* **2018**, *8*, 1227. (d) Chen, J.; Gao, S.; Gorden, J. D.; Chen, M. *Org. Lett*. **2019**, *21*, 4638. Some examples of diborylation reactions involving proximal and central positions: (a) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett*. **2005**, *7*, 5505. (b) Liu, J.; Nie, M.; Zhou, Q.; Gao, S.; Jiang, W.; Chung, L. W.; Tang, W.; Ding, K. *Chem. Sci*. **2017**, *8*, 5161.

[35] Liu, J.; Nie, M.; Zhou, Q.; Gao, S.; Jiang, W.; Chung, L. W.; Tang, W.; Ding, K. *Chem. Sci*. **2017**, *8*, 5161.

[36] Yang, F.; Cheng, C. *J. Am. Chem. Soc*. **2001**, *123*, 761.

with other methodologies which implies the oxidative addition of a B-B bond to the metal (Scheme 3.23).

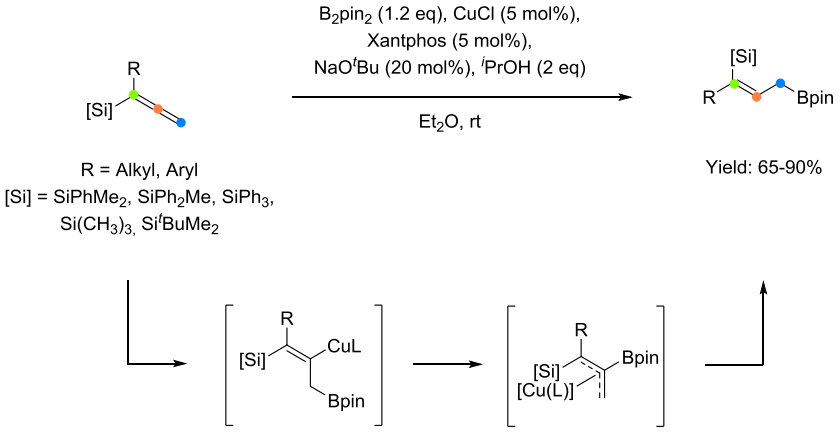


Scheme 3. 23. Palladium-catalyzed central and distal diborylation reaction of allenes employing B_2pin_2

Hydroborylation reactions can be also performed locating the boryl moiety in the central or distal position of the allene, but no examples involving proximal position have been reported.[37] Ma and coworkers published in 2016 an example of a copper-catalyzed hydroborylation reaction of 1,2-allenylsilanes.[38] The boronate scaffold ended up in the distal position with complete regioselectivity, furnishing 3-sillylallyl boronates in high yields. The reaction proceeded through a vinylcopper intermediate which showed a *trans* orientation of the C-CuL bond and C-Si bond due to steric effects (Scheme 3.24).

[37] An example of hydroborylation reaction involving distal position: (a) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125. Some examples of hydroborylation reaction involving central position: (a) Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett*. **2014**, *16*, 4658. (b) Fujihara, T.; Tsuji, Y. *Synthesis* **2018**, *50*, 1737.

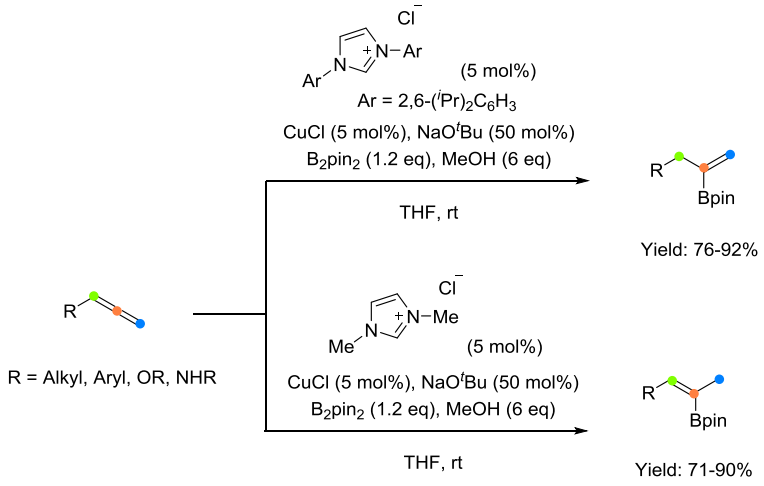
[38] Yuan, W.; Song, L.; Ma, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 3140.



Scheme 3. 24. Copper-catalyzed distal borylcupration reaction of allenylsilanes employing B_2pin_2

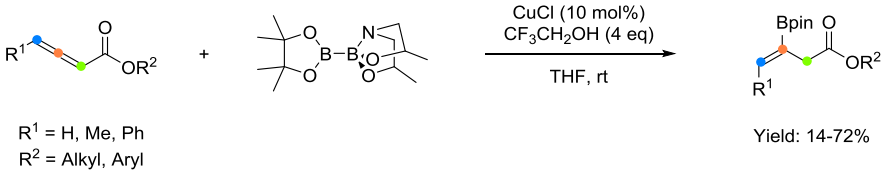
In a similar context, Hoveyda and coworkers reported in 2013 a ligand-controlled regioselective hydroborylation of allenes catalyzed by a Cu-NHC complex providing selectively 1,2 or 2,3-addition during the borylcuprate addition.[39] In all cases, the boryl unit was added to the central carbon of the allene, and the hydrogen atom was placed in the proximal or distal position depending on the bulkiness of the employed *N*-heterocyclic carbene, leading to disubstituted or trisubstituted alkenylboronates (Scheme 3.25). Smaller catalysts led to an easier protonation of the proximal position, while bulkier catalysts generated little 1,3-diaxial repulsion between the allene substituent and the Bpin and NHC-Cu unit, favoring the protonation of the distal position.

[39] Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett*. **2013**, *15*, 1414. Asymmetric example: Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett*. **2014**, *16*, 4658.



Scheme 3. 25. Ligand-controlled regioselective hydroborylation reaction of allenes employing B_2pin_2

Electrophilic allenes such as allenoates are also suitable reagents for hydroborylation reactions being able to change the regioselectivity of the transformation in comparison to simple allenes. Santos and coworkers described the addition of pinacolato diisopropanolaminato diboron (PDIPA) to these substrates which were converted into (*Z*)-vinylboronates in a regioselective and diastereoselective fashion.[40] The boryl moiety was located on the central position of the allene in all cases, being *Z* isomer favored due to the presence of unstabilizing 1,3-allylic strain in the *E* isomer (Scheme 3.26).



Scheme 3. 26. Copper-catalyzed central hydroborylation reaction of allenoates employing PDIPA

[40] Thorpe, S.; Guo, X.; Santos, L. W. *Chem. Commun.* **2011**, *47*, 424.

In summary, it can be concluded that allenes are considered excellent substrates to take part in borylation reactions affording important building blocks in synthetic chemistry. However, this chemistry is poorly explored with respect to the possibility of using allene scaffolds with different functionalities. In particular, other systems like allenylamides, which should be regarded as electron-rich allenes, have not been explored in borylation reactions. Research in this chapter will be focused in these unexplored systems and their reactivity towards diboron reagents.

2. SPECIFIC OBJECTIVES AND WORK PLAN

As it has been outlined in previous section, organoborane compounds constitute important synthetic intermediates in organic chemistry due to their possibility of constructing complex molecules. Regarding the borylation reaction of allenes, few examples can be found in the literature and none involved metal-free conditions. The π-donating ability of the nitrogen atom in allenylamines makes them more electron-rich compared with simple allenes, and hence they are more prone to electrophilic activation. As mentioned, allenylamides have not been explored as substrates in borylation reactions (Figure 3.2).

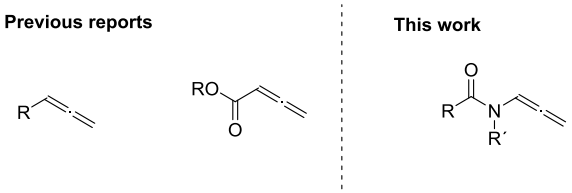
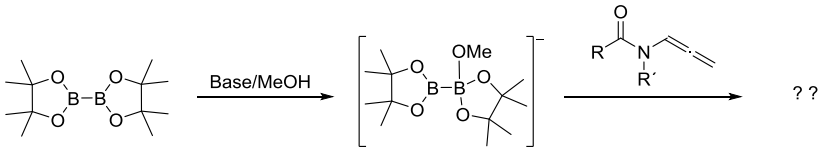


Figure 3. 2. Allene *vs* allenoate *vs* allenylamide

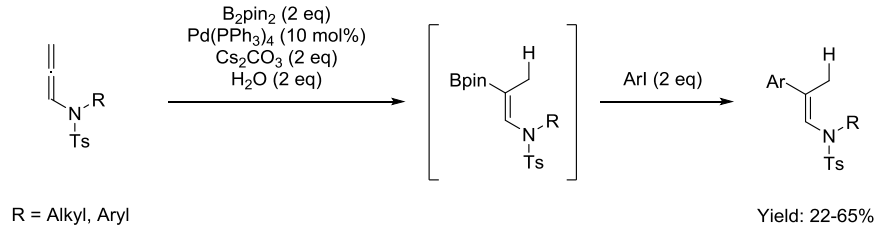
With these precedents in mind, we turned our attention to the construction of polisubstituted olefins by the borylation of these substrates. Taking advantage that the metal-free activation of diboron compounds is emerging in the last years, in this work we planned to **conduct the borylation of allenylamides in absence of transition metal complexes as catalyst**. This is conceptually based on the B-B bond activation by alkoxides and the subsequent nucleophilic boryl attack to the allene, as reported by the group of Fernández.[29] Our goal was to study the behavior of allenylamides towards the nucleophilic boron intermediate and to study the regio- and diastereoselectivity of the process (Scheme 3.27).



Scheme 3. 27. Study of the nucleophilic boron addition to allenylamides

It should be mentioned that after the publication of our work in 2018, which will be summarized in this chapter, a palladium-catalyzed regiocontrolled hydroarylation of

allenylamides was reported by Liu and coworkers which constituted an excellent methodology for the synthesis of polisubstituted alkenes.[41] They employed the system H_2O/B_2pin_2, being water an ideal hydrogen source which was activated by bis(pinacolato)diboron for its addition to the unsaturated system. A *one-pot* sequence was performed involving the borylation and a cross-coupling reaction, which furnished allylamines and enamines in moderate to good yields (Scheme 3.28).

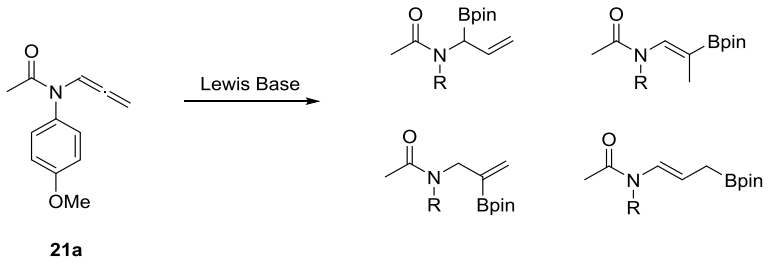


Scheme 3. 28. Pd-catalyzed regiocontrollable hydroarylation reaction

This research represented an straightforward method for the central borylation reaction using metal activation. Our objective was, however, the use of metal-free activation for performing borylation reactions. In order to accomplish our objective, the subsequent work plan was outlined:

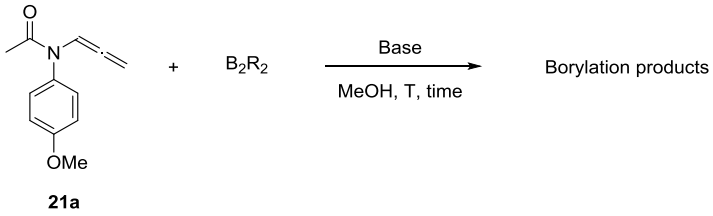
- *Reactivity studies:* we will survey the reaction of allenylamide **21a** as model substrate in the presence of B_2pin_2, a base and MeOH, as standard reaction conditions, and will observe the possible addition products that can be formed. The nucleophilic boryl moiety can be added to the proximal, central and distal positions of allenylamide furnishing 1,2 and/or 2,3 addition products (Scheme 3.29).

[41] Cui, J.; Meng, L.; Chi, X.; Liu, Q; Zhao, P.; Zhang, D.; Chen, L.; Li, X.; Dong, Y.; Liu, H. *Chem. Commun*. **2019**, *55*, 4355.



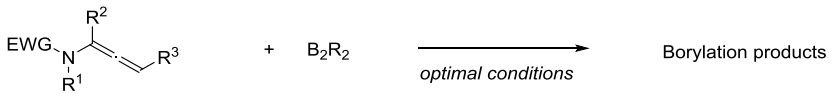
Scheme 3. 29. Envisioned model reaction

- *Optimization of the reaction conditions:* once the viability of the reaction has been demonstrated a variety of organoborane compounds (B_2R_2), bases and temperatures will be evaluated with the same model substrate **21a** using methanol as the most appropriate solvent, in order to obtain the desired product in high yield, regio- and diastereoselectivity (Scheme 3.30).



Scheme 3. 30. Studied borylation reaction

- *Scope of the reaction:* the scope and limitations of the developed method will be studied through the evaluation of structurally different substrates. First of all, *N*-aryl-*N*-allenylacetamides (EWG = Ac) will be studied with both EWG and EDG in the other position (R^1) of the nitrogen atom. Later on, substrates containing other electron withdrawing groups (EWG) will be evaluated under the optimized reaction conditions. Finally, differently substituted allenylamides (R^2, $R^3 \neq H$) will be also tested (Scheme 3.31).



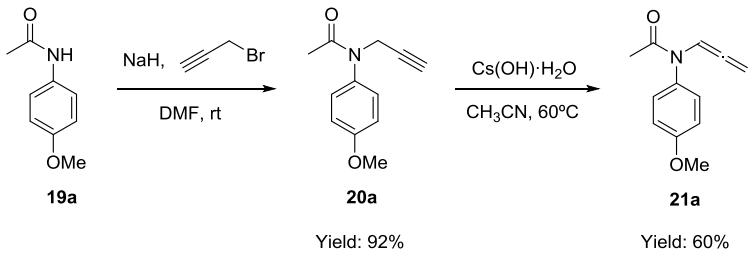
Scheme 3. 31. Scope of the reaction

3. RESULTS AND DISCUSSION

Once the objectives of the project have been determined and the work plan has been well defined, the most significant results during the development of this research will be presented in the following pages.

3.1. Proof of concept

We started our work with the synthesis of the model allenylacetamide **21a**. This was carried out in a two-step sequence, starting with the incorporation of the propargylic chain to 4-methoxyacetanilide **19a** which was carried out in 92% yield. Then, a base-mediated isomerization of **20a** was performed, rendering **21a** in 60% yield (Scheme 3.32).[42]

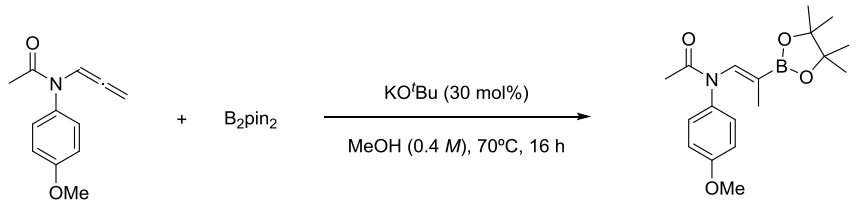


Scheme 3. 32. Synthesis of allenylacetamide **21a**

With this substrate in hand, we tested the borylation reaction with B_2pin_2, and MeOH/ KO^tBu running the reaction for 16 hours, which constitute standard reaction conditions used in the Lewis base activation of B_2pin_2 as developed in the group of Prof. Fernández.[43] The reaction was carried out employing 1.2 eq of bis(pinacolato)diboron, 30 mol% of KO^tBu and methanol as solvent at 70°C. After that time, the reaction crude was analyzed by ^{1}H-NMR employing naphthalene as internal standard. It was possible to observe the complete disappearance of the starting material and the appearance of signals corresponding to a single product. After purification by flash column chromatography we could isolate **22a** as an only product in 71% yield through a complete regioselective process (Scheme 3.33). It should be mentioned that although a complete transformation of the starting material to the product could be observed in the ^{1}H-NMR spectra, the yield decreased during the purification step due to organoboronates are strongly retained in silica. Product **22a** showed the boryl moiety located

[42] Li, Y.; Chen, J.; Qiu, R.; Wang, X.; Long, J.; Zhu, L.; Au, C.; Xu, X. *Tetrahedron Lett*. **2015**, *56*, 5504.
[43] Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415.

at the central carbon of allenylamide (^{11}B-NMR = 31.8 ppm) after a hydroborylation process along the terminal double bond. A *trans*-arrangement between the amide and the boryl moiety along the trisubstituted alkene was also observed.



21a **22a**

Conv: 98%
Yield: 71%

Scheme 3. 33. Preliminary study of the reaction[44]

Next, we verified whether the substrate **21a** needed 16 hours to be completely converted in the borylated product **22a**. Thus, the reaction mixture was analyzed by ^{1}H-NMR at different times, evaluating the disappearance of starting material **21a** and the formation of the reaction product **22a**. As it could be observed, the reaction needed more than two hours to start. It was not until five hours that formation of the adduct **22a** started to be observed, although the conversion was very low. After eight hours of reaction, the conversion still remained low, concluding that sixteen hours were strictly necessary to observe a complete conversion of the starting material **21a** into the borylated adduct **22a**.

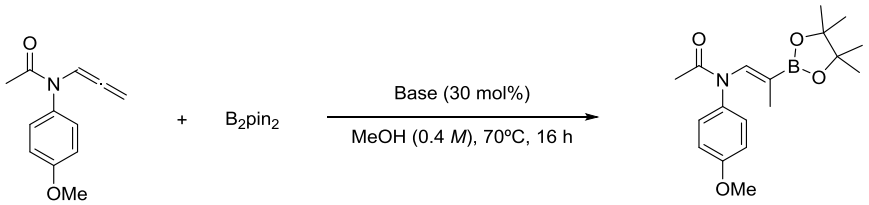
3.2. Optimization of the reaction conditions

Considering previous results as evidence of the feasibility of the reaction, next efforts were directed to the evaluation of the best conditions to carry out the borylation reaction. In this sense, we first proceeded to test different bases to analyze whether the yield of the reaction

[44] Reactions were carried out at 0.2 mmol scale of **21a**, using 30 mol% of KO^{t}Bu and 1.2 eq of B_2pin_2 in 0.5 mL of solvent. Conversions measured by ^{1}H-NMR in crude reaction mixtures using naphthalene as internal standard based on the consumption of substrate **21a**. Isolated yield of pure material after flash column chromatography purification.

could be improved (Table 3.2). As potassium *tert*-butoxide resulted to be a convenient base to carry out the reaction (Table 3.2, entry 1), we decided to evaluate the effect of sodium *tert*-butoxide. When the sodium base was employed, the conversion of the reaction was lower and there was unreacted starting material left (Table 3.2, entry 2). On the other hand, cesium carbonate was also tested but it did not turn to be a good base for the reaction and a moderate conversion was observed after 16 hours (Table 3.2, entry 3). Thus, potassium *tert*-butoxide still remained as the best base to further optimization.

Table 3. 2. Evaluation of different bases



21a **22a**

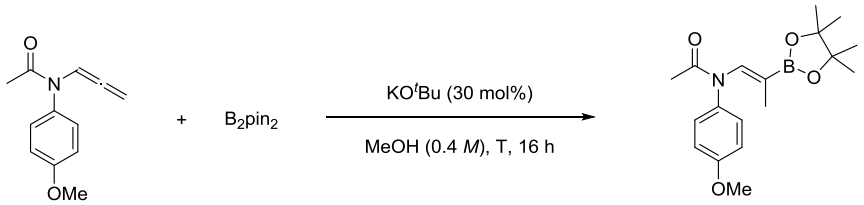
Entry[a]	Base	Conv (%)[b]	Yield 22a (%)[c]
1	KO^{t}Bu	98	71
2	NaO^{t}Bu	60	n.d.[d]
3	Cs_2CO_3	46	n.d.[d]

[a]Reactions were carried out at 0.2 mmol scale of **21a**, using 30 mol% of base and 1.2 eq of B_2pin_2 in 0.5 mL of solvent. [b]Conversions measured by ^{1}H-NMR in crude reaction mixtures using naphthalene as internal standard based on the consumption of substrate **21a**. [c]Isolated yield of pure material after flash column chromatography purification. [d]n.d.: Not determined

At this point, we also evaluated the effect of the temperature in the reaction. When the reaction was performed at room temperature, the starting material was recovered, observing only traces of the borylated product **22a** (Table 3.3, entry 1). At higher temperatures, both at 70°C and 100°C the same results were observed both with respect to conversion and isolated yield (Table 3.3, entries 2-3), being a temperature of 70°C selected for further screening. At this point, we also evaluated the effect of the addition of one equivalent of a polar aprotic cosolvent as THF. This combination of solvents has demonstrated good performance in several previous borylation reactions.[29] However, in our case, performing the reaction in MeOH and one equivalent of THF did not improve the reaction performance observing the

monodiborylated product **22a** in a slightly lower 55% yield (Table 3.3, entry 4). Thus, we selected 70ºC and MeOH as solvent as the optimal conditions for further screening.

Table 3. 3. Evaluation of different temperatures



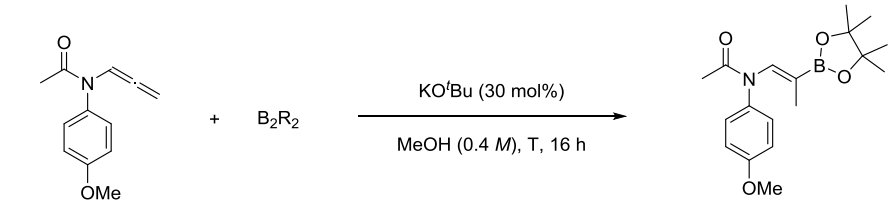
21a **22a**

Entry[a]	T (°C)	Conv (%)[b]	Yield 22a (%)[c]
1	25	10	n.d.[e]
2	70	98	71
3	100	99	70
4[d]	70	62	55

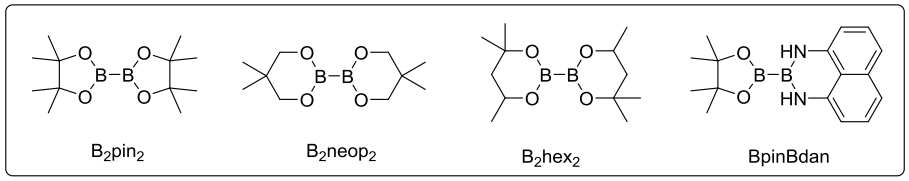
[a]Reactions were carried out at 0.2 mmol scale of **21a**, using 30 mol% of KO^{t}Bu and 1.2 eq of B_2pin_2 in 0.5 mL of solvent. [b]Conversions measured by ^{1}H-NMR in crude reaction mixtures using naphthalene as internal standard based on the consumption of substrate **21a**. [c]Isolated yield of pure material after flash column chromatography purification. [d]1 eq of THF was employed. [e]n.d.: Not determined.

Finally, we proceeded to survey different commercially available diboron reagents with the hitherto optimized conditions (Table 3.4). It was observed that the bulkier the diboron reagent was, the lower the yield of the adduct **22a** was obtained, being bis(pinacolato)diboron B_2pin_2 the one which gave the best results (Table 3.4, entry 1). In contrast, bis(neopentylglycolato)diboron B_2neop_2, considered more efficient and reactive than its analogues, provided a moderate yield of the borylated product **22a**, although the conversion of the reaction was high (Table 3.4, entry 2). When bis(hexyleneglycolato)diboron B_2hex_2 was employed, traces of the product were observed (Table 3.4, entry 3). Finally, non-symmetrical diboron reagent BpinBdan (dan = 1,8-diaminonaphtalene) was also tested but it failed to provide any borylation product even at higher temperatures (Table 3.4, entries 4-5).

Table 3. 4. Survey of different diboron reagents



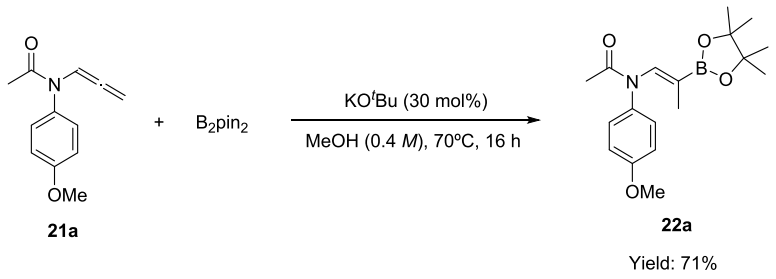
21a **22a**



Entry[a]	B_2R_2	T (°C)	Conv (%)[b]	Yield 22a (%)[c]
1	B_2pin_2	70	99	71
2	B_2neop_2	70	80	35
3	B_2hex_2	70	10	n.d.[e]
4	BpinBdan	70	n.r.[d]	n.d.[e]
5	BpinBdan	110	90	<5

[a]Reactions were carried out at 0.2 mmol scale of **21a**, using 30 mol% of KO^{t}Bu and 1.2 eq of B_2R_2 in 0.5 mL of solvent. [b]Conversions measured by ^{1}H-NMR in crude reaction mixtures using naphthalene as internal standard based on the consumption of substrate **21a**. [c]Isolated yield of pure material after flash column chromatography purification. [d]No reaction [e]Not determined

Once the most important parameters had been evaluated, it was concluded that the optimal conditions for carrying out the borylation reaction implied the use of bis(pinacolato)diboron as diboron reagent, 30 mol% of potassium *tert*-butoxide as base in MeOH (0.4 *M*) at 70°C, running the reaction for 16 hours (Scheme 3.34).



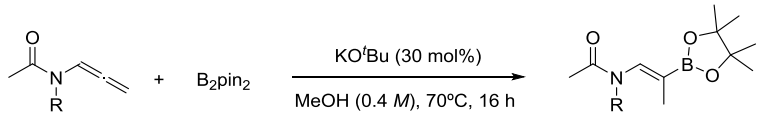
Scheme 3. 34. Optimal reaction conditions for the borylation reaction of *N*-allenylacetamide **21a**

3.3. Scope of the reaction

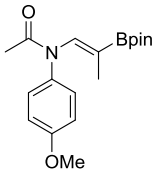
Once the optimal experimental procedure for the transition metal-free stereoselective borylation reaction of allenylamides had been established, we proceeded to extend the methodology to other structurally different allenylamides.

First of all, we carried out the borylation reaction of a series of *N*-allenyl-*N*-arylacetamides under optimal conditions (70ºC, 16 h) (Table 3.5). We changed the electron properties of the *para*-substituents of the aryl group in the allenylamide substrates and tested both electron-withdrawing and electron-donating substituents. It was observed that electron-donating *para*-substituents led to quantitative conversions with complete stereoselectivity towards the formation of the *Z*-isomer. Both products **22a** and **22b** were obtained in a 71% and 78% yield, respectively. When a *para*-methyl group, which presents less donating ability, was incorporated in the aromatic ring, the yield of the reaction remained high (Table 3.5, product **22c**). Instead, when the aromatic ring presented no substitution, product **22d** was only detected in a moderate 52% NMR yield, and it was isolated with a low 24% yield. Finally, an electron-withdrawing group in *para*-position made the allenylamide less reactive towards the nucleophilic boron, observing its formation with a low 25% NMR yield and isolating it as traces (Table 3.5, product **22e**).

Table 3. 5. Scope of the reaction using *N*-allenyl-*N*-arylacetamides.[a]

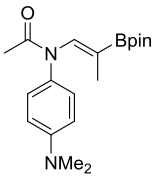


21a-e **22a-e**



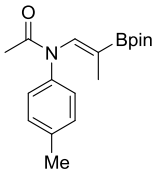
22a

NMR Yield: 98%
Isolated Yield: 71%



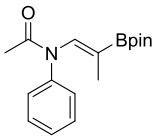
22b

NMR Yield: 99%
Isolated Yield: 78%



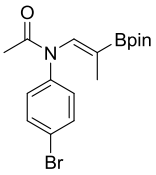
22c

NMR Yield: 96%
Isolated Yield: 62%



22d

NMR Yield: 52%
Isolated Yield: 24%



22e

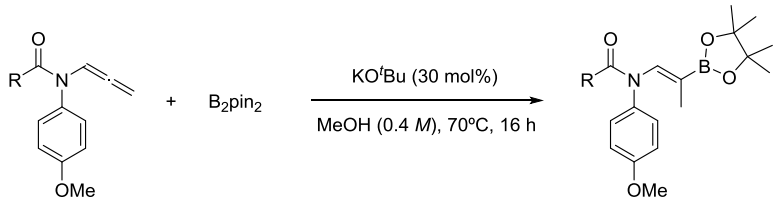
NMR Yield: 25%
Isolated Yield: <5%

[a]Reactions were carried out at 0.2 mmol scale of substrates **21a-e**, using 30 mol% of KO^{t}Bu, 1.2 eq of B_2pin_2 in 0.5 mL of MeOH at 70ºC in 16 h. NMR Yields calculated from ^{1}H-NMR spectra with naphthalene as internal standard. Isolated yield of pure material after flash column chromatography purification.

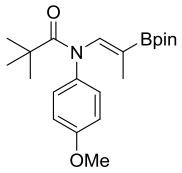
The reaction also tolerated the incorporation of other acyl substituents. Maintaining *para*-methoxyphenyl group as substituent in the nitrogen atom, we studied the influence of other alkanoyl and aryloyl groups (Table 3.6). Replacement of the acetyl group by a pivaloyl group did not influence the reaction outcome, and the product **22f** was obtained in quantitative NMR yield and 65% isolated yield as a single *Z*-isomer from **21f** (Table 3.6). Next, we proceeded with the evaluation of benzoyl derived allenylamides incorporating both electron-donating and electron-withdrawing substituents in *para* position of the benzoyl substituent. Electron-

donating groups favored the borylation reaction, as it could be observed in the case of *para*-methylbenzoyl substituted allenylamide **21g** which rendered **22g** in a 74% yield. The results were similar with benzoyl substituted allenylamide **21h**, which rendered **22h** in 72% yield. In both cases the NMR yields were almost quantitative. On the other hand, electron-withdrawing substituents made allenylamides unreactive towards the nucleophilic boron moiety isolating only traces of **22i**, in the case of *para*-bromobenzoyl substituted allenylamide **21i**. Finally, we incorporated a heterocycle containing chain in the acetyl substituent of the allenylamide, which turned not to be a suitable substrate for the borylation reaction due to the low conversion observed in **22j**.

Table 3. 6. Scope of the reaction using *N*-allenyl-*N*-(*para*-methoxyphenyl)amides.[a]

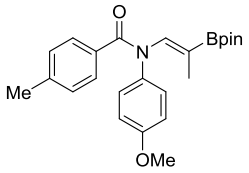


21f-j **22f-j**



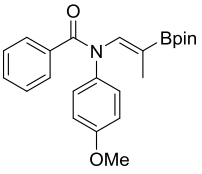
22f

NMR Yield: 94%
Isolated Yield: 65%



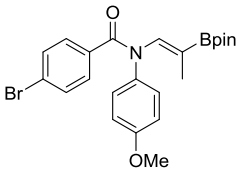
22g

NMR Yield: 99%
Isolated Yield: 74%



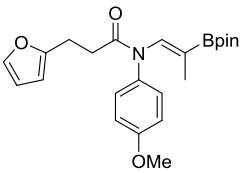
22h

NMR Yield: 90%
Isolated Yield: 72%



22i

NMR Yield: 16%
Isolated Yield: <5%

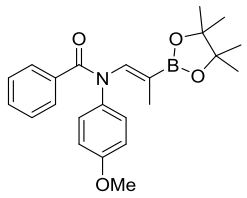


22j

NMR Yield: n.d.
Isolated Yield: 20%

[a] Reactions were carried out at 0.2 mmol scale of substrates **21f-j**, using 30 mol% of KO^{t}Bu, 1.2 eq of B_2pin_2 in 0.5 mL of MeOH at 70ºC in 16 h. NMR Yields calculated from ^{1}H-NMR spectra with naphthalene as internal standard. Isolated yield of pure material after flash column chromatography purification. n.d.: not determined

At this point, the exclusive formation of **22h** in the case of allenylamide **21h** gave us the opportunity of performing its fully characterization by means of single-crystal X-ray diffraction. Figure 3.3 shows the *E*-stereoselectivity observed for the amide and boryl moieties along the trisubstituted alkene.



22h

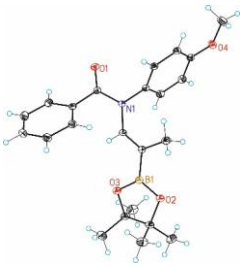
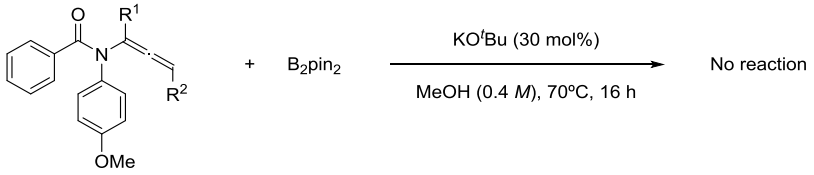


Figure 3. 3. X-Ray structure of **22h**

The reaction showed a limitation for the α- and γ-substituted allenylamides **23** and **24**, respectively, probably due to the steric hindrance offered by the substrates in the nucleophilic attack of the Bpin moiety (Scheme 3.35).



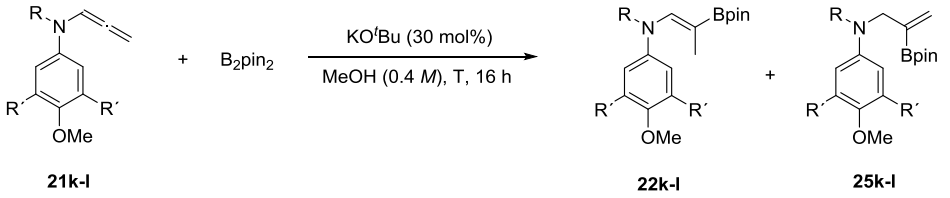
23, R^1 = Me, R^2 = H
24, R^1 = H, R^2 = Et

Scheme 3. 35. α- and γ-substituted *N*-allenyl-*N*-(*para*-methoxyphenyl)benzamides[45]

Next, we moved to study the nature of the electron-withdrawing substituents in the nitrogen atom and its influence in the borylation reaction. So, we tested *N*-Ts and *N*-Boc substituted allenylamides. When performing the reaction with *N*-allenyltosylamide **21k** under the optimal conditions, surprisingly we observed a very low conversion of the reaction (Scheme 3.36). In view of that result, we performed the reaction at higher temperatures (90°C and 110°C) observing that those temperatures favored the major conversion towards a mixture of two hydroborylated products. In both of these products, the boryl moiety was located at the central carbon of the allenylamide but with a 2:1 (**22**:**25**) ratio in favor of the hydroborylation along the terminal double bond. *tert*-butylallenylcarbamate **21l** showed the same behavior. It

[45] Reactions were carried out at 0.2 mmol scale of substrates **23** and **24**, using 30 mol% of KO^{t}Bu, 1.2 eq of B_2pin_2 in 0.5 mL of MeOH at 70°C in 16 h.

was necessary a temperature of 110ºC to observe the two hydroborylated products since at 70ºC the reaction did not take place.



21k-l **22k-l** **25k-l**

21k, R = Ts, R´= H
21l, R = Boc, R´= OMe

22k/25k
T = 70ºC, Conv: 16%
T = 90ºC, Conv: 53%
T = 110ºC, Conv: 82%, Yield: 81%

22l/25l
T = 70ºC, Conv: <5%
T = 110ºC, Conv: 75%, Yield: 53%

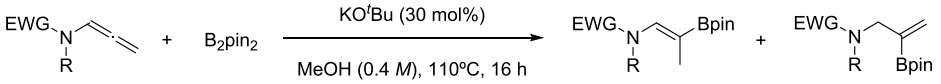
Scheme 3. 36. Borylation reaction over *N*-allenyltosylamide **21k** and *tert*-butylallenylcarbamate **21l**[46]

With these new conditions in hand, we focused on the study of the performance of allenyltosylamides and *tert*-butylallenylcarbamates with different *N*-aryl substituents (Table 3.7). In the case of *N*-Ts allenylamides, no significant differences were detected in the reaction outcome nor in the regioselectivity of the process when the aryl substituent presented no substitution, or was substituted by electron-rich or electron-poor substituents (Table 3.7, entries 1, 3). When the allenyltosylamide incorporated a phenyl group, the yield of the products **22m** and **25m** remained being high as the proportion of the both borylated products (Table 3.7, entry 2). When the aryl substituent was replaced by a methyl group in the nitrogen atom of the allenyltosylamide the reaction was less efficient detecting **22o** and **23o** in 60% NMR yield, although the ratio between the two borylated products remains being the same (2:1) (Table 3.7, entry 4). Replacement of Ts by Boc electron-withdrawing group, led to the conclusion that electron-withdrawing groups in the *para* position of the aromatic substituent favored the reaction obtaining the mixture of products with excellent NMR yield (Table 3.7, entry 6). On the other hand, *para*-electron-donating substituents in the aromatic ring, made

[46] Reactions were carried out at 0.2 mmol scale of substrates **21k-l**, using 30 mol% of KO^{t}Bu and 1.2 eq of B_2pin_2 in 0.5 mL of solvent. Conversions measured by ^{1}H-NMR in crude reaction mixtures using naphthalene as internal standard based on the consumption of substrate **21k-l**. Isolated yield of pure material after flash column chromatography purification.

the *tert*-butylallenylcarbamate less reactive towards the attack of the nucleophilic boron moiety resulting in a lower yield (Table 3.7, entry 5). *Tert*-butylallenylcarbamates with no substituents in the phenyl substituent placed at nitrogen atom or with a dimethylamino substituent in *para* position performed the reaction with very low yield (Table 3.7, entries 7-8).

Table 3. 7. Scope of the reaction of *N*-allenyltosylamides and *tert*-butylallenylcarbamates



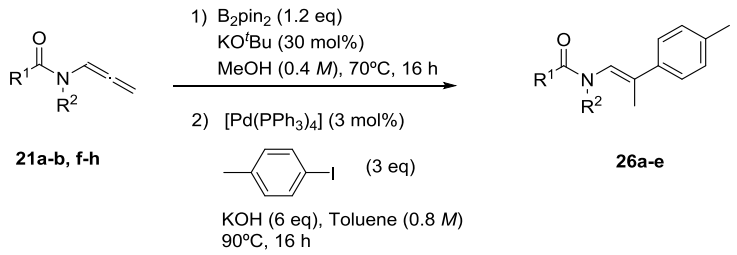
21k-r **22k-r** **25k-r**

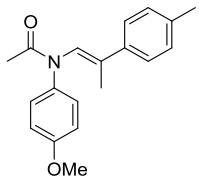
Entry[a]	EWG	R	Product	NMR Yield (%)[b]	Yield 22 (%)[c]	Yield 25 (%)[c]
1	Ts	*p*-$OMeC_6H_4$	**22k/25k**	82	53	28
2	Ts	Ph	**22m/25m**	86	48	9
3	Ts	*p*-BrC_6H_4	**22n/25n**	84	47	28
4	Ts	CH_3	**22o/25o**	60	20	11
5	Boc	3,4,5-$(MeO)_3C_6H_2$	**22l/25l**	74	41	12
6	Boc	*p*-BrC_6H_4	**22p/25p**	90	51	25
7	Boc	Ph	**22q/25q**	8	-	-
8	Boc	*p*-$(NMe_2)C_6H_4$	**22r/25r**	12	-	-

[a]Reactions were carried out at 0.2 mmol scale of substrates **21k-r**, using 30 mol% of KO^tBu, 1.2 eq of B_2pin_2 in 0.5 mL of MeOH at 110ºC in 16 h. [b]NMR Yields calculated from ^{1}H-NMR spectra with naphthalene as internal standard. [c]Isolated yield of pure material after flash column chromatography purifications.

The new developed borylation reaction of allenylamides and allenylcarbamates afforded a wide range of substituted olefins with a boryl moiety in the double bond. With the aim of demonstrating their potential in synthesis, we decided to carry out the functionalization of these borylated compounds through a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction with 4-iodotoluene in a *one-pot* process. All the reactions provided the corresponding borylation/coupling adducts with excellent conversions as it is shown in Table 3.8. *N*-allenylacetamide **21a** furnished the corresponding adduct in a good 72% yield (Table 3.8, product **26a**). However, replacing the acetyl group by a pivaloyl group, product **26b** was isolated in very low yield. On the other hand, the use of benzamides provided the borylation/coupling adduct in very good yields, as it is the case of *N*-allenylbenzamides **21h** and **21g** (Table 3.8, products **26c**, **26d**). Finally, the replacement of *para*-methoxyphenyl substituent of the *N*-allenylacetamide by a *para*-dimethylaminophenyl substituent provided the reaction product in good yield (Table 3.8, product **26e**).

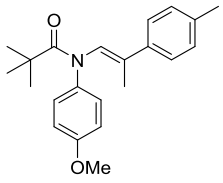
Table 3. 8. Sequential transition metal-free borylation and Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-allenyl-*N*-arylamides.[a]





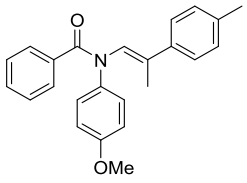
26a

NMR Yield: 99%
Isolated Yield: 72%



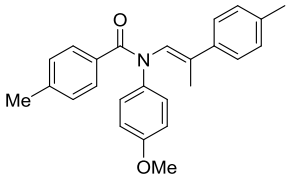
26b

NMR Yield: 98%
Isolated Yield: 26%



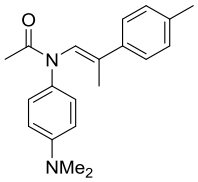
26c

NMR Yield: 99%
Isolated Yield: 94%



26d

NMR Yield: 99%
Isolated Yield: 65%



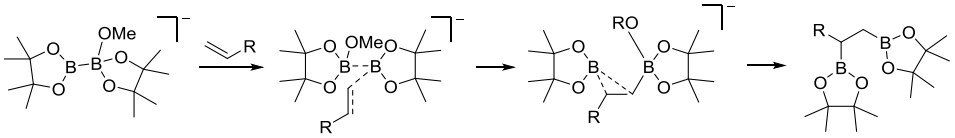
26e

NMR Yield: 99%
Isolated Yield: 74%

[a]Reactions were carried out at 0.2 mmol scale of substrates **21a-b, f-h**, using KO^{t}Bu (30 mol%), B_2pin_2 (1.2 eq), MeOH (0.4 *M*), 70ºC, 16h; $Pd(PPh_3)_4$ (3 mol%), 1-iodo-4-methylbenzene (3 eq), 3 *M* KOH, 90ºC, 16h. NMR Yields calculated from ^{1}H-NMR spectra with naphthalene as internal standard. Isolated yield of pure material after flash column chromatography purification.

3.5. Mechanistic insights

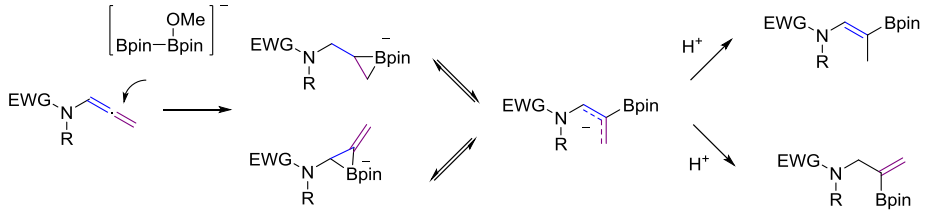
As it has been outlined in the introduction of this chapter, the generally accepted mechanism for the transition metal-free borylation of unsaturated systems consists on the alkoxide activation of B_2pin_2 which forms the nucleophilic boryl moiety in the acid-base Lewis aduct [MeO-Bpin-Bpin]$^-$[Hbase]$^+$. The nucleophilic sp^2 boron unit reacts then with the double bond of the unsaturated system after the overlapping between the highly polarized B-B σ orbital of the diboron reagent and the C–C π* orbital of the olefin. Afterwards, the B-B bond weakens increasing the negative charge density of the olefin and a boracycle-type intermediate is formed. After a protonation step, TS II furnishes diborylated product regenerating the catalytic species (Scheme 3.37).



Scheme 3. 37. Mechanism for the transition metal-free borylation of alkenes

This example of transition metal-free borylation of allenylamides consists on an umpolung of the natural reactivity trend of the allenylamide reagent. According with the literature, allenylamides bearing electron-withdrawing groups are known to undergo electrophilic activation assisted by transition metal complexes or Brønsted acids.[47] This activation generates a stabilized carbocation that reacts with nucleophilic reagents involving the proximal (attack in α position) or distal (attack in γ position) C=C bond.[48] However, computational studies performed by Dr. J. J. Carbó concluded that in our transition metal-free system, a nucleophilic Bpin moiety is *in situ* generated which is able to attack the central carbon of the allenylamide system. Afterwards, two anionic boracyclic intermediates are generated, which undergo a ring-opening process to form a more stable allylic anion which can be protonated in both α and γ positions yielding the final hydroborated products (Scheme 3.38).

[47] Lu, T.; Lu, Z.; Ma, Z-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev*. **2013**, *113*, 4862.
[48] Romano, C.; Jia, M.; Monari, M.; Manoni, E.; Bandini, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 10854.

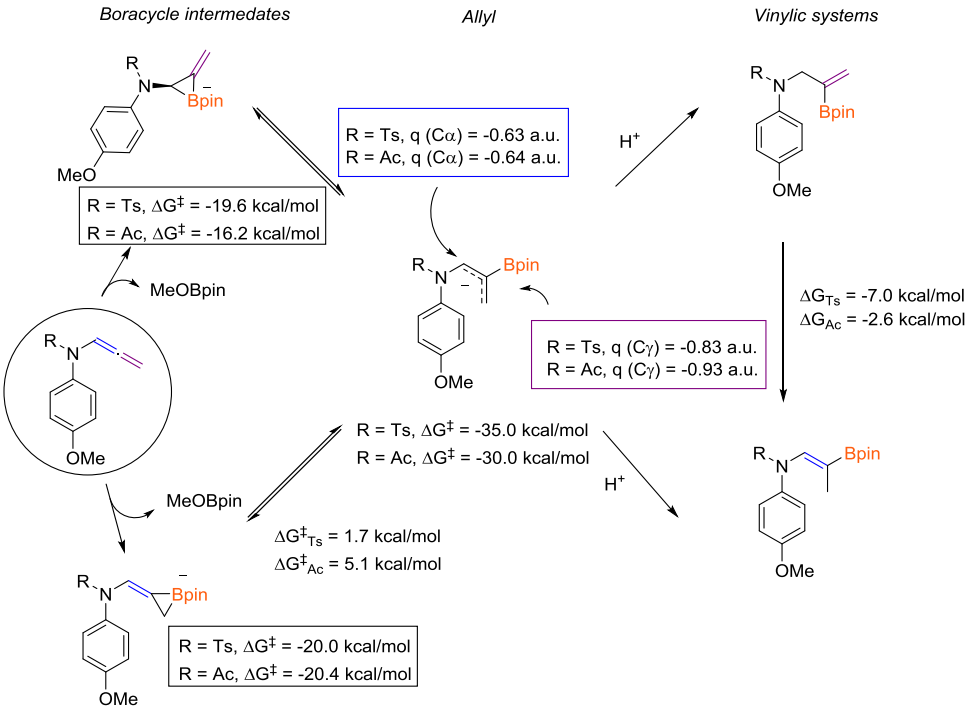


Scheme 3. 38. Umpolung reactivity of allenylamides through nucleophilic activation

To check this mechanistic proposal and to explain the observed stereoselectivity, DFT calculations on the key intermediates were also performed employing substrates **21a** and **21k** as examples (Scheme 3.39).[49] After locating the two boracycle intermediates formed after the borylation of the proximal and distal double bonds, it is possible to conclude that the functionalization of the distal C=C bond is thermodynamically preferred for the *N*-Ac substituted allenylamide due to the boracycle formed after the borylation of the distal position is energetically more stable (-20.4 kcal/mol *vs* -16.2 kcal/mol). However, in the case of *N*-Ts substituted allenylamide, both regioisomers are isoenergetic, as we appreciate in the energy values for both intermediates (-19.6 kcal/mol and -20.0 kcal/mol for the proximal and distal positions respectively). Nevertheless, in the case of both *N*-substituted allenylamides, the allylic species formed afterwards, bearing the Bpin moiety attached to the central position, is thermodynamically preferred due to the stabilization of the negative charge by conjugation with the exocyclic C=C bond (relative Gibbs free energies of -35.0 kcal/mol for **21k** and -30.0 kcal/mol for **21a**). Besides, through the low free-energy barrier involved in the formation of the allylic intermediate from the distal boracycles (1.7 kcal/mol and 5.1 kcal/mol for *N*-Ts and *N*-Ac-substituted allenylamides, respectively), it can be concluded that at high reaction temperatures, the process is a fast transformation. Finally, the protonation process takes place over the allylic intermediate, being the selectivity of the overall process determined in this step. In the structure of the allylic anion intermediate it can be observed an *anti* configuration of the amine which yields a *trans* configuration between the amine and the Bpin moiety as we see in the experimental part.

[49] Calculations were performed using Gaussian 09 (M06-2X functional) and the 6-311G(d,p) basis set. Energies include free energy corrections and the solvent effect of methanol (ε = 32.613) by SMD continuum solvent model.

With the aim of understanding the difference in reactivity between the α and γ positions of allenylamide, a charge distribution analysis was performed. The calculations showed that the Cγ is more reactive towards electrophiles since it is more negatively charged, as we can see in the values for electrostatic-based atomic charges for both positions, shown in Scheme 3.39. The products resulted from the protonation in Cγ are more stable than those obtained from protonation in Cα as the relative Gibbs free energy values indicates (7 kcal/mol and 2.6 kcal/mol for allenylamides **21k** and **21a**, respectively). However, the selectivity of the process is assumed to be kinetically controlled by the irreversible protonation step.



Scheme 3. 39. Proposed mechanism for the hydroborylation of allenylamides **21a** and **21k**.[50]

[50] Relative Gibbs free energies and barriers (ΔG‡) in kcal/mol. Electrostatic-based atomic charges for the α and γ carbons of allyl species in a.u.

4. CONCLUSIONS

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

- *N*-allenylamides and *N*-allenylcarbamates have been demonstrated to undergo a hydroborylation reaction of distal double bond with B_2pin_2 under Lewis base activation with complete stereocontrol, providing exclusively *Z*-isomers.

- The acetyl group results to be crucial for the total stereoselectivity of the reaction, obtaining a mixture of two borylated product when other electron-withdrawing groups are located in the nitrogen atom.

- The scope of the methodology has been demonstrated with a variety of substituents at the nitrogen atom, obtaining a wide range of borylated products in moderate to good yields.

- The value of the synthesized borylated products as building blocks has been demonstrated through the *in situ one-pot* metal-free borylation of the adducts followed by a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

- Mechanistic studies suggested the formation of a 3-membered boracycle intermediate formed after the nucleophilic attack of the Bpin moiety to the C=C double bond, which undergoes a protonation step leading to the hydroborylated product.

Chapter 4

4

Amide Activation: Synthesis of Chiral Isochromanones

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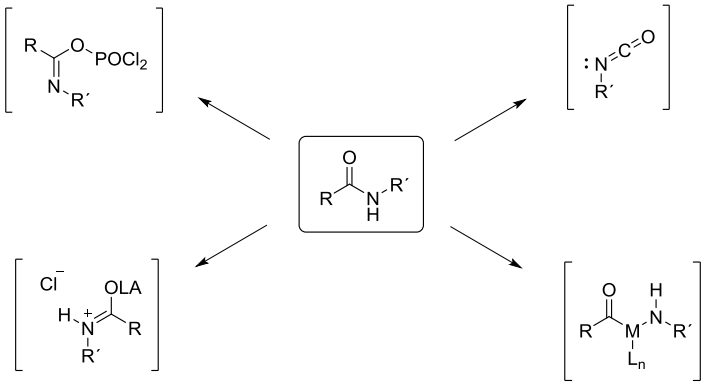
1. INTRODUCTION

Due to the lack of electrophilicity of amides compared to parent functional group such as esters, much effort has been made concerning the activation and functionalization of amides for their use as reagents in synthesis during the last century. The classic methods of activation of amides use reagents like $POCl_3$ as it is found in Bischler-Napieralski[1] and Vilsmeier-Haack reactions.[2] Other methodologies imply the activation of amides by the use of strong electrophiles such as Lewis acids, generating *in situ* an iminium ion which could undergo a reduction step rendering the corresponding amine.[3] Transition-metals can also promote the amide activation process by its insertion into the C-N bond.[4] Other transformations allow the conversion of amides into different functional groups, such as Hofmann rearrangement which converts primary amides into primary amines through an isocyanate intermediate (Scheme 4.1).[5]



Scheme 4. 1. General methods for activation of amides

[1] Bischler, A.; Napieralski, A. *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 1903. For a review, see: Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, 1797.

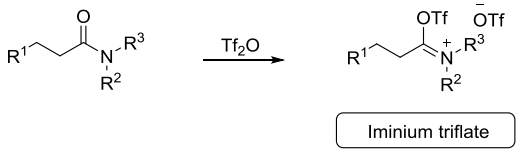
[2] Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges*. **1927**, *60*, 119. For some reviews, see: (a) Su, W.; Weng, Y.; Jiang, L.; Yang, Y.; Zhao, L.; Chen, Z.; Li, Z.; Li, J. *Org. Prep. Proced. Int.* **2010**, *42*, 503. (b) Rajput, AP.; Girase, P. D. *Int. J. Pharm., Chem. Biol. Sci.*, **2012**, *3*, 25.

[3] Ravinder, B.; Rajeswar, R. S.; Panasa Reddy, A.; Bandichor, R. *Tetrahedron Lett*. **2013**, *54*, 4908.

[4] (a) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79. (b) Kono, M.; Harada, S.; Hamada, Y.; Nemoto, T. *Tetrahedron* **2016**, *72*, 1395. (c) Chaudhari, M. B.; Gnanaprakasam, B. *Chem Asian J*. **2019**, *14*, 76.

[5] Hofmann, A. W. *Ber. Dtsch. Chem. Ges*. **1881**, *14*, 2725.

In recent years the use of trifluoromethanesulfonic anhydride (triflic anhydride) as amide activator has been exploited by different research groups successfully.[6] Through reaction with this reagent, amides are converted *in situ* into *O*-trifluoromethanesulfonyloxyiminium trifluoromethanesulfonates (iminium triflates) which are active electrophiles that can evolve to different species depending on the substitution pattern of the substrate and the employed reaction conditions (Scheme 4.2).[7]



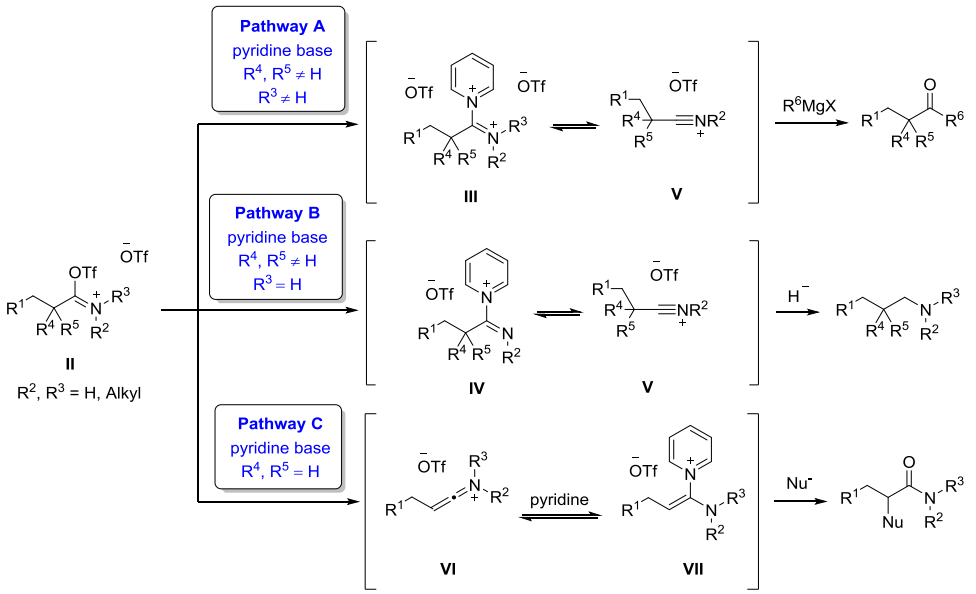
Scheme 4. 2. Activation of amides employing Tf_2O

Through the reaction of secondary and tertiary amides with triflic anhydride in the presence of various pyridine bases, it is possible to understand the mechanism and equilibria taking place (Scheme 4.3). After the reaction of amide with Tf_2O as the triflating agent iminium triflate **II** is formed which can undergo three reaction pathways depending on the substitution pattern of the amide. When R^4 and R^5 are not hydrogen, pyridine is added to the electrophilic center, eliminating the triflate and forming the dicationic pyridinium intermediates **III** or **IV**, depending on the substitution of the nitrogen atom in the amide, which are in equilibrium with nitrilium ion **V** (Pathways A and B). These structures can be employed in several reactions such as in the reduction to amines or carbonyl compounds with hydrides and/or organometallic reagents. On the other hand, if the substrate presents enolizable protons, the base abstracts

[6] (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc*, **2006**, *128*, 14254. (b) Movassaghi, M.; Hill, M. D.; Ahmad, D. K. *J. Am. Chem. Soc*. **2007**, *129*, 10096. (c) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc*. **2008**, *130*, 18. (d) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc*. **2010**, *132*, 12817. (e) Xiao, K.-J.; Wang, A.-E.; Huang, Y.-H.; Huang, P.-Q. *Asian. J. Org. Chem*. **2012**, *1*, 130. (f) Xiao, K.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem. Int. Ed*. **2012**, *51*, 8314. (g) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J.; Wang, Y.; Xia, X.-E. *J. Org. Chem*. **2015**, *80*, 2861. (h) Lumbroso, A.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett*. **2015**, *56*, 2397. (i) Lumbroso, A.; Behra, J.; Kolleth, A.; Dakas, P.-Y.; Karadeniz, U.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett*. **2015**, *56*, 6541. (j) Kolleth, A.; Lumbroso, A.; Tanriver, G.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett*. **2016**, *57*, 2697. (k) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J. *J. Org. Chem*. **2016**, *81*, 9020. (l) Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. *J. Am. Chem. Soc*. **2016**, *138*, 8348. (m) Di Mauro, G.; Maryasin, B.; Kaiser, D.; Shaaban, S.; González, L.; Maulide, N. *Org. Lett*. **2017**, *19*, 3815. (n) Shaaban, S.; Tona, V.; Peng, B.; Maulide, N. *Angew. Chem. Int. Ed*. **2017**, *56*, 10938. (o) Tona, V.; Maryasin, B.; de la Torre, A.; Sprachmann, J.; González, L.; Maulide, N. *Org. Lett*. **2017**, *19*, 2662.

[7] Kaiser, D.; Maulide, N. *J. Org. Chem*. **2016**, *81*, 4221.

the α proton, eliminating the triflate anion and *N*,*N*-dialkyl keteniminium **VI** is formed, which lays in equilibrium with pyridinium adduct **VII** (Pathway C). By the selection of the proper nucleophile (some examples are shown in the Scheme 4.3), it can be accessed to different functional groups containing products.



Scheme 4. 3. Different pathways during activation of amides with Tf_2O and a pyridine base

The possibility provided by this activation manifold to make amides reactive enough to take part in organic transformations has opened a new era in organic synthesis and gives chemists numerous opportunities to develop new chemical transformations among which nucleophilic addition to amides, the α-functionalization of amides and rearrangement processes deserve special mention (Figure 4.1).[8]

[8] Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. *Chem. Soc. Rev*. **2018**, *47*, 7899.

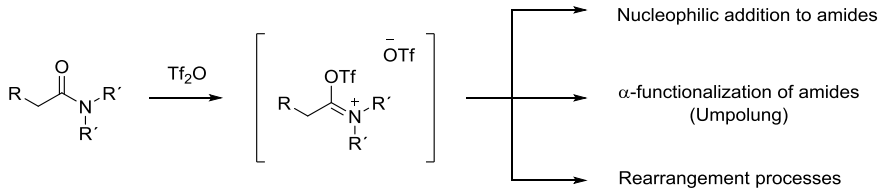
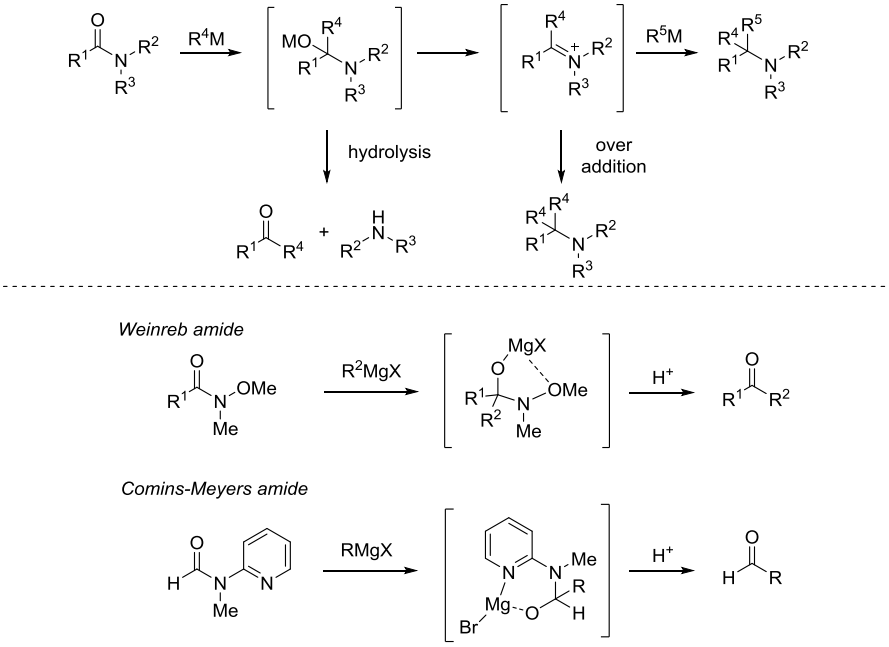


Figure 4. 1. Reactivity of amides

1.1. Nucleophilic addition to amides

While the addition of nucleophiles to different carbonyl functionalities is considered an easy transformation nowadays, the addition of nucleophiles to amides has been less explored. This could be attributed to the low electrophilicity of the amide carbonyl, as well as the high possibility of the hemiaminal intermediate to hydrolyze, and the possibility to suffer from over-reactions, as a consequence of the higher reactivity of the iminium ion intermediate towards the first organometallic reagent (Scheme 4.4). However, despite all the mentioned drawbacks, the nucleophilic addition to amides is thought to be a very important transformation these days both in the synthesis of pharmacologically active drugs and in the total synthesis of diverse natural products. Special mention deserves Weinreb and Comins-Meyers amides that have been intensively used in the last decades. Both amides avoid the over-addition phenomena of the organometallic reagent by the formation of a stabilized intermediate by the chelation of the metal at low temperatures.[9]

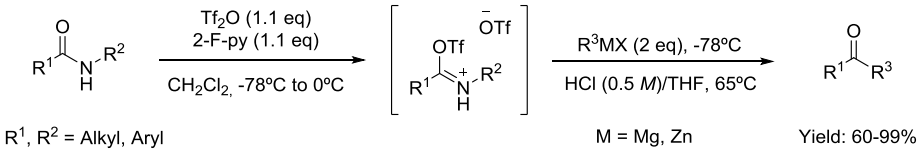
[9] (a) Comins, D.; Meyers, A. I. *Synthesis* **1978**, *5*, 403. (b) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett*. **1981**, *22*, 3815.



Scheme 4. 4. Nucleophilic addition to amides, Weinreb amide and Comins-Meyers amide

Out of all the amide activation methods, the use of triflic anhydride has allowed to carry out the synthesis of a wide number of products by the addition of different nucleophiles to the amide functionality. As it can be seen in the example developed by Charette and coworkers, the nucleophilic addition of Grignard or diorganozinc reagents to amides is possible through the generation of a highly electrophilic imidoyl triflate intermediate.[10] This intermediate played a dual role: on the one hand, it made the 1,2-addition of the organometallic reagent to take place faster than with other functionalities, and on the other hand, it prevented further addition reactions by the formation of a less electrophilic ketenimine intermediate (Scheme 4.5).

[10] Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem*. **2012**, *4*, 228.



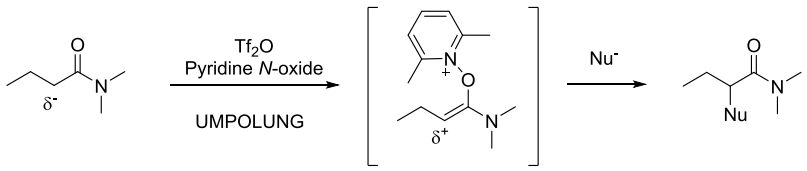
Scheme 4. 5. Nucleophilic addition of Grignard and organozinc reagents to amides

1.2. Nucleophilic α-functionalization of amides

The α-functionalization of carbonyl compounds has been traditionally carried out by enolate chemistry. In this field, the chemoselective α-functionalization of amides is still considered a challenging transformation. However, as a consequence of the inherent electronegativity that the oxygen- and nitrogen-based nucleophiles show, its addition to the α position of a carbonyl compound requires a prior oxidation step. Due to the requirements that enolate chemistry presents, such as the use of strong bases and the presence of over-reactions, other approaches have been performed over the years. In order to solve these issues, some methods have been developed such as the prefunctionalization of the α-position with a leaving group which makes the amide more sensitive for the S_N2-type substitution, and therefore for its functionalization.

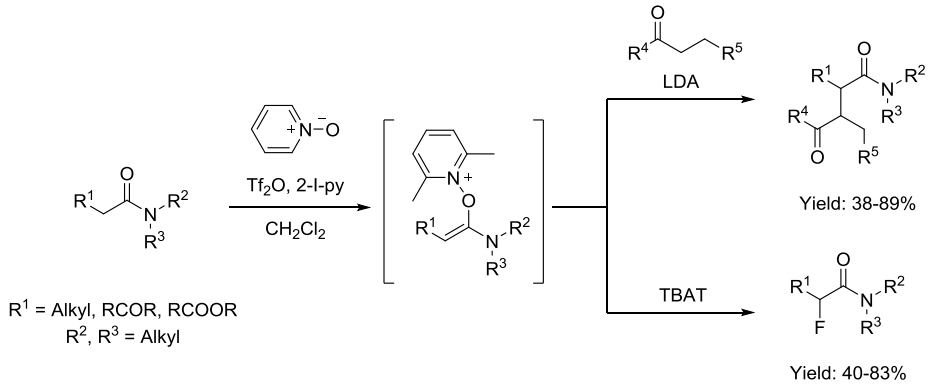
The activation of amides with triflic anhydride has allowed carrying out the synthesis of a wide number of branched amides by the addition of different nucleophiles through an umpolung process. By the amide activation with triflic anhydride followed by the addition of an oxidant (a suitable *O*-nucleophile, generally pyridine *N*-oxides), it is possible to convert the amide (d^2) into an enolonium intermediate (a^2).[11] This intermediate is electrophilic in nature, being able to react with a wide range of nucleophiles (Scheme 4.6).

[11] For a recent approach to the chemoselective α-functionalization of amides, see: Gonçalves, C. R.; Lemmerer, M.; Teskey, C. J.; Adler, P.; Kaiser, D.; Maryasin, B.; González, L.; Maulide, N. *J. Am. Chem. Soc*. **2019**, *141*, 18437.



Scheme 4. 6. Amide activation through an umpolung process: generation of electrophilic enolonium species

This umpolung event opened a new era in the chemoselective α-functionalization of amides employing mild conditions involving nucleophiles of different nature. Maulide and coworkers have applied this strategy in the construction of 1,4-dicarbonyl compounds by the chemoselective intermolecular cross-coupling of amides.[12] The electrophilic enolonium species is generated by the reaction of the amide with triflic anhydride and 2,6-lutidine-*N*-oxide (LNO) as oxidant. By the addition of enolates derived from malonates, ketones, esters and amides to the enolonium species, 1,4-dicarbonyl compounds could be synthesized in short times under mild conditions (Scheme 4.7). As an advantage of this strategy it can be highlighted the absence of side products formed after the attack of the nucleophiles to other electrophiles sites of the molecule. Years later, the methodology was extended carrying out the first direct α-fluorination of amides employing tetrabutylammonium difluorotriphenylsilicate (TBAT) as nucleophilic fluorine source which gave access to α-fluorinated amides (Scheme 4.7).[13]

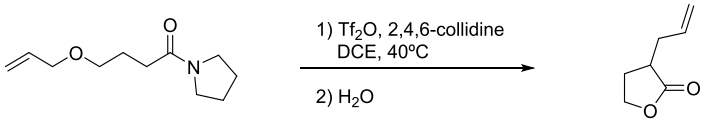


Scheme 4. 7. α-functionalization of amides through enolonium intermediates

[12] Kaiser, D.; Teskey, C. J.; Adler, P.; Maulide, N. *J. Am. Chem. Soc*. **2017**, *139*, 16040.
[13] Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nat. Chem*. **2019**, *11*, 329.

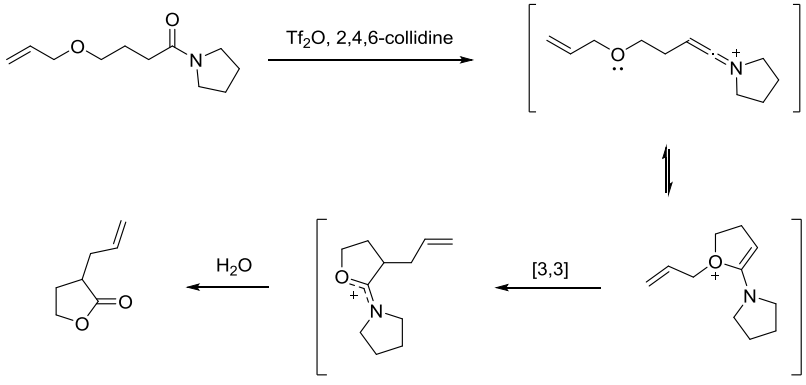
1.3. Rearrangement reactions

In addition to the nucleophilic additions and α-functionalization of amides, rearrangement reactions have been also reported in the field of amide activation by Tf_2O. In 2010, the group of Maulide developed a "Claisen-like" rearrangement of keteniminium salts during their work in the total synthesis of a natural product.[14] This [3,3]-sigmatropic rearrangement afforded substituted lactones after an hydrolysis process (Scheme 4.8).



Scheme 4. 8. [3,3]-sigmatropic rearrangement of amides

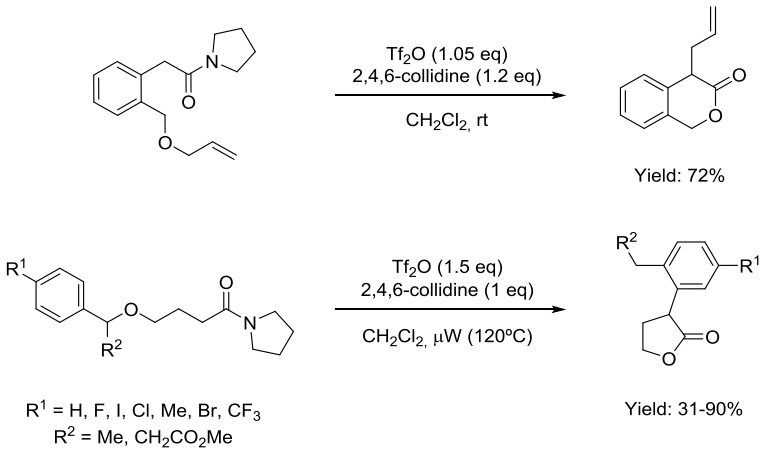
The mechanism of this transformation could be explained as follows: first of all, the activation of the amide by triflic anhydride takes place forming the keteniminium ion. Then, the nucleophilic attack of the lone pair of the oxygen atom of the ether to the central carbon of keteniminium generates a vinyl allyl oxonium intermediate which is ideal to suffer from a [3,3]-sigmatropic rearrangement, leading to a stabilized carbenium, which leads to the final lactone after an hydrolysis step (Scheme 4.9).



Scheme 4. 9. Proposed reaction mechanism for the [3,3] rearrangement

[14] Madelaine, C.; Valerio, V.; Maulide, N. *Angew. Chem. Int. Ed*. **2010**, *49*, 1583.

Taking advantage of this novel reactivity, in the following years, different variants of this unexpected rearrangement were developed. For example, when an arene was incorporated within the alkyl tether, which restricted the conformational freedom and facilitated the cyclization/rearrangement of the starting amide, the transformation took place in very mild conditions.[15] Besides, a "benzyl variant" of the reaction was also developed by replacing the allyl moiety by a benzyl group. This transformation furnished synthetically useful α-arylated lactones in short times under microwave irradiation (Scheme 4.10).[16]

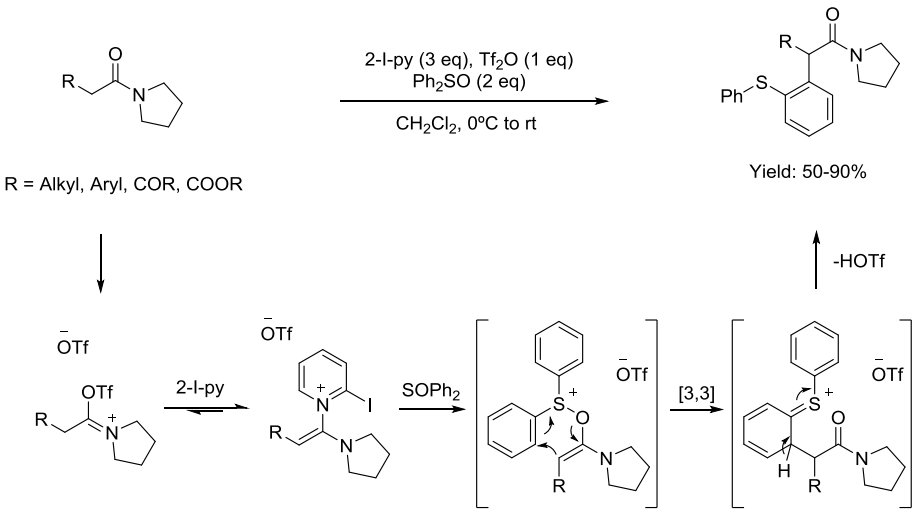


Scheme 4. 10. [3,3]-sigmatropic rearrangements of diverse substituted amides

Alternatively, a formal chemoselective α-arylation of amides through the application of a related strategy was developed by the same group in 2014,[17] a transformation which is considered a challenge in synthetic chemistry. This method resulted to be a breakthrough due to the advantages it presented over similar methodologies which employed strong bases or transition metals constituting the first arylation of amides in the presence of enolizable functional groups. In this process the preformation of the activated amide resulted to be crucial, being this process very sensitive towards some reaction parameters, such as the base. The base presented a dual role: on the one hand, it had to be nucleophilic and basic enough to convert the iminium triflate into the enamine, and on the other hand, it had to be a good

[15] Peng, B.; Donovan, D. H. O.; Jurberg, I. D.; Maulide, N. *Chem. Eur. J*. **2012**, *18*, 16292.
[16] Valerio, V.; Madelaine, C.; Maulide, N. *Chem. Eur. J*. **2011**, *17*, 4742.
[17] Peng, B.; Geerdink, D.; Farès, C.; Maulide, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 5462.

enough leaving group to be replaced by the sulfoxide furnishing the *O*-protected enamine which would undergo the [3,3] rearrangement (Scheme 4.11).

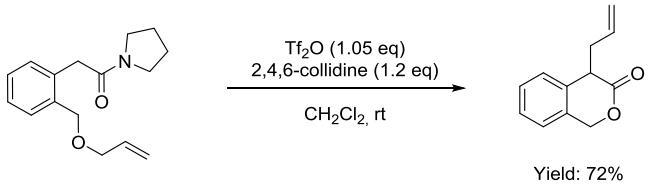


Scheme 4. 11. [3,3]-sigmatropic rearrangement directed to α-arylation of amides

In view of all the transformations that can be carried out through the novel Claisen-like rearrangement developed by the group of Maulide by the use of amide activation concept, more efforts are been doing in the development of more challenging methodologies, some of them will be explained in this chapter.

2. SPECIFIC OBJECTIVES AND WORK PLAN

The literature precedents presented in this chapter have clearly stated the capability of triflic anhydride to activate amides and allow them to participate in a wide range of synthetic transformations. Moreover, the unexpected [3,3]-sigmatropic rearrangement developed by the group has given the access to molecules difficult to prepare to date (Scheme 4.12). In this context, the group of Prof. Maulide in University of Vienna became interested in developing this rearrangement reaction in an asymmetric fashion.

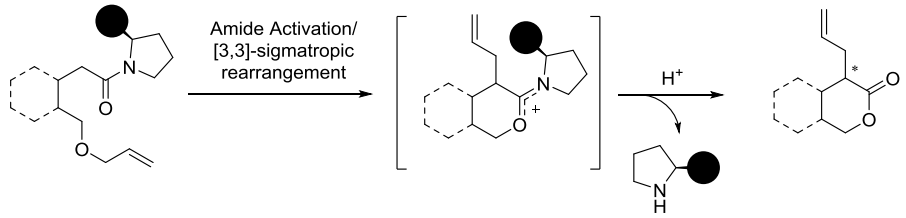


Scheme 4. 12. Previously developed non-asymmetric rearrangement

The induction of chirality will be carried out by the employment of chiral auxiliaries. These molecules consist on optically or enantiomerically pure compounds which are attached to substrates and influence the course of the reaction. This strategy is based on the transformation of the enantiotopic faces of the achiral substrate into diastereotopic by the introduction of chirality by an auxiliary. Thus, the overall process turned to be enantioselective proceeding through diastereoselective transformations which usually involve recovering the chiral auxiliary after the reaction takes place. In order to carry out the facial discrimination of the starting material, the auxiliary can play two different roles: on the one hand, it could act as a stereodirecting element by preventing sterically the approach of the reagent from one of the faces and on the other hand, it can direct the entry of the reagent by its coordination. Out of all developed chiral auxiliaries, such as Evans oxazolidinones,[18] Oppolzer sultam[19] or Myers pseudoephedrine,[20] the induction of chirality in the amide activation/[3,3]-sigmatropic rearrangement will be carried out employing chiral enantiopure substituted pyrrolidines as it is closely related to the previous works developed in the group.

[18] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737.
[19] Oppolzer, W.; Chapuis, C.; Bernardelli, G. *Helv. Chim. Acta,* **1984**, *67*, 1397.
[20] Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc*. **1994**, *116*, 9361.

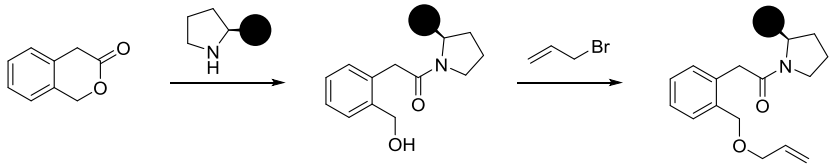
In view of these precedents, the goal of this short stay was **continuing with the enantioselective version of amide activation/[3,3]-sigmatropic rearrangement reaction with the optimal reaction conditions previously optimized by the group** (Scheme 4.13).



Scheme 4. 13. Proposed amide activation/asymmetric [3,3]-rearrangement

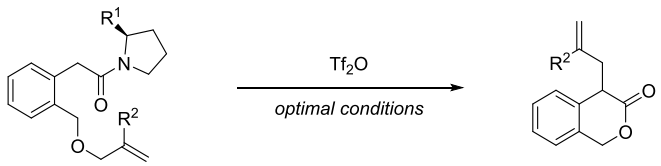
To achieve this objective, the following work plan was established:

- *Synthesis of the starting materials:* first of all, the synthesis of new substrates with different substitution pattern will be faced with the optimized synthetic route developed by the group (Scheme 4.14). Achiral substrates will be initially prepared by incorporation of pyrrolidine, while the use of 2-substituted enantiopure pyrrolidines will render chiral substrates for further evaluation.



Scheme 4. 14. Synthesis of the starting materials

- *Scope of the reaction:* once we have the starting materials in hand, they will be tested in the amide activation/[3,3]-sigmatropic rearrangement sequence. The scope and limitations of the developed method will be studied through the evaluation of structurally different substrates (Scheme 4.15).

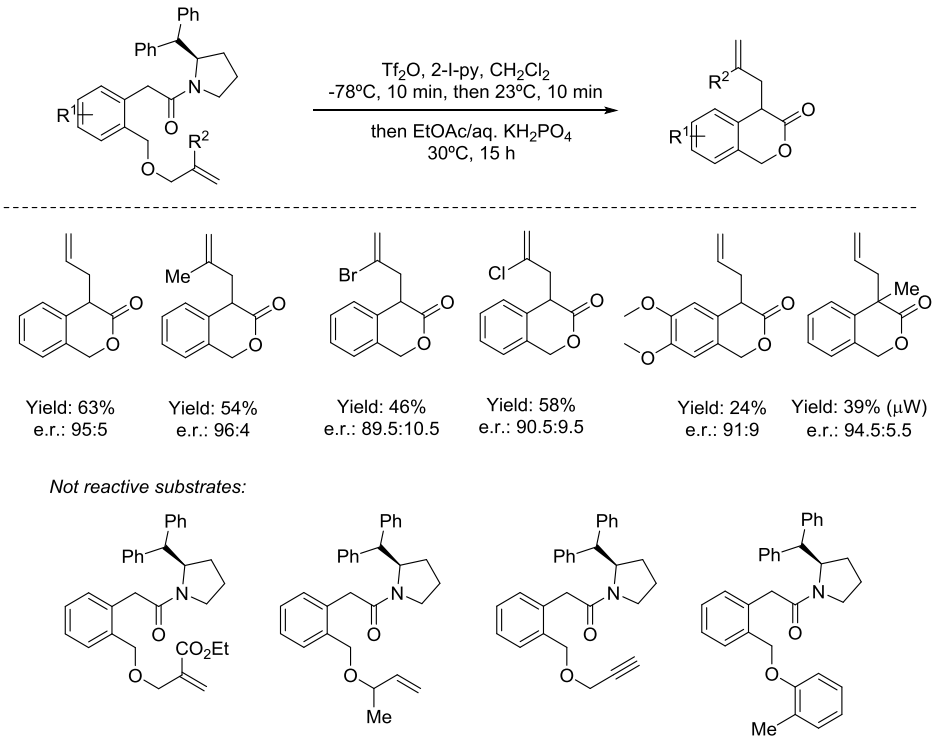


Scheme 4. 15. Scope of the reaction

3. RESULTS AND DISCUSSION

3.1. Previous work

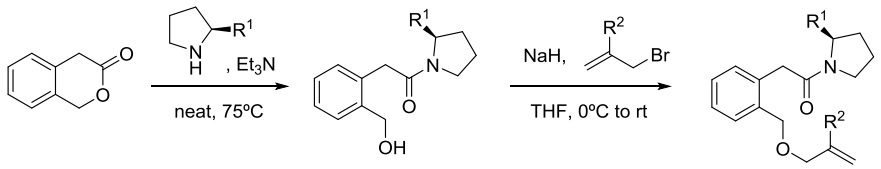
First attempts in developing the asymmetric version of the amide activation/[3,3]-sigmatropic rearrangement were carried out by Dr. Daniel Kaiser. Among the substrates studied, substrates of increased rigidity were chosen to carry out the stated objective since when linear substrates were employed, high values of enantioselectivity were not achieved. The initial studies for this reaction were based on the optimization of different parameters such as chiral pyrrolidines, bases, temperatures and a hydrolysis process, concluding that 2-(diphenylmethyl)pyrrolidine was the best auxiliary and 2-iodopyridine the best base (Scheme 4.16). The rearrangement was almost instantaneous at 23°C which was followed by a hydrolysis step performed in potassium dihydrogen phosphate at 30°C during 15 hours which enabled the removal of the chiral auxiliary. With these conditions in hand, model allyl isochromanone was obtained in 63% yield and 90% enantiomeric excess. These conditions were tested in other different substrates such as those with substitution at allylic moiety or in the aromatic ring, having moderate yields and good enantioselectivities in all cases, but unfortunately, additional substrates, such as those with alkylic or electron-withdrawing substituents at the allylic moiety, could not be transformed into the desired products.



Scheme 4. 16. Previous results

3.2. Synthesis of starting materials

With the optimal conditions in hand and in view of the substrates which were able to carry out the reaction, we initiated our work synthesizing substrates with substitution in the allylic moiety. For that purpose, both achiral and chiral substrates were prepared through a synthesis consisting first on the introduction of the auxiliary by a nucleophilic substitution which proceeded with a ring-opening reaction of the isochromanone and second, on the incorporation of the allylic moiety by a nucleophilic substitution with allyl bromides (Scheme 4.17).



27, R^1 = H, 95%

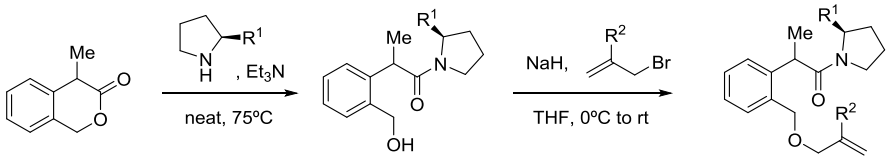
29a, R^1 = H, R^2 = CN, 17%
29b, R^1 = H, R^2 = CH_2Cl, 40%
29c, R^1 = H, R^2 = CH_2OAc, 28% (2 steps)
29d, R^1 = H, R^2 = CH_2OMe, 5% (5 steps)

28, R^1 = $CH(Ph)_2$, 15%

30a, R^1 = $CH(Ph)_2$, R^2 = CN, 47%
30b, R^1 = $CH(Ph)_2$, R^2 = CH_2Cl, 53%
30c, R^1 = $CH(Ph)_2$, R^2 = CH_2OAc, 40% (2 steps)

Scheme 4. 17. Synthesis of starting amides **29** and **30**

As it could be noticed in the previous work, due to the acidic proton to carbonyl, a possible epimerization process could be observed in the desired product. In order to avoid that problem, we also focused our attention into the synthesis of α-substituted amides that would generate a non-epimerizable quaternary stereocenter. For these reagents, (*R*)-2-methylpyrrolidine was selected as it was found to be the best auxiliary in some preliminary experiments (Scheme 4.18).



31

32, R^1 = H, 95%

34a, R^1 = H, R^2 = CN, 9%
34b, R^1 = H, R^2 = CH_2Cl, 21%
34c, R^1 = H, R^2 = CH_2OAc, 9% (2 steps)
34d, R^1 = H, R^2 = CH_2OMe, 4% (4 steps)

33, R^1 = Me, 49%

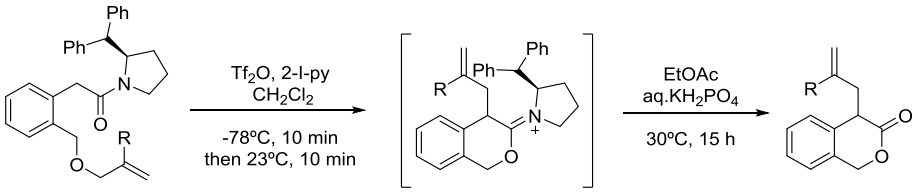
35a, R^1 = Me, R^2 = CN, 49%
35b, R^1 = Me, R^2 = CH_2Cl, 57%
35c, R^1 = Me, R^2 = CH_2OAc, 40% (2 steps)
35d, R^1 = Me, R^2 = CH_2OMe, 11% (4 steps)

Scheme 4. 18. Synthesis of α-substituted starting amides **34** and **35**

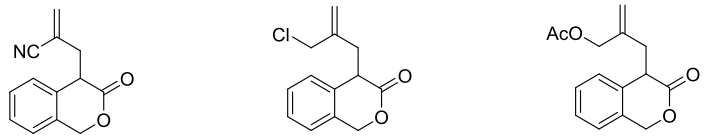
3.3. Amide activation/[3,3]-sigmatropic rearrangement

With all the substrates in hand, we moved to test the amide activation/[3,3]-sigmatropic rearrangement sequence. First of all, we tested substrates **30a-c** without a substituent in alfa position to carbonyl under the developed conditions (2.00 equivalents of 2-iodopyridine, 1.05 equivalents of triflic anhydride in CH_2Cl_2 running the reaction from -78ºC to room temperature). In all cases, the reaction took place after 10 minutes with full conversion of the starting material to the iminium intermediate (Table 4.1). However, the hydrolysis step took place with low yields. As it happened during the optimization of the reaction conditions carried out by Dr. Daniel Kaiser, the enantiomeric ratio of the obtained isochromanones was lower than the enantiomeric ratio obtained on the iminium intermediate, which was attributed to epimerization in the basic media of the reaction. However, neither doing a very quick purification in flash column chromatography, neither deactivating the silica with triethylamine, nor doing the purification step in basic alumina could the problem of epimerization be solved. As a solution, it was decided to use the reaction crudes to determine the e.e. values. However, due to the low conversion observed in the hydrolysis step, the enantiomeric excesses could not be precisely determined due to low UV-Vis absortion of obtained products.

Table 4. 1. Scope of the reaction using amides **30a-c**



30a-c **36a-c**



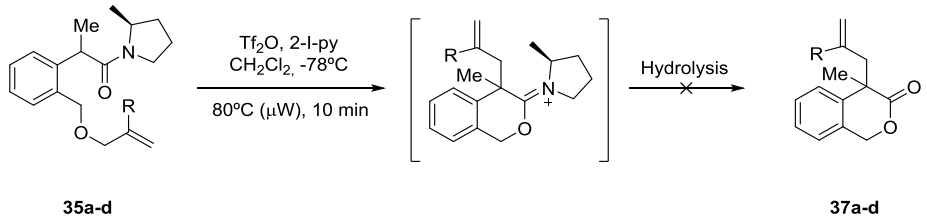
36a Yield: 30%

36b Yield: 20%

36c Yield: 36%

[a]Reactions were carried out at 0.1 mmol scale of substrates **30a-c**, using 0.2 mmol of 2-l-py, 0.105 mmol of Tf_2O in 0.5 mL of CH_2Cl_2 at -78ºC. Isolated yield of pure material after flash column chromatography purification.

In view of the epimerization problems that these substrates presented, we focused our attention in amides with a methyl group in alfa position to carbonyl to perform the amide activation/[3,3]-sigmatropic rearrangement in which this epimerization event cannot take place. When triflic anhydride was added to the substrates **35a-d**, after microwave heating at 80ºC for 10 minutes, formation of the iminium intermediate generated after the rearrangement step was observed. However, when the hydrolysis process was set up, no isochromanone could be isolated. In view of these results, the hydrolysis step was carried out at higher temperature although without success (Scheme 4.20).



Scheme 4. 19. Amide activation/[3,3]-sigmatropic rearrangement using amides **35a-d**

At this point, diverse hydrolysis conditions were tested with different substituted substrates with unfruitful results in all the cases (Table 4.2).

Table 4. 2. Tested hydrolysis conditions

Entry	R	Substrate	Hydrolysis Conditions	T (°C)
1	CN	**35a**	EtOAc/KH_2PO_4 aq.	30
2	CH_2Cl	**35b**	NaOAc/AcOH	25
3			NaOAc/AcOH	50
4			HCl 1 *M*	25
5	CH_2OAc	**35c**	KOH, MeOH/H_2O	25
6			NaOAc/AcOH	60
7	CH_2OMe	**35d**	EtOAc/KH_2PO_4 aq.	80
8			EtOAc/KH_2PO_4 aq., LiBr	60
9			EtOAc/KH_2PO_4 aq., LiBr	80
10			LiOH, MeOH/H_2O	60

None of the tested hydrolysis conditions indicated in Table 4.2 succeeded in the synthesis of tetrasubstituted isochromanones. When two electron-withdrawing groups were introduced at the allyl substituent (substrates **35a**, **35b**, **35c**), the desired product was not observed. However, when different hydrolysis conditions were tested over the ether **35d**, the product could be detected by HRMS, but only traces could be isolated. Development of a proper methodology for the synthesis of tetrasubstituted chiral isochromanones and further investigations are now in progress.

4. CONCLUSIONS

From the work presented in this chapter, the following conclusions can be outlined:

- Triflic anhydride is a convenient reagent for the activation of amides, allowing them to take part in a wide range of transformations.

- "Claisen-like" [3,3]-sigmatropic rearrangement constitutes an excellent methodology for the construction of substituted isochromanones, representing an alternative methodology to classical methods.

- 2-substituted pyrrolidines are useful chiral auxiliaries with promising results in terms of the yield and enantioselectivity.

- Exploration of the scope of the reaction with non-substituted and α-substituted amides shows variable yields and enantiomeric ratios. Further optimization will be done in due course.

Chapter 5

FINAL CONCLUSIONS

The present work covers the study and development of novel stereoselective transformations under Lewis base catalysis relying on the use of organocatalysts as efficient promoters of these processes. Experimental results collected during the accomplishment of the present work lead to the following conclusions:

Aminocatalytic enantioselective vinylcyclopropane-cyclopentene (VCP-CP) rearrangement. It has been demonstrated the ability of chiral secondary amines as suitable promoters for the development of the organocatalytic enantioselective version of vinylcyclopropane-cyclopentene (VCP-CP) rearrangement. 2-vinyl-substituted cyclopropylacetaldehydes were employed as substrates in this reaction, leading to a wide variety of cyclopentenes in good yields and good enantiocontrol. Experimental studies showed that the reaction proceeded stepwise.

Transition metal-free stereoselective borylation of allenylamides. It has been shown that allenylamides can be stereoselectively borylated through the metal-free activation of bis(pinacolato)diboron. *N*-substituted allenylamides undergo regioselective hydroborylation reaction of distal double bond under Lewis base activation of B_2pin_2. The reaction proceeded with a complete stereocontrol in the case of allenylacetamides, providing exclusively *Z*-isomers. When other electron-withdrawing groups were located in the allenamides system, a mixture of two borylated diastereoisomeric products was obtained. DFT studies demonstrated that this reaction constituted an umpolung reactivity of allenylamides, leading to a nucleophilic activation of these substrates.

Amide activation: synthesis of chiral isochromanones. The study of the asymmetric [3,3]-sigmatropic rearrangement has been carried out in the research group of Prof. N. Maulide in University of Vienna (Austria). By the use of 2-substituted pyrrolidines as chiral auxiliaries, asymmetric [3,3]-sigmatropic rearrangement was performed under amide activation conditions giving access to a variety of α-substituted isochromanones in moderate yields.

Chapter 6

6

Experimental section

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1. GENERAL METHODS AND MATERIALS[1]

Monodimensional and/or bidimensional nuclear magnetic resonance proton, carbon and boron spectra (^{1}H NMR, ^{13}C NMR, ^{11}B NMR) were acquired at 25ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H, 75.4 MHz for ^{13}C, 128.3 MHz for ^{11}B) or a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) at the indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals[2] ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.16 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, apparent; m, multiplet; br s, 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 configurations and to assist in deconvoluting complex multiplet signals.[3] **Infrared spectra** (IR) were measured in a Jasco FT/IR 4100 (ATR) in the interval between 4000 and 600 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. **Mass spectra** (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 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%). **High-resolution mass spectra (HRMS)** were recorded on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^+ or ESI^-). **Melting points** (M.p.) were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. The **enantiomeric excess** (e.e.) of the products was determined by High Performance Liquid Chromatography (HPLC) on a chiral stationary phase in a Waters chromatograph coupled to a Waters photodiode array detector. Daicel *Chiralpak* IA, IC, AD-H, ASH and IE-3 and *Chiralcel* OD3 and ID3 columns (0.46 × 25 cm) were used; specific conditions are indicated for each case. Specific optical rotations ($[\alpha]_D^{20}$) were measured at 20ºC 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 = 1.54184 Å, 250 µm FWHM beam size). The sample was kept at 150 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing miscroscope, and a suitable crystal or

[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR and X-ray analysis).

[2] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

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

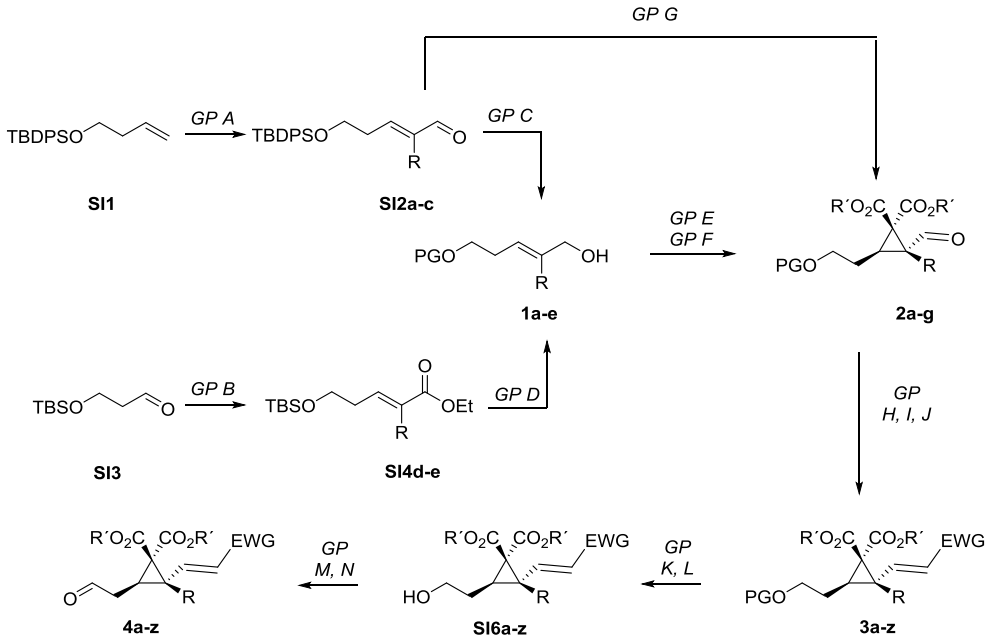
fragment was mounted on a Mitegen Micromount™ using Paratone N inert oil and transferred to the diffractometer.

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.[4] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140ºC, and allowed to cool under a dehumidified atmosphere. 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 stains.[5] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[6] For the removal of the solvents under reduced pressure Büchi R-210 rotatory evaporators were used. For precision weighing Sartorius Analytical Balance Practum 224-1S was used (± 0.1 mg).

[4] (a) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 7th ed.; Elsevier: Oxford, 2012. (b) Williams, D. B. G.; Lawton, M. *J. Org. Chem*. **2010**, *75*, 8351.
[5] Stahl, E. *Thin Layer Chromatography*, Springer Verlag: Berlin, 1969.
[6] Still, W. C.; Kahn, H.; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.

2. AMINOCATALYTIC ENANTIOSELECTIVE VINYLCYCLOPROPANE-CYCLOPENTENE (VCP-CP) REARRANGEMENT

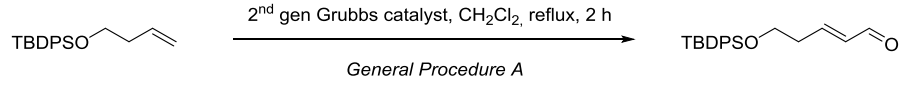
2.1. Synthesis of starting materials



SI1 and **SI3** were reported compounds and they were prepared following the procedure described in the literature. Spectroscopic data were consistent with those reported in the literature.[7]

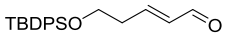
[7] (a) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc*. **2006**, *128*, 11693. (b) Zhou, Y.; Gupta, A. K.; Mukherje. M.; Zheng, L.; Wulff, W. D. *J. Org. Chem*. **2017**, *82*, 13121.

2.1.1. Synthesis of SI2a-c

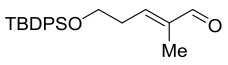


SI1 **SI2a-c**

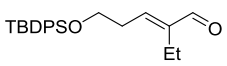
General procedure A: To a solution of **SI1** (8.0 mmol, 1.0 eq) in CH_2Cl_2 (33 mL, 0.24 *M*), corresponding aldehyde (16.0 mmol, 2.0 eq) was added. Then, a solution of 2nd generation Grubbs catalyst (0.02 mmol, 2.5 mol%) in CH_2Cl_2 (5 mL, 1.5 *M*) was added in portions, and the reaction mixture was heated to reflux for 2 hours. Once the reaction was finished, the solvent was removed and the crude was then purified by flash column chromatography to afford pure **SI2a-c**.



(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-2-enal (SI2a). Following the *general procedure A*, **SI2a** (2.10 g, 6.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 65% yield as a yellow oil starting from **SI1** (3.00 g, 9.7 mmol), crotonaldehyde (1.60 mL, 19.3 mmol), 2nd generation Grubbs catalyst (0.14 g, 0.2 mmol) and CH_2Cl_2 (47 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.49 (d, *J* = 7.9 Hz, 1H, CHO), 7.84-7.55 (m, 4H, C_{arom}-H), 7.50-7.33 (m, 6H, C_{arom}-H), 6.85 (dt, *J* = 15.7, 6.9 Hz, 1H, C*H*=CH), 6.16 (ddt, *J* = 15.7, 7.9, 1.4 Hz, 1H, CH=C*H*), 3.84 (t, *J* = 6.1 Hz, 2H, SiOCH_2CH$_2$), 2.56 (qd, *J* = 6.2, 1.4 Hz, 2H, SiOCH$_2$CH_2), 1.06 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 194.1 (CHO), 155.6 (*C*H=CH), 135.7 (C_{arom}-H), 134.5 (CH=*C*H), 133.5 (C_{arom}-Si), 129.9 (C_{arom}-H), 127.9 (C_{arom}-H), 62.1 (SiO*C*H$_2$CH$_2$), 36.0 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 19.3 (Si*C*(CH$_3$)$_3$). **IR** (ATR): 1699 (C=O st), 822 (C=CH$_2$ δ oop) cm^{-1}. **MS** (EI) m/z (%): 281 (M$^+$-^{t}Bu, 19), 251 (30), 199 (100), 173 (32), 143 (14), 123 (14), 105 (15), 77 (19), 53 (15).



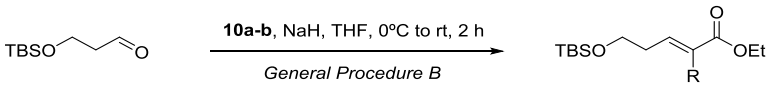
(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-methylpent-2-enal (SI2b). Following the *general procedure A*, **SI2b** (2.00 g, 5.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 49:1 to 9:1) in 65% yield as a brown oil starting from **SI1** (2.70 g, 8.6 mmol), methacrolein (1.40 mL, 17.1 mmol), 2nd generation Grubbs catalyst (0.13 g, 0.4 mmol) and CH_2Cl_2 (36 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.41 (s, 1H, CHO), 7.78-7.59 (m, 4H, C_{arom}-H), 7.49-7.39 (m, 6H, C_{arom}-H), 6.55 (t, *J* = 7.3 Hz, 1H, C*H*=C), 3.87 (t, *J* = 6.3 Hz, 2H, SiOCH_2CH$_2$), 2.62 (q, *J* = 6.6 Hz, 2H, SiOCH$_2$CH_2), 1.75 (s, 3H, CH_3), 1.10 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 195.1 (CHO), 151.2 (*C*H=C), 140.6 (CH=*C*), 135.6 (C_{arom}-H), 133.5 (C_{arom}-Si), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 62.2 (SiO*C*H$_2$CH$_2$), 32.4 (SiOCH$_2$*C*H$_2$), 26.9 (3 x CH_3), 19.2 (Si*C*(CH$_3$)$_3$), 9.4 (CH_3). **IR** (ATR): 2930 (C-H st), 1684 (C=O st), 1648 (C=C st) cm^{-1}. **MS (EI)** m/z (%): 295 (M$^+$-^{t}Bu, 75), 265 (37), 255 (M$^+$-OTBDPS, 1), 217 (26), 199 (100), 181 (34), 97 (M$^+$-C$_6$H$_9$O, 1), 78 (21), 57 (14). **HRMS**: Calculated for $[C_{22}H_{29}O_2Si]^+$: 353.1937 [(M+H)$^+$]; found: 353.1934.



(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-ethylpent-2-enal (SI2c). Following the *general procedure A*, **SI2c** (0.50 g, 1.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 49:1 to 9:1) in 40% yield as a yellow oil starting from **SI1** (1.00 g, 3.2 mmol), ethylacrolein (0.66 mL, 6.4 mmol), 2nd generation Grubbs catalyst (0.14 mg, 0.2 mmol) and CH_2Cl_2 (16 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances, d.r.: 1:2.8): 10.13* (s, 1H, CHO), 9.39 (s, 1H, CHO), 7.88-7.62 (m,

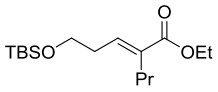
4H, C_{arom}-H), 7.50-7.40 (m, 6H, C_{arom}-H), 6.52 (dt, *J* = 14.8, 7.7 Hz, 1H, C*H*=C), 3.87 (dt, *J* = 11.3, 6.2 Hz, 2H, SiOCH_2CH$_2$), 2.83* (q, *J* = 6.8 Hz, 2H, CH_2CH$_3$), 2.64 (q, *J* = 6.6 Hz, 2H, CH_2CH$_3$), 2.28 (qd, *J* = 7.6, 2.5 Hz, 2H, SiOCH$_2$CH_2), 1.13 (s, 9H, 3 x CH$_3$), 0.99-0.96 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 194.8 (CHO), 191.1* (CHO), 150.9 (*C*H=C), 146.4* (C_{arom}-Si), 144.3 (CH=*C*), 143.2* (CH=*C*), 135.6 (C_{arom}-H), 133.5 (C_{arom}-Si), 129.9 (C_{arom}-H), 127.8 (C_{arom}-H), 62.8* (SiO*C*H$_2$CH$_2$), 62.4 (SiO*C*H$_2$CH$_2$), 32.1 (SiOCH$_2$*C*H$_2$), 29.9* (SiOCH$_2$*C*H$_2$), 26.9 (3 x CH$_3$), 26.8* (3 x CH$_3$), 23.3* (*C*H$_2$CH$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 17.4 (*C*H$_2$CH$_3$), 13.4 (CH$_2$*C*H$_3$), 13.1* (CH$_2$*C*H$_3$). **IR** (ATR): 2972 (C-H st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 295 (30), 265 (26), 227 (14), 199 (100), 181 (23), 147 (10), 123 (12), 105 (10), 78 (19), 57 (12). **HRMS**: calculated for [$C_{23}H_{31}O_2Si$]$^+$: 367.2093 [(M+H)$^+$]; found: 367.2099.

2.1.2. Synthesis of SI4d-e



SI3 **SI4d-e**

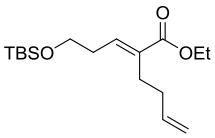
General procedure B: To a solution of phosphonate **10a-b**[8] (80.0 mmol, 2.0 eq) in THF (250 mL, 0.16 *M*) at 0ºC, NaH (60 wt.% in mineral oil, 80.0 mmol, 2.0 eq) was added and the solution was stirred at room temperature for 45 minutes. The reaction mixture was then cooled to 0ºC and a solution of the aldehyde **SI3** (40.0 mmol, 1.0 eq) in THF (150 mL, 0.27 *M*) was added dropwise, stirring at that temperature for 2 hours. Once the reaction was finished, it was quenched with H_2O (20 mL), diluted with Et_2O (20 mL) and the aqueous layer was extracted with Et_2O (3 x 20 mL). Combined organic extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **SI4d-e**.



Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2-propylpent-2-enoate (SI4d). Following the *general procedure B*, **SI4d** (6.00 g, 20.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 9:1) in 40% yield as a yellow oil starting from **SI3** (9.45 g, 50.0 mmol), ethyl 2-(diethoxyphosphoryl)pentanoate **10a** (26.50 g, 100.0 mmol), NaH (4.00 g, 100.0 mmol) and THF (275 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:0.9): 6.74 (t, *J* = 7.4 Hz, 1H, C*H*=C), 5.89* (t, *J* = 7.1 Hz, 1H, C*H*=C), 4.21-4.11 (m, 2H, OCH_2CH$_3$), 3.70-3.63 (m, 2H, SiOCH_2CH$_2$), 2.68-2.35 (m, 2H, CH_2CH$_2$CH$_3$), 2.32-2.16 (m, 2H, SiOCH$_2$CH_2), 1.46-1.34 (m, 2H, CH$_2$CH_2CH$_3$), 1.31-1.17 (m, 3H, OCH$_2$CH_3), 0.86 (s, 9H, 3 x CH$_3$, CH$_2$CH$_2$CH_3), 0.02 (s, 6H, 2

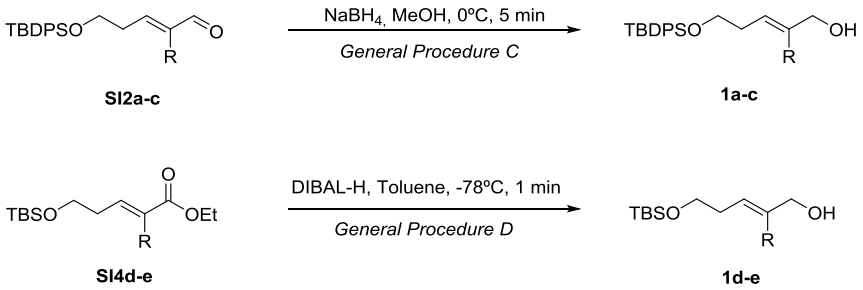
[8] **10a** and **10b** were reported compounds and they were prepared following the procedure described in the literature. Spectroscopic data were consistent with those reported in the literature. (a) Gastl, C.; Laschat, S. *Synthesis* **2010**, *15*, 2643. (b) Pieroni, M.; Annunziato, G.; Beato, C.; Wouters, R.; Benoni, R.; Campanini, B.; Pertinhez, T. A.; Bettati, S.; Mozarelli, A.; Constantino, G. *J. Med. Chem*. **2016**, *59*, 2567.

x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 168.2 (C=O), 167.9* (C=O), 138.7 (*C*H=C), 137.7* (*C*H=C), 134.0 (CH=*C*), 133.6* (CH=*C*), 62.7 (SiO*C*H_2CH_2), 62.1* (SiO*C*H_2CH_2), 60.3 (O*C*H_2CH_3), 60.1* (O*C*H_2CH_3), 36.7 (SiOCH$_2$*C*H_2), 33.3* (SiOCH$_2$*C*H_2), 32.4 (*C*$H_2CH_2CH_3$), 28.9* (*C*$H_2CH_2CH_3$), 26.0 (3 x CH_3), 22.6 (CH_2*C*H_2CH_3), 22.2* (CH_2*C*H_2CH_3), 18.4 (Si*C*$(CH_3)_3$), 18.3* (Si*C*$(CH_3)_3$), 14.4 (OCH_2*C*H_3), 14.3* (OCH_2*C*H_3), 14.1 (CH_2CH_2*C*H_3), 13.7* (CH_2CH_2*C*H_3), -5.2 (2 x CH_3), -5.2* (2 x CH_3). **IR** (ATR): 2959 (C-H st), 2878 (C-H st), 1713 (C=O st), 1099 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 257 (M^+-C_3H_7, 2), 243 (M^+-^{t}Bu, 100), 197 (24), 169 (M^+-OTBS, 7), 131 (M^+-$C_{10}H_{17}O_2$, 1), 103 (21), 89 (27), 75 (54), 73 (39).



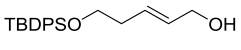
Ethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)propylidene)hex-5-enoate (SI4e). Following the *general procedure B*, **SI4d** (3.35 g, 10.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 9:1) in 30% yield as a yellow oil starting from **SI3** (6.74 g, 35.8 mmol), ethyl 2-(diethoxyphosphoryl)hex-5-enoate **10b** (19.90 g, 71.5 mmol), NaH (2.86 g, 71.5 mmol) and THF (200 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:0.6): 6.78 (t, *J* = 7.4 Hz, 1H, C*H*=C), 5.95* (t, *J* = 7.2 Hz, 1H, C*H*=C), 5.86-5.70 (m, 1H, CH_2CH_2*CH*=CH_2), 5.06-4.89 (m, 2H, CH_2CH_2CH=C*H*$_2$), 4.26-4.12 (m, 2H, OC*H*$_2CH_3$), 3.72-3.61 (m, 2H, SiOC*H*$_2CH_2$), 2.70-2.58 (m, 2H, SiOCH$_2$C*H*$_a$H$_b$), 2.44-2.29 (m, 3H, SiOCH$_2$CH$_a$*H*$_b$, CH$_2$C*H*$_2$CH=CH$_2$), 2.22-2.09 (m, 2H, C*H*$_2CH_2CH$=CH$_2$), 1.33-1.22 (m, 3H, OCH$_2$C*H*$_3$), 0.87 (s, 9H, 3 x CH_3), 0.04 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 167.9 (C=O), 167.7* (C=O), 139.3* (*C*H=C), 138.7 (*C*H=C), 138.1* (CH_2CH_2*C*H=CH_2), 138.0 (CH_2CH_2*C*H=CH_2), 133.3* (CH=*C*), 132.8 (CH=*C*), 115.0 (CH_2CH_2CH=*C*H$_2$), 115.0 (CH_2CH_2CH=*C*H$_2$), 62.6 (SiO*C*H_2CH_2), 62.1* (SiO*C*H_2CH_2), 60.4* (O*C*H_2CH_3), 60.2 (O*C*H_2CH_3), 34.2 (CH_2*C*H_2CH=CH_2), 33.5 (SiOCH$_2$*C*H_2), 33.4* (SiOCH$_2$*C*H_2), 33.3 (*C*H_2CH_2CH=CH_2), 32.4* (*C*H_2CH_2CH=CH_2), 26.0 (3 x CH_3), 18.4* (Si*C*$(CH_3)_3$), 18.4 (Si*C*$(CH_3)_3$), 14.4 (OCH_2*C*H_3), 14.4* (OCH_2*C*H_3), -5.2 (2 x CH_3), -5.2 (2 x CH_3). **IR** (ATR): 2926 (C-H st), 2861 (C-H st), 1716 (C=O st), 1095 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 257 (M^+-C_4H_7, 6), 255 (M^+-^{t}Bu, 100), 239 (M^+-$C_3H_5O_2$, 1), 197 (42), 181 (M^+-OTBS, 5), 131 (M^+-$C_{11}H_{17}$O2, 1), 103 (18), 89 (25), 75 (46), 73 (39).

2.1.3. Synthesis of 1a-e

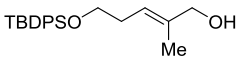


General procedure C: To a solution of the corresponding aldehyde **SI2a-c** (4.0 mmol, 1.0 eq) in MeOH (20 mL, 0.2 *M*) at 0ºC, $NaBH_4$ (4.4 mmol, 1.1 eq) was added portionwise and the reaction mixture was stirred at 0ºC for 5 minutes. Once the reaction was finished, it was quenched with H_2O (20 mL) and diluted with EtOAc (20 mL). HCl 1 *M* (20 mL) was added and the aqueous layer was

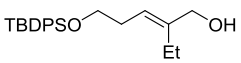
extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **1a-c**.



(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-2-en-1-ol (1a). Following the *general procedure C*, **1a** (1.40 g, 4.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 68% yield as a yellow oil starting from **SI2a** (2.00 g, 6.0 mmol), $NaBH_4$ (0.25 g, 6.6 mmol) and MeOH (30 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.76 (dt, *J* = 6.3, 1.7 Hz, 4H, C_{arom}-H), 7.40 (ddt, *J* = 8.7, 7.5, 4.6 Hz, 6H, C_{arom}-H), 5.72-5.62 (m, 2H, C*H*=C*H*), 4.07 (dd, *J* = 3.0, 1.7 Hz, 2H, CH_2OH), 3.71 (t, *J* = 6.6 Hz, 2H, SiOCH_2CH$_2$), 2.38-2.24 (m, 2H, SiOCH$_2$CH_2), 1.49-1.62 (br s, 1H, OH), 1.05 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 135.2 (C_{arom}-H), 133.5 (C_{arom}-Si), 130.9 (CH=*C*H), 129.3 (C_{arom}-H), 128.3 (*C*H=CH), 127.4 (C_{arom}-H), 63.4 (CH_2OH), 62.7 (SiO*C*H$_2$CH$_2$), 35.3 (SiOCH$_2$*C*H$_2$), 26.6 (3 x CH_3), 18.9 (Si*C*(CH$_3$)$_3$). **IR** (ATR): 3347 (O-H st), 1741 (C=C st), 1103 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 283 (M$^+$-^{t}Bu, 1), 265 (M$^+$-^{t}Bu-H_2O, 11), 229 (19), 199 (100), 181 (9), 129 (7), 105 (4), 78 (15), 51 (4).



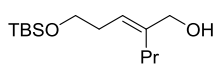
(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-methylpent-2-en-1-ol (1b). Following the *general procedure C,* **1b** (0.67 g, 1.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) in 85% yield as a yellow oil starting from **SI2b** (0.80 g, 2.2 mmol), $NaBH_4$ (0.92 g, 2.4 mmol) and MeOH (11 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.75-7.66 (m, 4H, C_{arom}-H), 7.42-7.35 (m, 6H, C_{arom}-H), 5.42 (tq, *J* = 7.3, 1.4 Hz, 1H, C*H*=C), 3.98 (s, 2H, CH_2OH), 3.72 (t, *J* = 6.9 Hz, 2H, SiOCH_2CH$_2$), 2.43-2.29 (m, 2H, SiOCH$_2$CH_2), 1.64 (s, 3H, CH_3), 1.61-1.55 (br s, 1H, OH), 1.10 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 136.7 (CH=*C*), 135.7 (C_{arom}-H), 134.1 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 122.2 (*C*H=C), 68.8 (CH_2OH), 63.6 (SiO*C*H$_2$CH$_2$), 31.3 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 19.3 (Si*C*(CH$_3$)$_3$), 13.8 (CH_3). **IR** (ATR): 3346 (O-H st), 2937 (C-H st), 1738 (C=C st) 1105 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 279 (M$^+$-^{t}Bu-H_2O, 6), 229 (18), 199 (100), 181 (11), 152 (3), 135 (6), 105 (5), 77 (9), 57 (7). **HRMS**: Calculated for [$C_{22}H_{30}O_2SiNa$]$^+$: 377.1913 [(M+Na)$^+$]; found: 377.1913.



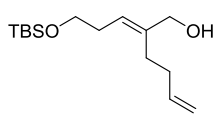
(*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-ethylpent-2-en-1-ol (1c). Following the *general procedure C*, **1c** (0.45 g, 1.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 77% yield as a yellow oil starting from **SI2c** (0.60 g, 1.6 mmol), $NaBH_4$ (0.65 g, 1.3 mmol) and MeOH (8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances, d.r.: 1:2.8): 7.74-7.63 (m, 4H, C_{arom}-H), 7.48-7.33 (m, 6H, C_{arom}-H), 5.34 (dt, *J* = 15.7, 6.7 Hz, 1H, C*H*=C), 4.08* (d, *J* = 13.8 Hz, 1H, CH_aH$_b$OH), 4.00 (d, *J* = 13.8 Hz, CH$_a$$H_b$OH), 3.73-3.60 (m, 2H, SiOCH_2CH$_2$), 2.36 (dq, *J* = 14.1, 7.0 Hz, 2H, SiOCH$_2$CH_2), 2.24-2.11* (m, 2H, CH_2CH$_3$), 2.06 (q, *J* = 7.6 Hz, CH_2CH$_3$), 1.06 (s, 9H, 3 x CH_3), 1.07* (s, 9H, 3 x CH_3), 0.95 (td, *J* = 7.5, 1.6 Hz, 3H, CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 143.3* (CH=*C*), 142.6 (CH=*C*), 135.7 (C_{arom}-H), 134.1 (C_{arom}-Si), 133.6* (C_{arom}-Si) 129.8* (C_{arom}-H), 129.7 (C_{arom}-H), 127.8* (C_{arom}-H), 127.7 (C_{arom}-H), 123.7* (*C*H=C), 122.1 (*C*H=C), 66.8 (CH_2OH), 63.9* (CH_2OH), 63.6 (SiO*C*H$_2$CH$_2$), 60.6* (SiO*C*H$_2$CH$_2$), 31.0 (SiOCH$_2$*C*H$_2$), 28.8* (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3),

26.9* (3 x CH_3), 21.2 (CH_2CH_3), 19.3 ($SiC(CH_3)_3$), 19.2* ($SiC(CH_3)_3$), 13.4 (CH_2CH_3), 12.9* (CH_2CH_3). **IR** (ATR): 3468 (O-H st), 2972 (C-H st) cm^{-1}. **MS** (EI) m/z (%): 311 (M^+- ^{t}Bu, 1), 293 (M^+-^{t}Bu-H_2O, 5), 229 (15), 199 (100), 18 (11), 78 (11), 57 (6). **HRMS**: Calculated for $[C_{23}H_{33}O_2Si]^+$: 369.2250 [$(M+H)^+$]; found: 369.2257.

General procedure D: To a solution of the corresponding ester **SI4d-e** (15.0 mmol, 1.0 eq) in toluene (75 mL, 0.2 *M*) at -78ºC, DIBAL-H (30.0 mmol, 2.0 eq) was added dropwise and the reaction mixture was stirred at that temperature for 1 minute. Once the reaction was finished, it was quenched with H_2O (20 mL) and a solution of NaOH 15% (20 mL) was added at -78ºC. The reaction mixture was stirred at room temperature for 1 hour, before filtering by celite®. It was extracted with CH_2Cl_2 (3 x 20 mL) and combined organic extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **1d-e**.



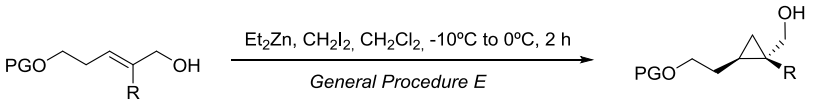
5-((*tert*-butyldimethylsilyl)oxy)-2-propylpent-2-en-1-ol (1d). Following the *general procedure D*, **1d** (4.95 g, 19.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 96% yield as a yellow oil starting from **SI4d** (6.00 g, 20.0 mmol), DIBAL-H (16.63 mL, 40.0 mmol), and toluene (100 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:0.9): 5.43 (t, *J* = 7.0 Hz, 1H, C*H*=C), 5.29* (t, *J* = 8.0 Hz, 1H, C*H*=C), 4.03 (d, *J* = 7.3 Hz, 2H, CH_2OH), 3.66-3.59 (m, 2H, $SiOCH_2CH_2$), 2.40-2.25 (m, 2H, $SiOCH_2CH_2$), 2.08 (t, *J* = 6.9 Hz, 2H, $CH_2CH_2CH_3$), 1.65 (s, 1H, OH), 1.52-1.23 (m, 5H, $CH_2CH_2CH_3$), 0.89 (s, 9H, 3 x CH_3), 0.06 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 142.4 (CH=*C*), 142.1* (CH=*C*), 125.0 (*C*H=C), 122.7* (*C*H=C), 67.1 ($SiOCH_2CH_2$), 63.2* ($SiOCH_2CH_2$), 62.5 (CH_2OH), 60.3* (CH_2OH), 38.8 ($CH_2CH_2CH_3$), 31.5 ($SiOCH_2CH_2$), 31.3* ($SiOCH_2CH_2$), 30.3* ($CH_2CH_2CH_3$), 27.1 (3 x CH_3), 21.9 ($CH_2CH_2CH_3$), 21.5* ($CH_2CH_2CH_3$), 18.8 ($SiC(CH_3)_3$), 18.5* ($SiC(CH_3)_3$), 14.3 ($CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_3$), -5.1 (2 x CH_3), -5.1 (2 x CH_3). **IR** (ATR): 3357 (O-H st), 2926 (C-H st), 2861 (C-H st), 1095 (Si-O) cm^{-1}. **MS** (EI) m/z (%): 201 (M^+-^{t}Bu, 3), 131 (M^+-$C_8H_{15}O$, 1), 127 (M^+-OTBS, 2), 109 (35), 105 (79), 75 (100), 73 (28), 67 (15).



2-(3-((*tert*-butyldimethylsilyl)oxy)propylidene)hex-5-en-1-ol (1e). Following the *general procedure D*, **1e** (1.60 g, 5.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 55% yield as a yellow oil starting from **SI4e** (3.35 g, 10.7 mmol), DIBAL-H (17.88 mL, 17.8 mmol), and toluene (54 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (*denotes minor diastereoisomer resonances; d.r.: 1:0.7): 5.85-5.69 (m, 1H, CH_2CH_2CH=CH_2), 5.40* (t, *J* = 7.3 Hz, 1H, CH=C), 5.26 (t, *J* = 8.0 Hz, 1H, CH=C), 5.06-4.83 (m, 2H, CH_2CH_2CH=CH_2), 3.99 (d, *J* = 7.6 Hz, 2H, CH_2OH), 3.64-3.55 (m, 2H, $SiOCH_2CH_2$), 2.83-2.60 (br s, 1H, OH), 2.35-2.20 (m, 2H, $SiOCH_2CH_2$), 2.20-2.05 (m, 4H, CH_2CH_2CH=CH_2), 0.85 (s, 9H, 3 x CH_3), 0.02 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 141.2* (CH=*C*), 140.2 (CH=*C*), 138.3 (CH_2CH_2CH=CH_2), 138.2* (CH_2CH_2CH=CH_2), 124.7 (*C*H=C), 122.5* (*C*H=C), 114.5* (CH_2CH_2CH=CH_2), 114.4 (CH_2CH_2CH=CH_2), 66.3 (CH_2OH), 62.9* ($SiOCH_2CH_2$), 62.4

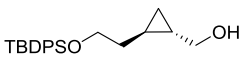
(SiO*C*$H_2$$CH_2$), 59.7 (*C*$H_2$OH), 35.4 (SiOCH$_2$*C*$H_2$), 32.7* (CH$_2$*C*$H_2$CH=$CH_2$), 32.4 (CH$_2$*C*$H_2$CH=$CH_2$), 31.3* (*C*$H_2$$CH_2$CH=$CH_2$), 31.0 (*C*$H_2$$CH_2$CH=$CH_2$), 27.5* (SiOCH$_2$*C*$H_2$), 25.9 (3 x CH_3), 25.8* (3 x CH_3), 18.4 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), -5.3 (2 x CH_3), -5.5 (2 x CH_3). **IR** (ATR): 3357 (O-H st), 2926 (C-H st), 2861 (C-H st), 1095 (Si-O) cm^{-1}. **MS** (EI) m/z (%): 213 (M$^+$-^{t}Bu, 1), 131 (M$^+$-$C_9H_{15}O$, 1), 121 (25), 105 (91), 93 (32), 89 (21), 79 (28), 75 (100), 73 (41).

2.1.4. Synthesis of SI5a-e

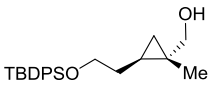


1a-e **SI5a-e**

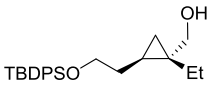
General procedure E: Et_2Zn (20.0 mmol, 2.0 eq) was added dropwise to a solution of **1a-e** (10.0 mmol, 1.0 eq) in dry CH_2Cl_2 (130 mL, 0.076 *M*) at -10ºC, followed by the addition of CH_2I_2 (20.0 mmol, 2.0 eq) in one portion under Ar and dark. The solution was then warmed to 0ºC and it was stirred at that temperature for 2 hours. Once the reaction was finished, it was quenched with saturated NH_4Cl solution (20 mL) and stirred for 10 minutes. HCl 1 *M* (20 mL) was then added to dissolve the resultant precipitate and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). Combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **SI5a-e**.



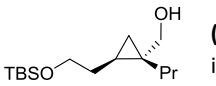
(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)methanol (SI5a). Following the *general procedure E*, **SI5a** (0.96 g, 2.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 90% yield as a yellow oil starting from **1a** (1.00 g, 2.9 mmol), Et_2Zn (6.00 mL, 6.0 mmol), CH_2I_2 (0.48 mL, 6.0 mmol) and CH_2Cl_2 (38 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.73-7.66 (m, 4H, C_{arom}-H), 7.49-7.34 (m, 6H, C_{arom}-H), 3.75 (t, *J* = 6.4 Hz, 2H, SiOC*H*$_2$CH$_2$), 3.43 (dd, *J* = 7.1, 2.9 Hz, 2H, C*H*$_2$OH), 1.62-1.38 (m, 3H, SiOCH$_2$C*H*$_2$, OH), 1.07 (s, 9H, 3 x CH_3), 0.94-0.81 (m, 1H, CHCH$_2$C*H*), 0.73 (dtdd, *J* = 8.4, 6.9, 5.2, 4.4 Hz, 1H, C*H*CH$_2$CH), 0.36 (ddt, *J* = 19.0, 8.1, 4.8 Hz, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 135.7 (C_{arom}-H), 134.1 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.8 (C_{arom}-H), 67.2 (CH_2OH), 64.1 (SiO*C*H$_2$CH$_2$), 36.6 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 21.0 (CHCH$_2$*C*H), 19.3 (Si*C*(CH$_3$)$_3$) 14.2 (*C*HCH$_2$CH), 9.8 (CH*C*H$_2$CH). **IR** (neat): 3370 (O-H st), 1106 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 297 (M$^+$-^{t}Bu, 1), 279 (M$^+$-^{t}Bu-H_2O, 9), 229 (14), 199 (100), 181 (10), 139 (6), 105 (6), 78 (20), 51 (6). **HRMS**: Calculated for [$C_{22}H_{30}O_2SiNa$]$^+$: 377.1913 [(M+H)$^+$]; found: 377.1919.



(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-methylcyclopropyl)methanol (SI5b). Following the *general procedure E*, **SI5b** (0.67 mg, 1.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 83% yield as a yellow oil starting from **1b** (0.67 g, 1.9 mmol), Et_2Zn (3.80 mL, 3.8 mmol), CH_2I_2 (0.31 mL, 3.8 mmol) and CH_2Cl_2 (25 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.86-7.71 (m, 4H, C_{arom}-H), 7.51-7.42 (m, 6H, C_{arom}-H), 3.82 (t, *J* = 6.7 Hz, 2H, SiOCH_2CH$_2$), 3.35 (d, *J* = 2.4 Hz, 2H, CH_2OH), 2.24-2.12 (br s, 1H, OH), 1.68 (dh, *J* = 27.7, 6.9 Hz, 2H, SiOCH$_2$CH_2), 1.16 (s, 9H, 3 x CH_3), 1.14 (s, 3H, CH_3), 0.75 (dt, *J* = 12.9, 6.3 Hz, 1H, C*H*CH$_2$C), 0.59 (dd, *J* = 8.8, 4.4 Hz, 1H, CHCH_aH$_b$C), 0.04 (t, *J* = 5.0 Hz, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 135.4 (C_{arom}-H), 133.8 (C_{arom}-Si), 129.4 (C_{arom}-H), 127.5 (C_{arom}-H), 71.9 (SiO*C*H$_2$CH$_2$), 64.1 (CH$_2$OH), 32.0 (SiOCH$_2$*C*H$_2$), 26.7 (3 x CH_3), 21.7 (CHCH$_2$*C*), 19.0 (Si*C*(CH$_3$)$_3$) 18.1 (CH_3), 16.3 (CH*C*H$_2$C), 15.3 (*C*HCH$_2$C). **IR** (ATR): 3386 (O-H st), 2937 (C-H st), 1105 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 311 (M$^+$-^{t}Bu, 2), 309 (41), 293 (M$^+$-^{t}Bu-H$_2$O, 8), 255 (M$^+$-C$_7$H$_{13}$O, 10), 231 (20), 199 (100), 183 (42), 139 (25), 105 (24), 91 (16), 78 (25), 57 (19). **HRMS**: Calculated for [C$_{23}$H$_{32}$O$_2$SiNa]$^+$: 391.2069 [(M+Na)$^+$]; found: 391.2071.

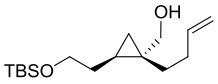


(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-ethylcyclopropyl)methanol (SI5c). Following the *general procedure E*, **SI5c** (0.48 g, 1.21 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 99% yield as a yellow oil starting from **1c** (0.45 g, 1.2 mmol), Et_2Zn (2.40 mL, 2.4 mmol), CH_2I_2 (0.19 mL, 2.4 mmol) and CH_2Cl_2 (16 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:2.8): 7.76-7.68 (m, 4H, C_{arom}-H), 7.48-7.36 (m, 6H, C_{arom}-H), 3.76 (t, *J* = 6.6 Hz, 2H, CH_2OH), 3.48-3.24 (m, 2H, SiOCH_2CH$_2$), 1.90* (tt, *J* = 15.4, 7.9 Hz, 2H, SiOCH$_2$CH_2), 1.82-1.64 (m, 2H, SiOCH$_2$CH_2), 1.59-1.26 (m, 2H, CH_2CH$_3$), 1.10* (s, 9H, 3 x CH_3), 1.09 (s, 9H, 3 x CH_3), 0.98 (td, *J* = 7.3, 2.5 Hz, 3H, CH$_2$CH_3), 0.72 (dtt, *J* = 22.7, 8.6, 5.6 Hz, 1H, C*H*CH$_2$C), 0.49 (dq, *J* = 7.3, 2.7 Hz, 1H, CHCH_aH$_b$C), 0.05* (t, *J* = 4.9 Hz, 1H, CHCH$_a$$H_b$C), -0.01 (t, *J* = 5.1 Hz, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 135.7* (C_{arom}-H), 135.6 (C_{arom}-H), 134.1 (C_{arom}-Si), 133.3* (C_{arom}-Si), 133.2 (C_{arom}-Si), 129.8 (C_{arom}-H), 129.7* (C_{arom}-H), 127.8 (C_{arom}-H), 127.7 (C_{arom}-H), 69.1 (CH$_2$OH), 65.3* (CH$_2$OH), 64.4 (SiO*C*H$_2$CH$_2$), 63.8* (SiO*C*H$_2$CH$_2$), 31.8 (SiOCH$_2$*C*H$_2$), 31.7* (SiOCH$_2$*C*H$_2$), 28.4 (*C*H$_2$CH$_3$), 28.1* (*C*H$_2$CH$_3$), 27.2 ((Si*C*(CH$_3$)$_3$), 27.0 (3 x CH_3), 26.9* (3 x CH_3), 21.7 (*C*HCH$_2$C), 19.3* (*C*HCH$_2$C), 19.1 (CHCH$_2$*C*), 15.7 (CH*C*H$_2$C), 15.0* (CH*C*H$_2$C), 11.2 (CH$_2$*C*H$_3$), 10.7* (CH$_2$*C*H$_3$). **IR** (neat): 3461 (O-H st), 2969 (C-H st), 1109 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 307 (M$^+$-^{t}Bu-H$_2$O, 12), 255 (M$^+$-C$_8$H$_{15}$O, 4), 200 (18), 199 (100), 183 (26), 181 (17), 135 (16), 127 (M$^+$-OTBDPS, 1), 109 (22), 107 (26), 91 (19), 79 (18), 78 (25), 77 (28), 67 (15).



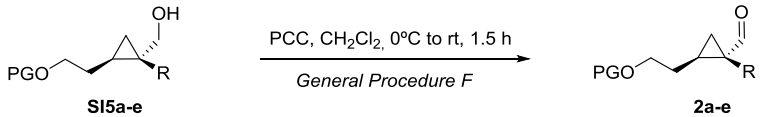
(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-propylcyclopropyl)methanol (SI5d). Following the *general procedure E*, **SI5d** (3.38 g, 11.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 62% yield as a colorless oil starting from **1d** (4.90 g, 19.2 mmol), Et_2Zn (31.90 mL, 47.9 mmol), CH_2I_2 (3.85 mL, 47.9 mmol) and CH_2Cl_2 (252 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances, d.r.: 1:1.3) (δ, ppm): 3.85-3.41 (m, 4H, CH_2OH, SiOCH_2CH$_2$), 3.24-3.10 (br s, 1H, OH), 1.95-1.17 (m, 9H, SiOCH$_2$CH_2, CH_2CH_2CH_3), 0.91 (s, 9H, 3 x CH_3), 0.88* (s, 9H, 3 x CH_3), 0.72-0.62* (m, 1H, C*H*CH$_2$C), 0.55-0.39 (m, 3H, C*H*CH$_2$C, CHCH_2C), 0.09 (s, 9H, 3 x CH_3), 0.04* (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 69.7 (CH$_2$OH), 64.9* (CH$_2$OH), 63.9 (SiO*C*H$_2$CH$_2$), 63.7*

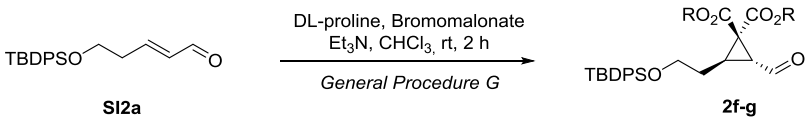
(SiO*C*H_2CH$_2$), 38.3 (*C*H_2CH$_2$CH$_3$), 31.9* (*C*H_2CH$_2$CH$_3$), 31.7 (SiOCH$_2$*C*H_2), 31.6 (SiOCH$_2$*C*H_2), 26.2 (3 x CH$_3$) 26.1* (3 x CH$_3$), 22.0 (*C*HCH$_2$C), 20.2 (CH$_2$*C*H$_2$CH$_3$), 19.7 (CH$_2$*C*H$_2$CH$_3$), 19.1* (*C*HCH$_2$C), 18.7 (Si*C*(CH$_3$)$_3$), 18.5* (Si*C*(CH$_3$)$_3$), 15.9 (CH*C*H$_2$C), 14.8* (CH*C*H$_2$C), 14.7 (CH$_2$CH$_2$*C*H$_3$), 14.5* (CH$_2$CH$_2$*C*H$_3$), -5.2 (2 x CH$_3$), -5.4* (2 x CH$_3$). **IR** (ATR): 3357 (O-H st), 2930 (C-H st), 2861 (C-H st), 1091 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 215 (M$^+$-^{t}Bu, 1), 131 (18), 141 (M$^+$-OTBS, 2), 131 (M$^+$-C$_9$H$_{17}$O, 18), 129 (21), 123 (24), 105 (58), 101 (34), 89 (19), 81 (69), 75 (100), 73 (38), 67 (27), 57 (18), 55 (17).



(1*S*,2*R*)-1-(but-3-en-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclopropyl)methanol (SI5e). Following the *general procedure E*, **SI5e** (1.00 g, 3.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 74% yield as a colorless oil starting from **1e** (1.28 g, 4.7 mmol), Et$_2$Zn (7.88 mL, 11.8 mmol), CH$_2$I$_2$ (0.95 mL, 11.8 mmol) and CH$_2$Cl$_2$ (62 mL). **^{1}H NMR** (300 MHz, CDCl$_3$) (δ, ppm) (* denotes minor diastereoisomer resonances) (d.r.: 1:0.8): 5.94-5.71 (m, 1H, CH$_2$CH$_2$C*H*=CH$_2$), 5.05-4.82 (m, 2H, CH$_2$CH$_2$CH=C*H*$_2$), 3.91-3.37 (m, 5H, SiOC*H*$_2$CH$_2$, C*H*$_2$O*H*), 2.29-1.23 (m, 7H, SiOCH$_2$C*H*$_2$, C*H*$_2$C*H*$_2$CH=CH$_2$, C*H*CH$_2$C), 0.91 (s, 9H, 3 x CH$_3$), 0.88* (s, 9H, 3 x CH$_3$), 0.57-0.42 (m, 2H, CHC*H*$_2$C), 0.09 (s, 6H, 2 x CH$_3$), 0.04* (s, 6H, 2 x CH$_3$). **^{13}C NMR** (75.4 MHz, CDCl$_3$) (δ, ppm): 139.4 (CH$_2$CH$_2$*C*H=CH$_2$), 139.2* (CH$_2$CH$_2$*C*H=CH$_2$), 114.4 (CH$_2$CH$_2$CH=*C*H$_2$), 114.2 (CH$_2$CH$_2$CH=*C*H$_2$), 69.7* (*C*H$_2$OH), 64.7 (*C*H$_2$OH), 63.8 (SiO*C*H$_2$CH$_2$), 63.6* (SiO*C*H$_2$CH$_2$), 35.6 (CH$_2$*C*H$_2$CH=CH$_2$), 31.9 (*C*H$_2$CH$_2$CH=CH$_2$), 31.6* (*C*H$_2$CH$_2$CH=CH$_2$), 31.4 (SiOCH$_2$*C*H$_2$), 31.1 (SiOCH$_2$*C*H$_2$), 28.9* (CH$_2$*C*H$_2$CH=CH$_2$), 27.1 (Si*C*(CH$_3$)$_3$), 26.2 (3 x CH$_3$), 26.1* (3 x CH$_3$), 22.3 (*C*HCH$_2$C), 19.4* (*C*HCH$_2$C), 18.8 (CHCH$_2$*C*), 18.5* (CHCH$_2$*C*), 16.0 (CH*C*H$_2$C), 14.9* (CH*C*H$_2$C), -5.1 (2 x CH$_3$), -5.1 (2 x CH$_3$). **IR** (ATR): 3357 (O-H st), 2930 (C-H st), 2861 (C-H st), 1091 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 203 (M$^+$-^{t}Bu-H$_2$O, 3), 153 (M$^+$-OTBS, 1), 131 (M$^+$-C$_{10}$H$_{17}$O, 17), 129 (22), 107 (20), 105 (55), 101 (32), 93 (44), 89 (20), 81 (20), 79 (27), 75 (100), 73 (40), 67 (22), 55 (M$^+$-C$_{12}$H$_{25}$O$_2$Si, 14).

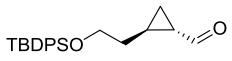
2.1.5. Synthesis of 2a-e, f-g



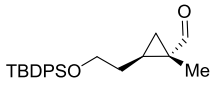


General procedure F: To a solution of the corresponding alcohol **SI5a-e** (8.0 mmol, 1.0 eq) and celite® (2g, g alcohol) in CH$_2$Cl$_2$ (80 mL, 0.1 *M*), PCC (16.0 mmol, 2.0 eq) was added at 0ºC. The solution was stirred at 0ºC for 30 minutes, warmed to room temperature and stirred at that

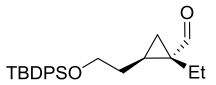
temperature for 1 hour. Once the reaction was finished, it was filtered and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **2a-e**.



2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropane-1-carbaldehyde (2a). Following the *general procedure F*, **2a** (0.87 mg, 2.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 87% yield as a yellow oil starting from **SI5a** (1.00 g, 2.8 mmol), PCC (1.20 g, 5.6 mmol), celite® (2.00 g) and CH_2Cl_2 (28 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.01 (d, *J* = 5.3 Hz, 1H, CHO), 7.75-7.59 (m, 4H, C_{arom}-H), 7.55-7.32 (m, 6H, C_{arom}-H), 3.74 (t, *J* = 5.8 Hz, 2H, SiOCH_2CH$_2$), 1.69-1.54 (m, 4H, SiOCH$_2$CH_2, CHCH$_2$CH), 1.29 (dd, *J* = 8.9, 4.6 Hz, 1H, CHCH_aH$_b$CH), 1.06 (s, 9H, 3 x CH_3), 0.92 (tdd, *J* = 7.2, 4.0, 1.9 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.0 (CHO), 135.7 (C_{arom}-H), 133.8 (C_{arom}-Si), 133.7 (C_{arom}-Si), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 63.3 (SiOCH$_2$CH$_2$), 35.7 (SiOCH$_2$$CH_2$), 30.2 (CHCH$_2$$C$H), 27.0 (3 x CH_3), 19.9 (CHCH$_2$CH), 19.3 (SiC(CH$_3$)$_3$), 14.7 (CHCH$_2$CH). **IR** (ATR): 1710 (C=O st), 1031 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 295 (M$^+$-^{t}Bu, 36), 265 (9), 237 (11), 217 (37), 199 (100), 181 (35), 161 (17), 139 (33), 105 (24), 78 (21), 51 (6).

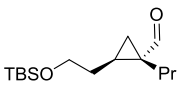


2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-methylcyclopropane-1-carbaldehyde (2b). Following the *general procedure F*, **2b** (0.50 g, 1.4 mmol) was isolated by FC (petroleum ether /EtOAc gradient from 9:1 to 7:3) in 75% yield as a yellow oil starting from **SI5b** (0.67 g, 1.8 mmol), PCC (0.78 g, 3.6 mmol), celite® (1.00 g) and CH_2Cl_2 (18 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.63 (s, 1H, CHO), 7.83-7.61 (m, 4H, C_{arom}-H), 7.48-7.38 (m, 6H, C_{arom}-H), 3.77 (t, *J* = 6.4 Hz, 2H, SiOCH_2CH$_2$), 1.81-1.63 (m, 2H, SiOCH$_2$CH_2), 1.49 (dq, *J* = 8.9, 6.9 Hz, 1H, CHCH$_2$CH), 1.36-1.27 (m, 1H, CHCH_aH$_b$C), 1.19 (s, 3H, CH_3), 1.09 (s, 9H, 3 x CH_3), 0.64 (dd, *J* = 6.7, 4.7 Hz, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.6 (CHO), 135.5 (C_{arom}-H), 133.8 (C_{arom}-Si), 133.7 (C_{arom}-Si), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 63.5 (SiOCH$_2$CH$_2$), 31.6 (CHCH$_2$$C$), 31.4 (SiOCH$_2$$CH_2$), 26.9 (3 x CH_3), 21.9 (CHCH$_2$C), 19.8 (CHCH$_2$C), 19.3 (SiC(CH$_3$)$_3$), 11.2 (CH_3). **IR** (ATR): 2934 (C-H st), 1701 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 309 (M$^+$-^{t}Bu, 41), 255 (M$^+$-$C_7H_{11}O$, 1), 231 (20), 199 (100), 183 (42), 161 (11), 139 (25), 123 (12), 111 (M$^+$-OTBDPS, 1), 105 (24), 91 (16), 78 (25). **HRMS**: Calculated for $[C_{23}H_{34}NO_2Si]^+$: 384.2359 $[(M+NH_4)^+]$; found: 384.2363.

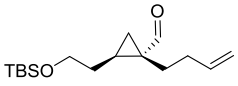


2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-ethylcyclopropane-1-carbaldehyde (2c). Following the *general procedure F*, **2c** (0.40 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 83% yield as a yellow oil starting from **SI5c** (0.50 g, 1.3 mmol), PCC (0.60 g, 2.5 mmol), celite® (0.80 g) and CH_2Cl_2 (13 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances, d.r.: 1:2): 9.19* (s, 1H, CHO), 8.70 (s, 1H, CHO), 7.75-7.67 (m, 4H, C_{arom}-H), 7.48-7.36 (m, 6H, C_{arom}-H), 3.73 (dt, *J* = 17.0, 6.3 Hz, 2H, SiOCH_2CH$_2$), 1.88-1.15 (m, 6H, CH_2CH$_3$, CHCH_aH$_b$C, CHCH$_2$C, SiOCH$_2$CH_2), 1.08 (s, 9H, 3 x CH_3), 0.98 (td, *J* = 7.4, 3.8 Hz, 3H, CH$_2$CH_3), 0.62 (dd, *J* = 6.8, 4.7 Hz, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.9* (CHO), 202.6 (CHO), 135.7 (C_{arom}-H), 133.9 (C_{arom}-Si), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 63.9* (SiOCH$_2$CH$_2$), 63.7

($SiOCH_2CH_2$), 37.3* ($CHCH_2C$), 37.1 ($CHCH_2C$), 37.3* ($SiC(CH_3)_3$), 37.1 ($SiC(CH_3)_3$), 31.5 ($SiOCH_2CH_2$), 31.3* ($SiOCH_2CH_2$), 27.0 (3 x CH_3), 23.0 ($CHCH_2C$), 19.4* (CH_2CH_3), 19.3 (CH_2CH_3), 18.4 ($CHCH_2C$), 12.1 (CH_2CH_3), 11.7* (CH_2CH_3). **IR** (ATR): 2969 (C-H st), 1741 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 323 (M^+-^{t}Bu, 14), 245 (15), 200 (19), 199 (100), 183 (26), 139 (16). **HRMS**: Calculated for $[C_{24}H_{32}O_2SiNa]^+$: 403.2069 [$(M+Na)^+$]; found: 403.2069.

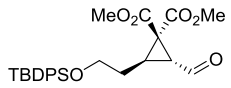


2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-propylcyclopropane-1-carbaldehyde (2d). Following the *general procedure F*, **2d** (1.95 g, 6.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) in 63% yield as a brown oil starting from **SI5d** (3.00 g, 10.9 mmol), PCC (4.72 g, 21.9 mmol), celite® (6.00 g) and CH_2Cl_2 (110 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances; d.r.: 1:1.05) (δ, ppm): 9.23* (s, 1H, CHO), 9.72 (s, 1H, CHO), 3.66 (t, *J* = 6.5 Hz, 2H, $SiOCH_2CH_2$), 3.59* (t, *J* = 6.2 Hz, 2H, $SiOCH_2CH_2$), 1.87-1.02 (m, 9H, $SiOCH_2CH_2$, $CH_2CH_2CH_3$), 0.92-0.84 (m, 11H, 3 x CH_3, $CHCH_2C$), 0.70-0.61 (m, 1H, $CHCH_2C$), 0.02 (s, 9H, 3 x CH_3), 0.01 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.7* (CHO), 202.6 (CHO), 63.0* ($SiOCH_2CH_2$), 62.8 ($SiOCH_2CH_2$), 36.1* ($CHCH_2C$), 35.9 ($CHCH_2C$), 35.4* ($CH_2CH_2CH_3$), 31.8 ($SiOCH_2CH_2$), 31.4* ($SiOCH_2CH_2$), 28.5 ($CH_2CH_2CH_3$), 28.1 ($CHCH_2C$), 26.0 (3 x CH_3), 23.0* (3 x CH_3), 21.7* ($CHCH_2C$), 20.8 ($CH_2CH_2CH_3$), 20.6* ($CH_2CH_2CH_3$), 18.6 ($CHCH_2C$), 18.4 ($SiC(CH_3)_3$), 14.5 ($CH_2CH_2CH_3$), 14.3* ($CH_2CH_2CH_3$), -5.2 (2 x CH_3), -5.3 (2 x CH_3). **IR** (ATR): 2959 (C-H st), 2857 (C-H st), 1724 (C=O st), 1092 (Si-O st) cm^{-1}. **MS** (IE) m/z: 213 (M^+-^{t}Bu, 31), 139 (M^+-OTBS, 3), 131 (M^+-$C_9H_{15}O$, 7), 101 (17), 89 (20), 79 (17), 75 (100), 73 (42), 59 (17).

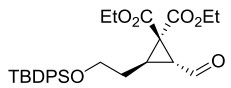


1-(but-3-en-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclopropane-1-carbaldehyde (2e). Following the *general procedure F*, **2e** (0.50 g, 1.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) in 50% yield as a brown oil starting from **SI5e** (1.00 g, 3.5 mmol), PCC (1.50 g, 7.0 mmol), celite® (2.00 g) and CH_2Cl_2 (35 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances) (d.r.: 1:0.8): 9.18 (s, 1H, CHO), 8.66* (s, 1H, CHO), 5.76 (ddq, *J* = 16.8, 10.2, 6.6 Hz, 1H, $CH_2CH_2CH{=}CH_2$), 5.05-4.78 (m, 2H, $CH_2CH_2CH{=}CH_2$), 3.62 (dt, *J* = 18.4, 6.1 Hz, 2H, $SiOCH_2CH_2$), 2.20-2.05 (m, 2H, $SiOCH_2CH_2$), 1.80-1.47 (m, 4H, $CH_2CH_2CH{=}CH_2$), 1.08-1.00 (m, 1H, $CHCH_2C$), 0.85* (s, 9H, 3 x CH_3), 0.84 (s, 9H, 3 x CH_3), 0.72-0.54 (m, 1H, $CHCH_aH_bC$), 0.38-0.31 (m, 1H, $CHCH_aH_bC$), 0.01* (s, 6H, 2 x CH_3), 0.00 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.3 (CHO), 202.1* (CHO), 138.3* ($CH_2CH_2CH{=}CH_2$), 138.2 ($CH_2CH_2CH{=}CH_2$), 114.8 ($CH_2CH_2CH{=}CH_2$), 62.9 ($SiOCH_2CH_2$), 62.7* ($SiOCH_2CH_2$), 35.7* ($CHCH_2C$), 35.6 ($CHCH_2C$), 31.9* ($SiOCH_2CH_2$), 31.7 ($SiOCH_2CH_2$), 28.1 ($SiC(CH_3)_3$), 26.0 (3 x CH_3), 20.7 ($CH_2CH_2CH{=}CH_2$), 20.6* ($CH_2CH_2CH{=}CH_2$), 18.4* ($CH_2CH_2CH{=}CH_2$), 18.3 ($CH_2CH_2CH{=}CH_2$), 11.1 ($CHCH_2C$), 10.9 ($CHCH_2C$), 4.6 ($CHCH_2C$), 4.5 ($CHCH_2C$), -5.3 (2 x CH_3), -5.3 (2 x CH_3). **IR** (ATR): 2959 (C-H st), 2857 (C-H st), 1724 (C=O st), 1092 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 225 (M^+-^{t}Bu, 31), 87 (16), 85 (94), 83 (100), 73 (26), 55 (19).

General procedure for G: A mixture of aldehyde **SI2a** (5.0 mmol, 1.0 eq), the corresponding dialkyl bromomalonate (6.0 mmol, 1.2 eq), triethylamine (5.0 mmol, 1.0 eq) and (±)-Pyrrolidine-2-carboxylic acid (1.0 mmol, 0.2 eq) in $CHCl_3$ (20 mL, 0.25 *M*) was stirred at room temperature for 2 hours. Once the reaction was finished, the solvent was removed and the crude was then purified by flash column chromatography to afford pure **2f-g**.

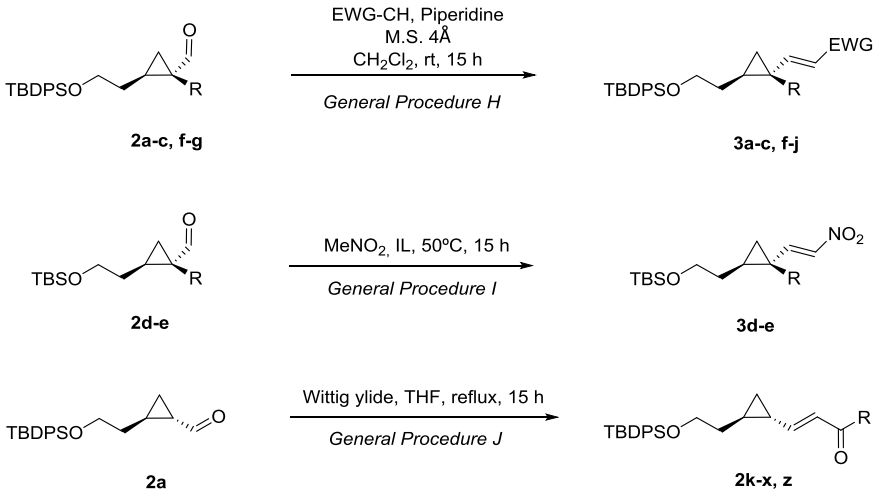


Dimethyl 2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-formylcyclopropane-1,1-dicarboxylate (2f). Following the *general procedure G*, **2f** (3.36 g, 7.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 88% yield as a orange oil starting from **SI2a** (2.75 g, 8.1 mmol), dimethylbromomalonate (1.30 mL, 9.8 mmol), Et_3N (1.10 mL, 8.1 mmol), (±)-Pyrrolidine-2-carboxylic acid (0.19 g, 1.6 mmol) and $CHCl_3$ (32 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances; d.r.: 1:4) (δ, ppm): 9.46-9.41* (m, 1H, CHO), 9.31-9.25 (m, 1H, CHO), 7.67-7.62 (m, 4H, C_{arom}-H), 7.43-7.30 (m, 6H, C_{arom}-H), 3.80 (s, 6H, 2 x OCH_3), 3.69-3.65 (m, 2H, $SiOCH_2CH_2$), 2.80-2.65 (m, 2H, $SiOCH_2CH_2$), 1.88-1.76 (m, 1H, CHCC*H*), 1.76-1.62 (m, 1H, C*H*CCH), 1.04 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 196.4 (CHO), 195.9* (CHO), 166.7 (C=O), 166.4 (C=O), 135.5 (C_{arom}-H), 135.5* (C_{arom}-H), 133.3 (C_{arom}-Si), 133.3* (C_{arom}-Si), 129.7 (C_{arom}-H), 129.7* (C_{arom}-H), 127.7 (C_{arom}-H), 127.7* (C_{arom}-H), 62.8* ($SiOCH_2CH_2$), 62.3 ($SiOCH_2CH_2$), 53.9 (OCH_3), 53.0* (OCH_3), 42.4 ($SiC(CH_3)_3$), 41.6 (CHCCH), 40.0 (*C*HCCH), 29.7 ($SiOCH_2CH_2$), 26.7 (3 x CH_3), 19.1 (CH*C*CH). **IR** (ATR): 2955 (C-H st), 1738 (C=O st), 1105 (Si-O st) cm^{-1}.

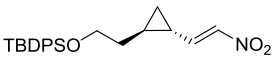


Diethyl 2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-formylcyclopropane-1,1-dicarboxylate (2g). Following the *general procedure G*, **2g** (0.14 g, 0.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 37% yield as a yellow oil starting from **SI2a** (0.24 g, 0.7 mmol), diethylbromomalonate (0.16 mL, 0.9 mmol), Et_3N (0.10 mL, 0.7 mmol), (±)-Pyrrolidine-2-carboxylic acid (0.02 g, 0.1 mmol) and $CHCl_3$ (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances; d.r.: 1:6) (δ, ppm): 9.44* (d, *J* = 4.9 Hz, 1H, CHO), 9.26 (d, *J* = 4.6 Hz, 1H, CHO), 7.69-7.63 (m, 4H, C_{arom}-H), 7.47-7.33 (m, 6H, C_{arom}-H), 4.34-4.07 (m, 4H, OCH_2CH_3), 3.78-3.66 (m, 2H, $SiOCH_2CH_2$), 2.80-2.68 (m, 2H, $SiOCH_2CH_2$), 1.90-1.79 (m, 1H, C*H*CCH), 1.74-1.61 (m, 1H, CHCC*H*), 1.35-1.18 (m, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 196.7 (CHO), 166.4 (C=O), 166.1 (C=O), 135.6 (C_{arom}-H), 135.6* (C_{arom}-H), 133.5 (C_{arom}-Si), 133.5* (C_{arom}-Si), 129.8 (C_{arom}-H), 129.8* (C_{arom}-H), 127.8 (C_{arom}-H), 127.8* (C_{arom}-H), 62.5 ($SiOCH_2CH_2$), 62.3 (OCH_2CH_3), 42.6 (CH*C*CH), 40.2 (CHCCH), 29.9 ($SiOCH_2CH_2$), 29.6 (*C*HCCH), 26.9 (3 x CH_3), 19.2 ($SiC(CH_3)_3$), 14.2 (OCH_2CH_3), 14.1* (OCH_2CH_3). **IR** (ATR): 2934 (C-H st), 2861 (C-H st), 1726 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 440 (32), 439 (100), 255 (M^+-$C_{12}H_{18}O_5$, 3), 241 (M^+-OTBDPS, 1), 227 (32), 200 (18), 199 (95), 197 (26), 183 (38), 181 (20), 139 (20), 135 (27).

2.1.6. Synthesis of 3a-z

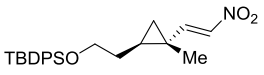


General procedure H: To a solution of the corresponding aldehyde **2a-c, f-g** (4.0 mmol, 1.0 eq) in CH_2Cl_2 (10 mL, 0.4 *M*) under argon at room temperature, 4 Å molecular sieves, the active hydrogen compound (4.0 mmol, 1.0 eq) and piperidine (2.4 mmol, 0.6 eq) were added and the reaction mixture was stirred at that temperature for 15 hours. Once the reaction was finished, it was filtered by celite® and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **3a-c, f-j**.

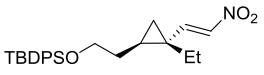


***trans*-(*E*)-tert-butyl(2-(2-(2-nitrovinyl)cyclopropyl)ethoxy)diphenylsilane (3a).** Following the *general procedure H*, **3a** (1.50 g, 3.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 49:1 to 8:2) in 65% yield as a yellow oil starting from **2a** (2.00 g, 5.8 mmol), nitromethane (0.34 mL, 6.3 mmol), piperidine (0.35 mL, 3.5 mmol), M.S. and CH_2Cl_2 (14 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.69-7.61 (m, 4H, C_{arom}-H), 7.49-7.33 (m, 6H, C_{arom}-H), 7.02 (d, *J* = 13.2 Hz, 1H, CH=C*H*), 6.80 (dd, *J* = 13.2, 10.5 Hz, 1H, C*H*=CH), 3.73 (t, *J* = 6.1 Hz, 2H, SiOCH_2CH$_2$), 1.71-1.50 (m, 2H, SiOCH$_2$CH_2), 1.41-1.22 (m, 2H, C*H*CH$_2$C*H*), 1.06 (s, 9H, 3 x CH_3), 0.95 (dd, *J* = 8.0, 5.7 Hz, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 148.2 (CH=*C*H), 136.9 (*C*H=CH), 135.5 (C_{arom}-H), 133.6 (C_{arom}-Si), 133.5 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 63.1 (SiO*C*H$_2$CH$_2$), 36.2 (SiOCH$_2$*C*H$_2$), 26.8 (3 x CH_3), 21.7 (CHCH$_2$*C*H), 19.1 (Si*C*(CH$_3$)$_3$), 18.7 (*C*HCH$_2$CH), 16.6 (CH*C*H$_2$CH). **IR** (ATR): 1637 (C=C st), 1512 (NO_2 st as), 1339 (NO_2 st sim), 1110 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 338 (M$^+$-^{t}Bu, 18), 308 (8), 199 (100), 181 (20), 155 (6), 141 (M$^+$-OTBDPS, 1), 139 (14),

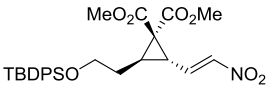
135 (19), 105 (13), 77 (13), 51 (5). **HRMS**: Calculated for $[C_{23}H_{30}NO_3Si]^+$: 396.1995 $[(M+H)^+]$; found: 396.1993.



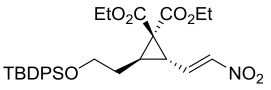
(*E*)-*tert*-butyl(2-(2-methyl-2-(2-nitrovinyl)cyclopropyl)ethoxy)diphenylsilane (3b). Following the *general procedure H*, **3b** (0.60 g, 1.3 mmol) was isolated by FC (pentane/Et_2O gradient from 49:1 to 8:2) in 35% yield as a yellow oil starting from **2b** (1.40 g, 3.7 mmol), nitromethane (0.22 mL, 4.1 mmol), piperidine (0.23 mL, 2.2 mmol), M.S. and CH_2Cl_2 (10 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.73-7.69 (m, 4H, C_{arom}-H), 7.50-7.36 (m, 6H, C_{arom}-H), 6.97 (d, *J* = 13.3 Hz, 1H, CH=C*H*), 6.86 (d, *J* = 13.3 Hz, 1H, C*H*=CH), 3.78 (t, *J* = 6.4 Hz, 2H, SiOCH_2CH$_2$), 1.76 (qd, *J* = 6.7, 3.3 Hz, 2H, SiOCH$_2$CH_2), 1.40-1.28 (m, 2H, CHCH_aH$_b$C, C*H*CH$_2$C), 1.18 (s, 3H, CH_3), 1.11 (s, 9H, 3 x CH_3), 0.71 (dd, *J* = 6.7, 4.8 Hz, 1H, CHCH$_a$*H*$_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 153.7 (CH=C*H*), 136.1 (C*H*=CH), 135.6 (C_{arom}-H), 133.7 (C_{arom}-Si), 133.6 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 63.4 (SiO*C*H$_2$CH$_2$), 31.9 (SiOCH$_2$*C*H$_2$), 26.9 (3 x CH_3), 26.2 (*C*HCH$_2$C), 23.6 (CH*C*H$_2$C), 20.7 (Si*C*(CH$_3$)$_3$), 19.2 (CHCH$_2$*C*), 15.1 (CH_3). **IR** (ATR): 2940 (C-H st), 1634 (C=C st), 1428 (NO_2 st as), 1339 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 352 (M^+-^{t}Bu, 6), 255 (M^+-$C_8H_{13}NO_2$, 18), 200 (19), 199 (100), 197 (36), 183 (17), 155 (M^+-OTBPS, 6), 139 (15), 135 (29), 91 (16), 77 (15). **HRMS**: Calculated for $[C_{24}H_{32}NO_3Si]^+$: 410.2151 $[(M+H)^+]$; found: 410.2148.



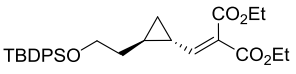
(*E*)-*tert*-butyl(2-(2-ethyl-2-(2-nitrovinyl)cyclopropyl)ethoxy)diphenylsilane (3c). Following the *general procedure H*, **3c** (0.10 g, 0.2 mmol) was isolated by FC (pentane/Et_2O gradient from 49:1 to 7:3) in 23% yield as a yellow oil starting from **2c** (0.40 g, 1.0 mmol), nitromethane (0.11 mL, 2.1 mmol), piperidine (0.06 mL, 0.6 mmol), M.S. and CH_2Cl_2 (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.73-7.60 (m, 4H, C_{arom}-H), 7.49-7.34 (m, 6H, C_{arom}-H), 6.90 (s, 2H, C*H*=C*H*), 3.74 (t, *J* = 5.8 Hz, 2H, SiOCH_2CH$_2$), 1.90-1.79 (m, 1H, OSiCH$_2$CH_2), 1.71-1.20 (m, 5H, SiOCH$_2$CH_2, C*H*CH$_2$C, CHCH_aH$_b$C, CH_2CH$_3$), 1.07 (s, 9H, 3 x CH_3), 0.97 (t, *J* = 7.1 Hz, 3H, CH$_2$CH_3), 0.63 (dd, *J* = 6.8, 4.7 Hz, 1H, CHCH$_a$*H*$_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 152.1 (CH=C*H*), 136.5 (C*H*=CH), 135.7 (C_{arom}-H), 133.8 (C_{arom}-Si), 133.7 (C_{arom}-Si), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 63.6 (SiO*C*H$_2$CH$_2$), 32.0 (SiOCH$_2$*C*H$_2$), 27.7 (*C*HCH$_2$C), 27.0 (3 x CH_3), 26.4 (Si*C*(CH$_3$)$_3$), 22.8 (*C*H$_2$CH$_3$), 22.7 (CH*C*H$_2$C), 19.3 (CHCH$_2$*C*), 11.5 (CH$_2$*C*H$_3$). **IR** (ATR): 2926 (C-H st), 2857 (C-H st), 1738 (C=C st), 1515 (NO_2 st as), 1347 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 296 (27), 295 (100), 225 (24), 217 (55), 199 (76), 197 (20), 187 (21), 183 (59), 181 (28), 175 (16), 135 (18), 105 (15).



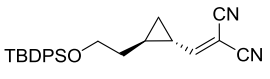
Dimethyl (*E*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-(2-nitrovinyl)cyclopropane-1,1-dicarboxylate (3f). Following the *general procedure H*, **3f** (0.68 g, 1.3 mmol) was obtained and it was used in the next step without further purification.



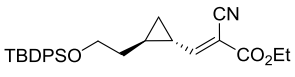
Diethyl (*E*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-(2-nitrovinyl)cyclopropane-1,1-dicarboxylate (3g). Following the *general procedure H*, **3g** (0.68 g, 1.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 69% yield as a yellow oil starting from **2g** (0.91 g, 1.8 mmol), nitromethane (0.2 mL, 3.6 mmol), piperidine (0.2 mL, 1.8 mmol), M.S. and CH_2Cl_2 (5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.66-7.62 (m, 4H, C_{arom}-H), 7.46-7.32 (m, 6H, C_{arom}-H), 7.11 (d, *J* = 13.3 Hz, 1H, CH=C*H*), 6.94 (dd, *J* = 13.3, 10.0 Hz, 1H, C*H*=CH), 4.37-4.06 (m, 4H, OC*H*$_2$CH$_3$), 3.73 (t, *J* = 6.1 Hz, 2H, SiOC*H*$_2$CH$_2$), 2.69 (app t, *J* = 5.3 Hz, 1H, CHCC*H*), 2.59-2.43 (m, 1H, C*H*CCH), 1.88-1.77 (m, 1H, SiOCH$_2$C*H*$_a$H$_b$), 1.67-1.54 (m, 1H, SiOCH$_2$CH$_a$*H*$_b$), 1.32-1.18 (m, 6H, OCH$_2$C*H*$_3$), 1.06 (s, 9H, 3 x CH$_3$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances) (δ, ppm): 166.8 (C=O), 166.5 (C=O), 140.9 (CH=*C*H), 138.5 (*C*H=CH), 135.5 (C_{arom}-H), 133.3* (C_{arom}-Si), 133.2 (C_{arom}-Si), 129.8* (C_{arom}-H), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 62.2 (O*C*H$_2$CH$_3$), 62.1* (O*C*H$_2$CH$_3$), 61.4 (SiO*C*H$_2$CH$_2$), 61.1* (SiO*C*H$_2$CH$_2$), 51.5* (SiOCH$_2$*C*H$_2$), 42.5 (CH*C*CH), 31.5 (CHC*C*H), 30.7 (SiOCH$_2$*C*H$_2$), 30.4 (*C*HCCH), 26.8 (3 x CH$_3$), 19.1 (Si*C*(CH$_3$)$_3$), 14.0 (OCH$_2$*C*H$_3$). **IR** (ATR): 3012 (C-H st), 1726 (C=C st), 1526 (NO_2 st as), 1390 (NO_2 st sim), 1105 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 483 (25), 482 (79), 284 (M$^+$-OTBDPS, 2), 255 (M$^+$-$C_{13}H_{19}NO_6$, 2), 227 (37), 207 (30), 200 (17), 199 (100), 197 (31), 183 (39), 181 (19), 139 (17), 135 (36), 105 (22), 91 (15), 78 (15), 77 (21).



Diethyl 2-((2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)methylene)malonate (3h). Following the *general procedure H*, **3h** (0.96 mg, 5.7 mmol) was isolated by FC (*pentane*/Et$_2$O gradient from 19:1 to 8:2) in 60% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), diethyl malonate (0.24 mL, 1.4 mmol), piperidine (0.09 mL, 0.9 mmol), M.S. and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (coelutes with diethyl malonate in a ratio 2:1): 7.55-7.51 (m, 4H, C_{arom}-H), 7.31-7.20 (m, 6H, C_{arom}-H), 6.27 (d, *J* = 11.3 Hz, 1H, C*H*=C), 4.20-4.02 (m, 6H, OC*H*$_2$CH$_3$, C*H*$_2$CH$_3$CO$_2$CH$_2$CO$_2$C*H*$_2$CH$_3$), 3.60 (t, *J* = 6.3 Hz, 2H, SiOC*H*$_2$CH$_2$), 3.23 (s, 1H, CH$_2$CH$_3$CO$_2$C*H*$_2$CO$_2$CH$_2$CH$_3$), 1.66-1.47 (m, 2H, SiOCH$_2$C*H*$_2$), 1.38 (dt, *J* = 13.8, 6.8 Hz, 1H, C*H*CH$_2$CH), 1.18-1.12 (m, 10H, OCH$_2$C*H*$_3$, CHCH$_2$C*H*, CH$_2$C*H*$_3$CO$_2$CH$_2$CO$_2$CH$_2$C*H*$_3$), 0.91 (s, 9H, 3 x CH$_3$), 0.79 (t, *J* = 6.8 Hz, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 166.7 (CH$_2$CH$_3$*C*O$_2$CH$_2$*C*O$_2$CH$_2$CH$_3$), 165.8 (C=O), 164.5 (*C*H=C), 155.7 (*C*H=C), 135.6 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 125.1 (CH=*C*), 63.3 (SiO*C*H$_2$CH$_2$), 61.6 (*C*H$_2$CH$_3$CO$_2$CH$_2$CO$_2$*C*H$_2$CH$_3$), 61.1 (O*C*H$_2$CH$_3$), 41.7 (CH$_2$CH$_3$CO$_2$*C*H$_2$CO$_2$CH$_2$CH$_3$), 36.4 (SiOCH$_2$*C*H$_2$), 26.9 (3 x CH$_3$), 21.5 (*C*HCH$_2$CH), 20.5 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 17.1 (CH*C*H$_2$CH), 14.2 (OCH$_2$*C*H$_3$), 14.0 (OCH$_2$*C*H$_3$). **IR** (ATR): 2972 (C-H st), 1734 (C=C st), 1724 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 438 (34), 437 (M$^+$-^{t}Bu, 100), 255 (M$^+$-$C_{11}H_{15}NO_2$, 1), 227 (24), 199 (59), 197 (24), 193 (M$^+$-OTBDPS, 1), 183 (28), 181 (19), 147 (15), 135 (35). **HRMS**: Calculated for [$C_{15}H_{20}NO_4$]$^+$: 495.2567 [(M+H)$^+$]; found: 495.2577.



2-((2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)methylene)malononitrile (3i). Following the *general procedure H*, **3i** (0.28 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 32% yield as a yellow oil starting from **2a** (0.77 g, 2.2 mmol), malononitrile (0.16 g, 2.4 mmol), piperidine (0.13 mL, 1.3 mmol), M.S. and CH_2Cl_2 (5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.72-7.59 (m, 4H, C_{arom}-H), 7.50-7.36 (m, 6H, C_{arom}-H), 6.60 (d, *J* = 11.3 Hz, 1H, CH=C), 3.81.3.71 (m, 2H, SiOCH_2CH$_2$), 1.88 (ddt, *J* = 11.5, 7.9, 3.9 Hz, 1H, C*H*CH$_2$CH), 1.73-1.52 (m, 3H, SiOCH$_2$CH_2, CHCH$_2$C*H*), 1.34-1.25 (m, 1H, CHCH_aH$_b$CH), 1.21 (dt, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$$H_b$CH), 1.07 (s, 9H, 3 x CH$_3$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 173.2 (*C*H=C), 135.6 (C_{arom}-H), 133.6 (C_{arom}-Si), 133.5 (C_{arom}-Si), 129.9 (C_{arom}-H), 127.9 (C_{arom}-H), 112.8 (CN), 111.7 (CN), 84.4 (CH=*C*), 62.9 (SiO*C*H$_2$CH$_2$), 36.0 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH$_3$), 25.2 (*C*HCH$_2$CH), 24.6 (CHCH$_2$*C*H), 19.9 (CH*C*H$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$). **IR** (ATR): 2233 (C-N st), 1591 (C=C st), 1103 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 343 (M$^+$-^{t}Bu, 100), 313 (23), 199 (37), 181 (23), 146 (M$^+$-OTBDPS, 1), 135 (18), 105 (13), 91 (8), 77 (12). **HRMS**: Calculated for [$C_{25}H_{28}N_2OSiNa$]$^+$: 423.1869 [(M+Na)$^+$]; found: 423.1862.

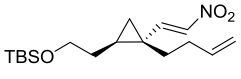


Ethyl (*Z*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-2-cyanoacrylate (3j). Following the *general procedure H*, **3j** (1.00 g, 2.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 78% yield as a yellow oil starting from **2a** (1.00 g, 2.8 mmol), ethyl cyanoacetate (0.33 mL, 3.1 mmol), piperidine (0.17 mL, 1.7 mmol), M.S. and CH_2Cl_2 (7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.76-7.69 (m, 4H, C_{arom}-H), 7.47-7.38 (m, 6H, C_{arom}-H), 7.08 (d, *J* = 11.4 Hz, 1H, CH=C), 4.30 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.79 (t, *J* = 6.0 Hz, 2H, SiOCH_2CH$_2$), 1.90 (ddt, *J* = 11.6, 8.0, 4.2 Hz, 1H, C*H*CH$_2$CH), 1.67 (q, *J* = 6.3 Hz, 2H, SiOCH$_2$CH_2), 1.56 (dt, *J* = 13.6, 4.7 Hz, 1H, CHCH$_2$C*H*), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.19-1.15 (m, 2H, CHCH_2CH), 1.11 (s, 9H, 3 x CH$_3$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 167.7 (*C*H=C), 161.5 (C=O), 135.3 (C_{arom}-H), 133.4 (C_{arom}-Si), 133.3 (C_{arom}-Si), 129.6 (C_{arom}-H), 127.5 (C_{arom}-H), 114.4 (CN), 105.0 (CH=*C*), 62.9 (SiO*C*H$_2$CH$_2$), 61.8 (O*C*H$_2$CH$_3$), 35.9 (SiOCH$_2$*C*H$_2$), 26.7 (3 x CH$_3$), 23.5 (*C*HCH$_2$), 23.4 (CH$_2$*C*HCH=C), 19.2 (Si*C*(CH$_3$)$_3$), 18.7 (CH*C*H$_2$CH), 14.2 (OCH$_2$*C*H$_3$). **IR** (ATR): 2930 (C-H st), 2226 (C-N st), 1726 (C=C st), 1612 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 391 (31), 390 (M$^+$-^{t}Bu, 100), 255 (M$^+$-$C_{11}H_{15}NO_2$, 1), 199 (45), 197 (19), 193 (M$^+$-OTBDPS, 1), 183 (22), 181 (20), 135 (25). **HRMS**: Calculated for [$C_{27}H_{37}N_2O_3Si$]$^+$: 465.2573 [(M+NH$_4$)$^+$]; found: 465.2573.

General procedure I: To a solution of cyclopropane carbaldehyde **2d-e** (4.0 mmol, 1.0 eq) in ionic liquid[9] (metoxyl propylamine, 1.0 eq/acetic acid, 5.0 mmol, 1.25 eq) (10.0 eq), nitromethane (40.0 mmol, 10.0 eq) was added and the reaction mixture was stirred at 50°C for 15 hours. The crude was filtered by celite® and it was concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **3d-e**.

[9] Wang, W.; Cheng, W.; Shao, L.; Liu, C. H.; Yang, J. *Kinet Catal*, **2009**, *2*, 186.

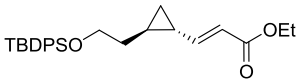
(*E*)-*tert*-butyldimethyl(2-(2-(2-nitrovinyl)-2-propylcyclopropyl)ethoxy)silane (3d). Following the *general procedure I,* **3d** (1.66 g, 5.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 49:1 to 19:1) in 77% yield as a brown oil starting from **2d** (1.87 g, 6.9 mmol), $MeNO_2$ (3.74 mL, 69.0 mmol) and ionic liquid (8.00 mL, 69.0 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.20-6.85 (m, 2H, C*H*=C*H*), 3.71-3.61 (m, 2H, SiOCH_2CH$_2$), 1.89-1.06 (m, 9H, SiOCH$_2$CH_2, CH_2CH_2CH_3), 0.96-0.89 (m, 11H, 3 x CH_3, CHCH_2C), 0.76-0.63 (m, 1H, C*H*CH$_2$C), 0.06 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) (*denotes minor diastereoisomer resonances, d.r.: 1:1.3): 152.4 (*C*H=CH), 148.3* (*C*H=CH), 138.2* (CH=*C*H), 136.4 (CH=*C*H), 62.7 (SiO*C*H$_2$CH$_2$), 62.7* (SiO*C*H$_2$CH$_2$), 38.8 (*C*H$_2$CH$_2$CH$_3$), 33.0* (*C*H$_2$CH$_2$CH$_3$), 32.4 (SiOCH$_2$*C*H$_2$), 32.2* (SiOCH$_2$*C*H$_2$), 28.0* (*C*HCH$_2$C), 27.5 (*C*HCH$_2$C), 26.0 (3 x CH_3), 25.8 (Si*C*(CH$_3$)$_3$), 25.3* (Si*C*(CH$_3$)$_3$), 23.5* (CH*C*H$_2$C), 22.8 (CH*C*H$_2$C), 20.5 (CH$_2$*C*H$_2$CH$_3$), 19.9* (CH$_2$*C*H$_2$CH$_3$), 18.4 (CHCH$_2$*C*), 18.4* (CHCH$_2$*C*), 14.4 (CH$_2$CH$_2$*C*H$_3$), 14.2* (CH$_2$CH$_2$*C*H$_3$), -5.3 (2 x CH_3), -5.3* (2 x CH_3). **IR** (ATR): 2926 (C-H st), 2851 (C-H st), 1515 (NO_2 st as), 1095 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 267 (M$^+$-NO_2, 4), 225 (23), 183 (M$^+$-OTBS, 26), 143 (28), 140 (38), 135 (26), 131 (M$^+$-$C_{10}H_{17}NO_2$, 6), 117 (30), 107 (20), 105 (30), 104 (87), 103 (24), 93 (74), 91 (42), 79 (59), 77 (34), 75 (100), 73 (69), 67 (26).



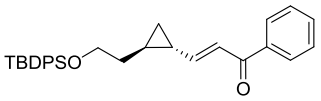
(*E*)-(2-(2-(but-3-en-1-yl)-2-(2-nitrovinyl)cyclopropyl)ethoxy)(*tert*-butyl)dimethylsilane (3e). Following the *general procedure I*, **3e** (0.15 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 49:1 to 19:1) in 40% yield as a yellow oil starting from **2e** (0.30 g, 1.1 mmol), $MeNO_2$ (0.60 mL, 10.6 mmol) and ionic liquid (2.00 mL, 10.6 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.21-6.86 (m, 2H, C*H*=C*H*), 5.92-5.68 (m, 1H, CH$_2$CH$_2$C*H*=CH$_2$), 5.11-4.87 (m, 2H, CH$_2$CH$_2$CH=CH_2), 3.74-3.39 (m, 2H, SiOCH_2CH$_2$), 2.22-2.07 (m, 2H, CH$_2$CH_2CH=CH$_2$), 1.70-1.40 (m, 5H, SiOCH$_2$CH_2, CH_2CH$_2$CH=CH$_2$, C*H*CH$_2$C), 0.90-0.88 (m, 9H, 3 x CH_3), 0.76-0.69 (m, 2H, CHCH_2C), 0.05 (app d, *J* = 3.2 Hz, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:0.8): 152.0 (CH=*C*H), 148.0* (CH=*C*H), 138.4* (CH$_2$CH$_2$*C*H=CH$_2$), 137.6 (*C*H=CH), 136.6 (CH$_2$CH$_2$*C*H=CH$_2$), 115.4 (CH$_2$CH$_2$CH=*C*H$_2$), 115.3* (CH$_2$CH$_2$CH=*C*H$_2$), 62.8* (SiO*C*H$_2$CH$_2$), 62.7 (SiO*C*H$_2$CH$_2$), 34.3 (*C*H$_2$CH$_2$CH=CH$_2$), 33.1* (SiOCH$_2$*C*H$_2$), 32.3 (SiOCH$_2$*C*H$_2$), 31.4 (CH$_2$*C*H$_2$CH=CH$_2$), 31.0* (CH$_2$*C*H$_2$CH=CH$_2$), 28.2* (*C*HCH$_2$C), 27.6 (*C*HCH$_2$C), 27.0 (3 x CH_3), 25.6 (Si*C*(CH$_3$)$_3$), 25.0* (Si*C*(CH$_3$)$_3$), 23.6* (CH*C*H$_2$C), 22.8 (CH*C*H$_2$C), 18.5 (CHCH$_2$*C*), 18.4 (CHCH$_2$*C*), -5.2* (2 x CH_3), -5.2 (2 x CH_3). **IR** (ATR): 2926 (C-H st), 2861 (C-H st), 1511 (NO_2 st as), 1099 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 223 (M$^+$-^{t}Bu-NO_2, 2), 195 (M$^+$-OTBS, 2), 131 (M$^+$-$C_{11}H_{17}NO_2$, 29), 115 (18), 105 (53), 104 (24), 91 (46), 89 (80), 79 (25), 77 (24), 75 (100), 73 (96), 59 (21).

General procedure J: To a solution of **2a** (2.0 mmol, 1.0 eq) in toluene (31 mL, 0.064 *M*) the corresponding ylide[10] (4.0 mmol, 2.0 eq) was added and the reaction was heated to reflux for 15 hours. Once the reaction was finished, it was concentrated in vacuo and the crude was then purified by flash column chromatography to afford pure **3k-x, z**.

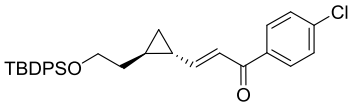
[10] The ylides were prepared according procedures described in the literature. It will be shown in each case.



Ethyl (*E*)-3-((1*S*,2*R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)acrylate (3k). Following the *general procedure J*, **3k** (0.34 g, 0.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 9:1) in 92% yield as a yellow oil starting from **2a** (0.40 g, 1.1 mmol), (carbethoxymethylene)triphenylphosphorane (0.79 g, 2.2 mmol) and toluene (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.70-7.64 (m, 4H, C_{arom}-H), 7.44-7.35 (m, 6H, C_{arom}-H), 6.47 (dd, *J* = 15.4, 10.0 Hz, 1H, C*H*=CH), 5.81 (d, *J* = 15.4 Hz, 1H, CH=C*H*), 4.23-4.14 (m, 2H, OCH_2CH$_3$), 3.75-3.70 (m, 2H, SiOCH_2CH$_3$), 1.64-1.51 (m, 2H, SiOCH$_2$CH_2), 1.33-1.26 (m, 4H, OCH$_2$CH_3, CHCH$_2$C*H*), 1.17-1.11 (m, 1*H*, CHCH$_2$CH), 1.06 (s, 9H, 3 x CH$_3$), 0.88-0.69 (m, 2H, CHCH_2CH).



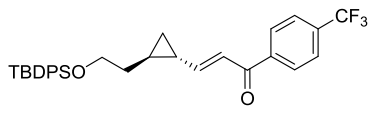
(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-phenylprop-2-en-1-one (3l). Following the *general procedure J*, **3l** (0.30 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 78% yield as a yellow oil starting from **2a** (0.30 g, 0.8 mmol), 1-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[11] (0.65 g, 1.6 mmol) and toluene (13 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99-7.89 (m, 2H, C_{arom}-H), 7.76-7.64 (m, 4H, C_{arom}-H), 7.59-7.34 (m, 10H, C_{arom}-H), 6.96 (dd, *J* = 15.1, 0.8 Hz, 1H, CH=C*H*), 6.64 (ddd, *J* = 15.1, 10.2, 0.8 Hz, 1H, C*H*=CH), 3.77 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.63 (appq, *J* = 6.4 Hz, 2H, SiOCH$_2$CH_2), 1.49 (dp, *J* = 12.2, 4.3 Hz, 1H, CHCH$_2$C*H*), 1.33-1.20 (m, 1H, C*H*CH$_2$CH), 1.09 (s, 9H, 3 x CH$_3$), 0.98-0.83 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 190.0 (C=O), 154.8 (CH=*C*H), 138.3 (C_{arom}-C), 135.7 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 132.5 (C_{arom}-H), 129.7 (C_{arom}-H), 128.6 (C_{arom}-H), 127.8 (C_{arom}-H), 127.7 (C_{arom}-H), 122.6 (*C*H=CH), 63.5 (SiO*C*H$_2$CH$_2$), 36.7 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH$_3$), 23.0 (CHCH$_2$*C*H), 21.1 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.4 (CH*C*H$_2$CH). **IR** (ATR): 2934 (C-H st), 2855 (C-H st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 397 (47), 255 (M$^+$-C$_{14}$H$_{16}$O, 1), 207 (15), 200 (17), 199 (M$^+$-OTBDPS, 89), 197 (20), 183 (22), 181 (27), 135 (29), 115 (24), 105 (M$^+$-C$_{23}$H$_{29}$OSi, 55), 91 (27), 78 (100), 77 (83), 56 (20), 52 (21), 51 (38).



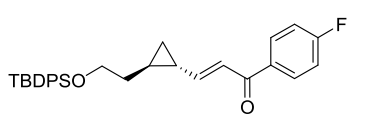
(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(4-chlorophenyl)prop-2-en-1-one (3m). Following the *general procedure J*, **3m** (0.71 g, 1.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 85% yield as a yellow oil starting from **2a** (0.60 g, 1.7 mmol), 1-(4-chlorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[13] (1.41 g, 3.4 mmol), and toluene (26 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.90-7.78 (m, 2H, C_{arom}-H), 7.70-7.65 (m, 4H, C_{arom}-H), 7.46-7.31 (m, 8H, C_{arom}-H), 6.89 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.63 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.75 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.62 (q, *J* = 4.8, 3.2 Hz, 2H, SiOCH$_2$CH_2), 1.52-1.44 (m, 1H, CHCH$_2$C*H*), 1.29-1.20 (m, 1H, C*H*CH$_2$CH), 1.06 (s, 9H, 3 x CH$_3$), 0.96-0.83 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.6 (C=O), 155.5 (*C*H=CH), 138.9 (C_{arom}-C), 136.7 (C_{arom}-C), 135.7 (C_{arom}-H), 134.0 (C_{arom}-Si), 133.9 (C_{arom}-Si), 129.9 (C_{arom}-H), 129.7 (C_{arom}-H), 128.9 (C_{arom}-H), 127.8 (C_{arom}-H), 122.1 (CH=*C*H), 63.5 (SiOCH$_2$CH$_2$),

[11] Xie, P.; Fu, W.; Sun, Z.; Wu, Y.; Li, S.; Gao, C.; Yang, X.; Loh, T.-P. *Org. Lett*. **2019**, *21*, 7055.

36.7 ($SiOCH_2\mathit{C}H_2$), 27.0 (3 x CH_3), 23.1 ($CHCH_2\mathit{C}H$), 21.3 ($\mathit{C}HCH_2CH$), 19.3 ($Si\mathit{C}(CH_3)_3$), 18.6 ($CH\mathit{C}H_2CH$). **IR** (ATR): 2930 (C-H st), 2857 (C-H st), 1734 (C=C st), 1609 (arC-C), 1091 (Si-O st) cm^{-1}.

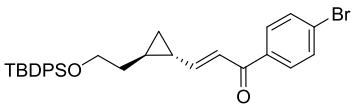


(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (3n). Following the *general procedure J*, **3n** (0.35 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 48% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 1-(4-(trifluoromethyl)phenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[12] (1.27 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.72-7.65 (m, 5H, C_{arom}-H), 7.45-7.32 (m, 7H, C_{arom}-H), 6.91 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.66 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3,77 (t, *J* = 6.2 Hz, 1H, $SiOC\mathit{H}_2CH_2$), 1.63 (qd, *J* = 6.3, 1.9 Hz, 2H, $SiOCH_2C\mathit{H}_2$), 1.56-1.47 (m, 1H, $CHCH_2C\mathit{H}$), 1.35-1.22 (m, 1H, $C\mathit{H}CH_2CH$), 1.07 (s, 9H, 3 x CH_3), 1.01-0.83 (m, 2H, $CHC\mathit{H}_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.0 (C=O), 156.3 (*C*H=CH), 141.3 (C_{arom}-C), 135.7 (C_{arom}-H), 133.9 (C_{arom}-C), 131.3 (q, J_{CF} = 280.0 Hz, CF_3), 129.8 (C_{arom}-H), 128.7 (C_{arom}-H), 127.8 (C_{arom}-H), 125.6 (q, $^3J_{CF}$ = 3.8 Hz, $\mathit{C}H_{arom}CCF_3$), 122.2 (CH=*C*H), 63.5 ($SiO\mathit{C}H_2CH_2$), 36.7 ($SiOCH_2\mathit{C}H_2$), 27.0 (3 x CH_3), 23.3 ($CHCH_2\mathit{C}H$), 21.5 ($\mathit{C}HCH_2CH$), 19.3 ($Si\mathit{C}(CH_3)_3$), 16.7 ($CH\mathit{C}H_2CH$). **IR** (ATR): 2937 (C-H st), 1605 (C=C st), 1322 (C-F st), 761 (CF_3) cm^{-1}. **MS** (EI) m/z (%): 466 (35), 465 (M^+-^{t}Bu, 100), 349 (M^+-$C_8H_4F_3O$, 1), 267 (M^+-OTBDPS, 1), 255 (M^+-$C_{15}H_{14}F_3O$, 2), 225 (17), 213 (22), 200 (17), 199 (97), 197 (32), 183 (38), 181 (30), 173 (M^+-$C_{23}H_{29}OSi$, 30), 145 (39), 135 (30), 78 (24), 77 (23).

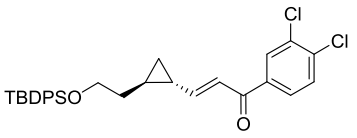


(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(4-fluorophenyl)prop-2-en-1-one (3o). Following the *general procedure J*, **3o** (0.53 g, 1.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 80% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 1-(4-fluorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[13] (1.13 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.00-7.89 (m, 2H, C_{arom}-H), 7.71-7.66 (m, 4H, C_{arom}-H), 7.44-7.34 (m, 6H, C_{arom}-H), 7.16-7.10 (m, 2H, C_{arom}-H), 6.91 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.63 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.76 (t, *J* = 6.2 Hz, 2H, $SiOC\mathit{H}_2CH_2$), 1.62 (appq, *J* = 6.4 Hz, 2H, $SiOCH_2C\mathit{H}_2$), 1.53-1.44 (m, 1H, $CHCH_2C\mathit{H}$), 1.30-1.20 (m, 1H, $C\mathit{H}CH_2CH$), 1.07 (s, 9H, 3 x CH_3), 0.96-0.81 (m, 2H, $CHC\mathit{H}_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.2 (C=O), 165.5 (d, $^1J_{C\text{-}F}$ = 254.0 Hz, *C*-F) 155.1 (*C*H=CH), 135.7 (C_{arom}-H), 134.6 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, *C*CHCHCF), 134.0 (C_{arom}-Si), 133.9 (C_{arom}-Si), 131.0 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, CCHCHCF), 129.7 (C_{arom}-H), 127.8 (C_{arom}-H), 122.2 (CH=*C*H), 115.8 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, CCH*C*HCF), 63.5 ($SiO\mathit{C}H_2CH_2$), 36.7 ($SiOCH_2\mathit{C}H_2$), 27.0 (3 x CH_3), 23.1 ($CHCH_2\mathit{C}H$), 21.2 ($\mathit{C}HCH_2CH$), 19.3 ($Si\mathit{C}(CH_3)_3$), 16.5 ($CH\mathit{C}H_2CH$). **IR** (ATR): 2972 (C-H st), 1741 (C=O st), 1368 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 415 (M^+-^{t}Bu, 32), 199 (45), 197 (21), 181 (23), 135 (18), 123 (M^+-$C_{23}H_{29}OSi$, 65), 95 (35), 91 (25), 77 (20), 57 (100).

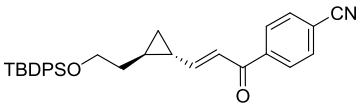
[12] Farley, C. M.; Zhou, Y.; Banka, N.; Uyeda, C. *J. Am. Chem. Soc*. **2018**, *140*, 12710.
[13] Wu, J.-Q.; Yang, Z.; Zhang, S.-S.; Jiang, C.-Y.; Li, Q.; Huang, Z.-S.; Wang, H. *ACS Catal*. **2015**, *5*, 6543.



(*E*)-1-(4-bromophenyl)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)prop-2-en-1-one (3p). Following the *general procedure J*, **3p** (0.64 g, 1.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 71% yield as a yellow oil starting from **2a** (0.60 g, 1.7 mmol), 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[13] (1.56 g, 3.4 mmol), and toluene (26mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.83-7.75 (m, 2H, C_{arom}-H), 7.75-7.65 (m, 4H, C_{arom}-H), 7.62-7.58 (m, 2H, C_{arom}-H), 7.46-7.35 (m, 6H, C_{arom}-H), 6.90 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.65 (dd, *J* = 15.2, 10.2 Hz, 2H, C*H*=CH), 3.78 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.67-1.57 (m, 2H, SiOCH$_2$CH_2), 1.54-1.46 (m, 1H, CHCH$_2$C*H*), 1.33-1.24 (m, 1H, C*H*CH$_2$CH), 1.09 (s, 9H, 3 x CH_3), 0.97-0.83 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.6 (C=O), 155.5 (*C*H=CH), 137.0 (C_{arom}-C), 135.6 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 131.8 (C_{arom}-H), 130.0 (C_{arom}-H), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 127.5 (C_{arom}-C), 122.0 (CH=*C*H), 63.5 (SiO*C*H$_2$CH$_2$), 36.7 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 23.1 (CHCH$_2$*C*H), 21.3 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.5 (CH*C*H$_2$CH). **IR** (ATR): 2934 (C-H st), 1734 (C=O st), 1662 (C=C st), 757 (C-Br st) cm^{-1}.



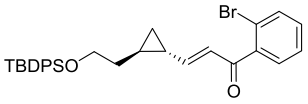
(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(3,4-dichlorophenyl)prop-2-en-1-one (3q). Following the *general procedure J*, **3q** (0.41 g, 0.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 56% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 1-(3,4-dichlorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[14] (1.28 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.01 (d, *J* = 2.0 Hz, 1H, C_{arom}-H), 7.76-7.64 (m, 5H, C_{arom}-H), 7.53 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 7.45-7.34 (m, 6H, C_{arom}-H), 6.86 (d, *J* = 15.0 Hz, 1H, CH=C*H*), 6.66 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.76 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.67-1.59 (m, 2H, SiOCH$_2$CH_2), 1.50 (ddt, *J* = 10.1, 8.2, 4.3 Hz, 1H, CHCH$_2$C*H*), 1.28 (dqd, *J* = 13.2, 6.7, 3.8 Hz, 1H, C*H*CH$_2$CH), 1.07 (s, 9H, 3 x CH_3), 0.98-0.85 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 187.3 (C=O), 156.4 (*C*H=CH), 137.9 (C_{arom}-C), 136.9 (C_{arom}-C), 135.7 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 133.2 (C_{arom}-C), 130.7 (CH=*C*H), 130.5 (C_{arom}-H), 129.7 (C_{arom}-H), 127.8 (C_{arom}-H), 127.5 (C_{arom}-H), 121.6 (C_{arom}-H), 63.5 (SiO*C*H$_2$CH$_2$), 36.7 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 23.3 (CHCH$_2$*C*H), 21.5 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.7 (CH*C*H$_2$CH). **IR** (ATR): 3016 (C-H st), 1734 (C=O st) cm^{-1}.



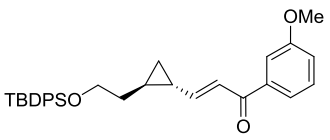
(*E*)-4-(3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)acryloyl)benzonitrile (3r). Following the *general procedure J*, **3r** (0.40 g, 0.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 59% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 4-(2-(triphenyl-λ^5-phosphanylidene)acetyl)benzonitrile[12] (1.15 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99-7.93 (m, 2H, C_{arom}-H), 7.78-7.73 (m, 2H, C_{arom}-H), 7.72-7.63 (m, 4H, C_{arom}-H), 7.44-7.34 (m, 6H, C_{arom}-H), 6.87 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.66 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.76 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.67-1.59 (m,

[14] Yang, X.-Y.; Tay, W. S.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. *Organometallics*, **2015**, *34*, 5196.

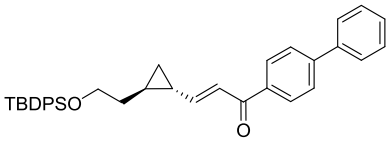
2H, $SiOCH_2CH_2$), 1.56-1.47 (m, 1H, $CHCH_2CH$), 1.35-1.22 (m, 1H, $CHCH_2CH$), 1.06 (s, 9H, 3 x CH_3), 0.98-0.88 (m, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.4 (C=O), 157.1 (*C*H=CH), 141.7 (C_{arom}-C), 135.6 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 132.4 (C_{arom}-H), 129.7 (C_{arom}-C), 128.8 (C_{arom}-C), 127.8 (C_{arom}-H), 121.9 (CH=*C*H), 118.2 (CN), 115.7 (C_{arom}-C), 63.5 ($SiOCH_2CH_2$), 36.6 ($SiOCH_2CH_2$), 27.0 (3 x CH_3), 23.4 ($CHCH_2CH$), 21.7 ($CHCH_2CH$), 19.3 ($SiC(CH_3)_3$), 16.9 ($CHCH_2CH$). **IR** (ATR): 3012 (C-H st), 1738 (C=O st) cm^{-1}.



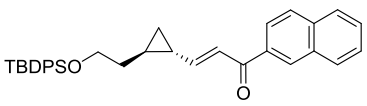
(*E*)-1-(2-bromophenyl)-3-((1*S*,2*R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)prop-2-en-1-one (3s). Following the *general procedure J*, **3s** (0.52 g, 0.9 mmol) was isolated by FC (*petroleum ether*/EtOAc gradient from 19:1 to 8:2) in 52% yield as a yellow oil starting from **2a** (0.65 g, 1.8 mmol), 1-(2-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.70 g, 3.7 mmol) and toluene (29 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.47-7.35 (m, 14H, C_{arom}-H), 6.50 (dd, *J* = 15.6, 1.7 Hz, 1H, CH=C*H*), 6.28 (ddt, *J* = 15.7, 9.9, 1.6 Hz, 1H, C*H*=CH), 3.76 (t, *J* = 6.3 Hz, 2H, $SiOCH_2CH_2$), 1.66-1.58 (m, 2H, $SiOCH_2CH_2$), 1.45 (ddt, *J* 13.4, 10.3, 4.7 Hz, 1H, $CHCH_2CH$), 1.25-1.19 (m, 1H, $CHCH_2CH$), 1.11 (s, 9H, 3 x CH_3), 0.88 (dd, *J* = 7.8, 5.8 Hz, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 194.3 (C=O), 157.7 (*C*H=CH), 141.3 (C_{arom}-C), 135.6 (C_{arom}-H), 134.9 (C_{arom}-H), 133.4 (C_{arom}-Si), 129.7 (C_{arom}-C), 129.0 (CH=*C*H), 127.8 (C_{arom}-H), 119.4 (C_{arom}-Si), 63.4 ($SiOCH_2CH_2$), 36.6 ($SiOCH_2CH_2$), 27.0 (3 x CH_3), 22.8 ($CHCH_2CH$), 21.5 ($CHCH_2CH$), 19.3 ($SiC(CH_3)_3$), 16.8 ($CHCH_2CH$). **IR** (ATR): 3023 (C-H st), 1644 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 200 (18), 199 (100), 155 (M^+-$C_{24}H_{29}O_2Si$, 1), 78 (25), 77 (23), 57 (62), 51 (24).



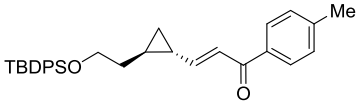
(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(3-methoxyphenyl)prop-2-en-1-one (3t). Following the *general procedure J*, **3t** (0.60 g, 1.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 88% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 1-(3-methoxyphenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[13] (1.17 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.71-7.66 (m, 4H, C_{arom}-H), 7.53-7.45 (m, 2H, C_{arom}-H), 7.45-7.32 (m, 7H, C_{arom}-H), 7.10 (ddd, *J* = 8.2, 2.6, 1.2 Hz, 1H, C_{arom}-H), 6.93 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.63 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.86 (s, 3H, OCH_3), 3.76 (t, *J* = 6.2 Hz, 2H, $SiOCH_2CH_2$), 1.62 (app q, *J* = 6.5 Hz, 2H, $SiOCH_2CH_2$), 1.48 (ddt, *J* = 10.1, 8.2, 4.3 Hz, 1H, $CHCH_2CH$), 1.32-1.19 (m, 1H, $CHCH_2CH$), 1.07 (s, 9H, 3 x CH_3), 0.97-0.79 (m, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.7 (C=O), 159.9 (C_{arom}-C), 154.9 (*C*H=CH), 139.8 (C_{arom}-C), 135.7 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.9 (C_{arom}-Si), 129.7 (CH=*C*H), 129.5 (C_{arom}-H), 127-8 (C_{arom}-H), 122.6 (C_{arom}-H), 121.0 (C_{arom}-H), 119.1 (C_{arom}-H), 112.8 (C_{arom}-H), 63.5 ($SiOCH_2CH_2$), 55.5 (OCH_3), 36.7 ($SiOCH_2CH_2$), 27.0 (3 x CH_3), 23.0 ($CHCH_2CH$), 21.1 ($CHCH_2CH$), 19.3 ($SiC(CH_3)_3$), 16.4 ($CHCH_2CH$). **IR** (ATR): 3012 (C-H st), 1738 (C=O st) cm^{-1}.



(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)prop-2-en-1-one (3u). Following the *general procedure J*, **3u** (1.64 g, 3.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 87% yield as a yellow oil starting from **2a** (1.25 g, 3.6 mmol), 1-([1,1'-biphenyl]-4-yl)-2-(triphenyl- λ^5-phosphanylidene)ethan-1-one[15] (3.24 g, 7.1 mmol), and toluene (47 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.03-7.97 (m, 2H, C_{arom}-H), 7.76-7.62 (m, 10H, C_{arom}-H), 7.44-7.35 (m, 7H, C_{arom}-H), 6.99 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.65 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.76 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.66-1.59 (m, 2H, SiOCH$_2$CH_2), 1.49 (ddt, *J* = 10.1, 8.3, 4.3 Hz, 1H, CHCH$_2$C*H*), 1.25 (dtd, *J* = 13.2, 5.5, 5.0, 2.6 Hz, C*H*CH$_2$CH), 1.08 (s, 9H, 3 x CH_3), 0.98-0.83 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.5 (C=O), 154.8 (*C*H=CH), 145.3 (C_{arom}-C), 140.2 (C_{arom}-C), 137.0 (C_{arom}-C), 135.7 (C_{arom}-H), 134.9 (C_{arom}-H), 134.0 (C_{arom}-C), 133.9 (C_{arom}-C), 129.8 (C_{arom}-H), 129.1 (C_{arom}-H), 129.0 (C_{arom}-H), 127.8 (C_{arom}-H), 127.7 (C_{arom}-H), 127.4 (C_{arom}-H), 127.3 (C_{arom}-H), 122.5 (C_{arom}-H), 63.6 (SiO*C*H$_2$CH$_2$), 36.8 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 23.1 (CHCH$_2$*C*H), 21.1 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.5 (CH*C*H$_2$CH). **IR** (ATR): 2926 (C-H st), 2858 (C-H st), 1738 (C=O st), 1659 (C=C st) cm^{-1}



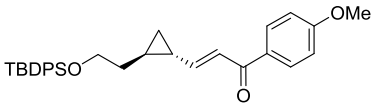
(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(naphthalen-2-yl)prop-2-en-1-one (3v). Following the *general procedure J*, **3v** (0.63 g, 1.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 93% yield as a yellow oil starting from **2a** (0.50 g, 1.4 mmol), 1-(naphthalen-2-yl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[12] (1.22 g, 2.8 mmol), and toluene (22 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.48 (s, 1H, C_{arom}-H), 8.08 (dd, *J* = 8.6, 1.7 Hz, 1H, C_{arom}-H), 8.03-7.87 (m, 3H, C_{arom}-H), 7.82-7.71 (m, 4H, C_{arom}-H), 7.65-7.53 (m, 2H, C_{arom}-H), 7.49-7.38 (m, 6H, C_{arom}-H), 7.16 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.75 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.82 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.67 (appq, *J* = 6.4 Hz, 2H, SiOCH$_2$CH_2), 1.61-1.57 (m, 1H, CHCH$_2$C*H*), 1.36-1.26 (m, 1H, C*H*CH$_2$CH), 1.14 (s, 9H, 3 x CH_3), 1.03-0.82 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.6 (C=O), 154.7 (*C*H=CH), 135.6 (C_{arom}-C), 135.4 (C_{arom}-H), 134.9 (C_{arom}-C), 133.9 (C_{arom}-C), 133.8 (C_{arom}-C), 132.6 (C_{arom}-H), 129.7 (C_{arom}-H), 129.6 (C_{arom}-H), 129.5 (C_{arom}-H), 128.4 (C_{arom}-H), 128.2 (C_{arom}-H), 127.8 (C_{arom}-H), 127.7 (C_{arom}-H), 126.7 (C_{arom}-H), 124.6 (C_{arom}-H), 122.5 (CH=*C*H), 63.5 (SiO*C*H$_2$CH$_2$), 36.7 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 23.1 (CHCH$_2$*C*H), 21.1 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.4 (CH*C*H$_2$CH). **IR** (ATR): 3016 (C-H st), 1734 (C=O st) cm^{-1}.



(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(p-tolyl)prop-2-en-1-one (3w). Following the *general procedure J*, **3w** (0.70 g, 1.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 88% yield as a yellow oil starting from **2a** (0.60 g, 1.7 mmol), 1-(*p*-tolyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[13] (1.35 g, 3.4 mmol), and toluene (26mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.85-7.81 (m, 2H, C_{arom}-H), 7.69-7.64 (m, 4H, C_{arom}-H), 7.45-7.33 (m, 6H, C_{arom}-H), 7.27-7.24

[15] Jadhav, S. B.; Thopate, S. B.; Nannubolu, J. B.; Chegandi, R. *Org. Biomol. Chem*. **2019**, *17*, 1937.

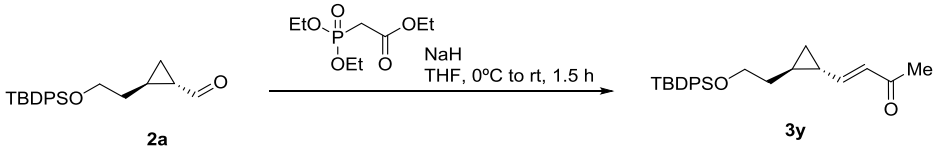
(m, 2H, C_{arom}-H), 6.93 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.60 (dd, *J* = 15.1, 10.1 Hz, 1H, C*H*=CH), 3.74 (t, *J* = 6.3 Hz, 2H, SiOCH_2CH$_2$), 2.42 (s, 3H, CH_3), 1.65-1.54 (m, 3H, SiOCH$_2$CH_2, CHCH$_2$C*H*), 1.50-1.43 (m, 1H, C*H*CH$_2$CH), 1.06 (s, 9H, 3 x CH_3), 0.94-0.78 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.6 (C=O), 154.3 (*C*H=CH), 143.3 (C_{arom}-C), 135.7 (C_{arom}-H), 134.0 (C_{arom}-Si), 133.9 (C_{arom}-Si), 129.7 (C_{arom}-H), 129.3 (C_{arom}-H), 128.7 (C_{arom}-H), 127.8 (C_{arom}-H), 122.6 (CH=*C*H), 63.6 (SiO*C*H$_2$CH$_2$), 36.8 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 23.0 (CH_3), 21.8 (CHCH$_2$*C*H), 21.0 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.4 (CH*C*H$_2$CH). **IR** (ATR): 3012 (C-H st), 2947 (C-H st), 1741 (C=O st) cm^{-1}.



(*E*)-3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-1-(4-methoxyphenyl)prop-2-en-1-one (3x). Following the *general procedure J*, **3x** (0.61 g, 1.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 76% yield as a yellow oil starting from **2a** (0.60 g, 1.7 mmol), 1-(4-methoxyphenyl)-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one[11] (1.40 g, 3.4 mmol) and toluene (26 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99-7.91 (m, 2H, C_{arom}-H), 7.73-7.66 (m, 4H, C_{arom}-H), 7.47-7.34 (m, 6H, C_{arom}-H), 7.00-6.91 (m, 3H, C_{arom}-H, CH=C*H*), 6.61 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.87 (s, 3H, OCH_3), 3.76 (t, *J* = 6.3 Hz, 2H, SiOCH_2CH$_2$), 1.66-1.58 (m, 2H, SiOCH$_2$CH_2), 1.52-1.42 (m, 1H, CHCH$_2$C*H*), 1.33-1.20 (m, 1H, C*H*CH$_2$CH), 1.07 (s, 9H, 3 x CH_3), 0.94-0.80 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.2 (C=O), 163.2 (C_{arom}-C), 153.7 (*C*H=CH), 135.7 (C_{arom}-H), 134.0 (C_{arom}-Si), 133.9 (C_{arom}-Si), 130.7 (C_{arom}-H), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 122.3 (CH=*C*H), 113.8 (C_{arom}-H), 63.6 (SiO*C*H$_2$CH$_2$), 55.5 (OCH_3), 36.8 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 22.9 (CHCH$_2$*C*H), 20.9 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.2 (CH*C*H$_2$CH). **IR** (ATR): 2930 (C-H st), 1666 (C=O st), 1605 (C=C st), 1105 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 294 (81), 293 (62), 185 (47), 184 (16), 183 (100), 139 (22), 135 (M$^+$-$C_{23}H_{29}OSi$, 2), 77 (15), 51 (15).

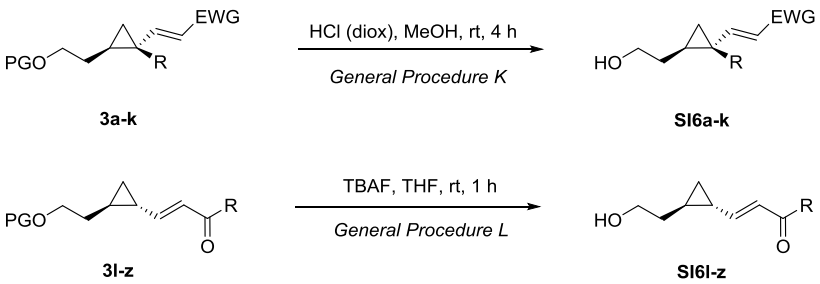
(*E*)-1-((1*S*,2*R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)-4,4-dimethylpent-1-en-3-one (3z). Following the *general procedure J*, **3z** (0.32 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 48% yield as a yellow oil starting from **2a** (0.54 g, 1.5 mmol), 3,3-dimethyl-1-(triphenyl-λ^5-phosphaneylidene)butan-2-one[11] (1.00 g, 2.8 mmol) and toluene (24 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.71-7.66 (m, 4H, C_{arom}-H), 7.45-7.34 (m, 6H, C_{arom}-H), 6.59-6.40 (m, 2H, 2H, CH=CH), 3.73 (t, *J* = 6.2 Hz, 2H, SiOCH_2CH$_2$), 1.62-1.53 (m, 3H, SiOCH$_2$CH_2, CHCH$_2$C*H*), 1.39-1.32 (m, 1H, C*H*CH$_2$CH), 1.15 (s, 9H, 3 x CH_3), 1.06 (s, 9H, 3 x CH_3), 0.94-0.70 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.7 (C=O), 152.4 (*C*H=CH), 147.5 (C_{arom}-C), 135.7 (C_{arom}-H), 133.9 (C_{arom}-Si), 129.7 (C_{arom}-H), 127.7 (C_{arom}-H), 124.3 (C_{arom}-Si), 121.1 (CH=*C*H), 63.5 (SiO*C*H$_2$CH$_2$), 42.7 (*C*(CH$_3$)), 36.7 (SiOCH$_2$*C*H$_2$), 27.0 (3 x CH_3), 26.5 (3 x CH_3), 22.5 (CHCH$_2$*C*H), 20.6 (*C*H-CH$_2$-CH), 19.3 (Si*C*(CH$_3$)$_3$), 15.9 (CH*C*H$_2$CH). **MS** (EI) m/z (%): 377 (M$^+$-^{t}Bu, 52), 255 (M$^+$-$C_{12}H_{20}O$, 2), 200 (19), 199 (100), 197 (30), 183 (28), 181 (25), 180 (M$^+$-$C_{16}H_{19}OSi$, 6), 135 (46), 121 (15), 105 (18), 91 (17), 85 (M$^+$-$C_{23}H_{29}OSi$, 1), 77 (19), 57 (52).

Synthesis of (*E*)-4-((1*S*,2*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclopropyl)but-3-en-2-one (3y)



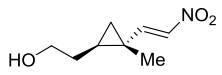
To a cooled (0ºC) stirring suspension of NaH (60 wt.% in mineral oil, 0.11 g, 2.8 mmol, 2.0 eq) in THF (5 mL, 0.3 *M*), dietyl (2-oxopropyl)phosphonate (0.57 mL, 2.8 mmol, 2.0 eq) was added and the reaction mixture was stirred at room temperature for 30 minutes. Then, **2a** (0.50 g, 1.4 mmol, 1.0 eq) was added at 0ºC dropwise and the reaction was stirred ar toom temperature for 1 hour. The crude was quenched with H_2O (10 mL) and aqueous phase was extracted with EtOAc (3 x 20 mL). Organic extract were dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 8:2) to afford pure **3y** in 61% yield as a yellow oil (0.34 g, 0.9 mmol). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.72-7.66 (m, 4H, C_{arom}-H), 7.49-7.33 (m, 6H, C_{arom}-H), 6.34 (dd, *J* = 15.7, 9.7 Hz, 1H, C*H*=CH), 6.12 (d, *J* = 15.7 Hz, 1H, CH=C*H*), 3.74 (t, *J* = 6.3 Hz, 2H, SiOC*H*$_2$CH$_2$), 2.19 (s, 3H, CH_3), 1.64-1.55 (m, 2H, SiOCH$_2$C*H*$_2$), 1.38-1.27 (m, 1H, CHCH$_2$C*H*), 1.26-1.11 (m, 1H, C*H*CH$_2$CH), 1.07 (s, 9H, 3 x CH_3), 0.88-0.79 (m, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 197.8 (C=O), 153.0 (CH=*C*H), 135.6 (C_{arom}-H), 133.9 (C_{arom}-Si), 133.8 (C_{arom}-Si), 129.7 (C_{arom}-H), 128.0 (*C*H=CH), 127.7 (C_{arom}-H), 63.5 (Si-O-*C*H$_2$-CH$_2$), 36.6 (SiOCH$_2$*C*H$_2$), 27.1 (CH_3), 26.9 (3 x CH_3), 22.1 (CHCH$_2$*C*H), 20.9 (*C*HCH$_2$CH), 19.3 (Si*C*(CH$_3$)$_3$), 16.1 (CH*C*H$_2$CH). **IR** (ATR): 3012 (C-H st), 1734 (C=O st), 1109 (Si-O st) cm^{-1}. **MS** (EI) m/z (%): 335 (M$^+$-^{t}Bu, 29), 255 (M$^+$-$C_9H_{13}O$, 2), 213 (18), 200 (19), 199 (100), 183 (28), 181 (25), 137 (M$^+$-OTBDPS, 5), 135 (25), 105 (16), 91 (19), 78 (23), 77 (24).

2.1.7. Synthesis of SI6a-z

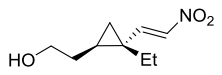


General procedure K: To a solution of **3a-k** (1 mmol, 1.0 eq) in MeOH or EtOH (2 mL, 0.5 *M*) at room temperature, a solution of HCl in dioxane 4 *M* (2.5 mmol, 2.5 eq) in MeOH or EtOH (2 mL, 0.5 *M*) was added dropwise, and the reaction was stirred at that temperature for 4 hours. Once the reaction was finished, it was quenched with H_2O (20 mL), the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **SI6a-k**.

(*E*)-2-(2-(2-nitrovinyl)cyclopropyl)ethan-1-ol (SI6a). Following the *general procedure K*, **SI6a** (0.96 g, 5.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 80% yield as a yellow oil starting from **3a** (1.20 g, 3.0 mmol), HCl in dioxane (1.90 mL, 7.5 mmol) and MeOH (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.05 (d, *J* = 13.2 Hz, 1H, CH=C*H*), 6.77 (dd, *J* = 13.1, 10.7 Hz, 1H, C*H*=CH), 3.63 (t, *J* = 6.4 Hz, 2H, OHCH_2CH_2), 2.46-2.57 (br s, 1H, OH), 1.55 (appt, *J* = 6.5 Hz, 2H, OHCH_2CH_2), 1.43-1.31 (m, 1H, CHC$H_a$$H_b$CH), 1.23 (ddtd, *J* = 13.7, 10.0, 6.9, 3.5 Hz, 1H, CHC$H_a$$H_b$CH), 1.01-0.91 (m, 2H, C*H*CH_2C*H*). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 148.6 (CH=*C*H), 136.8 (*C*H=CH), 61.8 (OH*C*H_2CH_2), 36.1 (OHCH_2*C*H_2), 21.4 (CHCH_2*C*H), 18.7 (*C*HCH_2CH), 16.6 (CH*C*H_2CH). **IR** (ATR): 3357 (O-H st), 1627 (C=C st), 1512 (NO_2 st as), 1339 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 140 (M^+-H_2O, 4), 119 (7), 111 (M^+-NO_2, 3), 110 (20), 91 (41), 85 (M^+-$C_2H_2NO_2$, 18), 79 (100), 66 (81), 53 (75), 51 (41). **HRMS**: Calculated for $[C_7H_{12}NO_3]^+$: 158.0817 $[(M+H)^+]$; found: 158.0811.

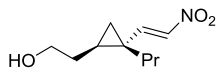


(*E*)-2-(2-methyl-2-(2-nitrovinyl)cyclopropyl)ethan-1-ol (SI6b). Following the *general procedure K*, **SI6b** (0.96 g, 5.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 65% yield as a yellow oil starting from **3b** (0.40 g, 0.9 mmol), HCl in dioxane (0.54 mL, 2.2 mmol) and MeOH (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.94 (d, *J* = 13.2 Hz, 1H, CH=C*H*), 6.81 (d, *J* = 13.2 Hz, 1H, C*H*=CH), 3.67 (t, *J* = 6.5 Hz, 2H, OHCH_2CH_2), 2.32-2.16 (br s, 1H, OH), 1.84-1.55 (m, 2H, OHCH_2CH_2), 1.33-1.10 (m, 5H, CH_3, C*H*CH_2C, CHC$H_a$$H_b$C), 0.73 (dd, *J* = 6.5, 4.6 Hz, 1H, CHC$H_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 153.9 (CH=*C*H), 136.2 (*C*H=CH), 62.2 (OH*C*H_2CH_2), 31.9 (OHCH_2*C*H_2), 25.9 (*C*HCH_2C), 23.6 (CH*C*H_2C), 20.7 (CHCH_2*C*), 15.2 (CH_3) **IR** (ATR): 3457 (O-H st), 2972 (C-H st), 1630 (C=C st), 1505 (NO_2 st as), 1349 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 214 (20), 213 (100), 183 (33), 181 (16), 82 (12).

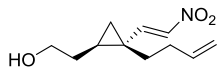


(*E*)-2-(2-ethyl-2-(2-nitrovinyl)cyclopropyl)ethan-1-ol (SI6c). Following the *general procedure K*, **SI6c** (0.28 g, 0.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 65% yield as a yellow oil starting from **3c** (0.10 g, 0.2 mmol), HCl in dioxane (0.15 mL, 0.6 mmol) and MeOH (1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.04-6.85 (m, 2H, C*H*=C*H*), 3.78-7.67 (m, 2H, OHCH_2CH_2), 1.98-1.81 (m, 1H, C*H*CH_2C), 1.74-1.43 (m, 4H, CH_2CH_3), 1.36-1.21 (m, 2H, OHCH_2CH_2), 1.15 (dd, *J* = 9.0, 4.8 Hz, 1H, CHC$H_a$$H_b$C), 1.02 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.71 (dd, *J* = 6.7, 4.8 Hz, 1H, CHC$H_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 151.7 (CH=*C*H), 136.7 (*C*H=CH), 62.6 (OH*C*H_2CH_2), 31.9 (OHCH_2*C*H_2), 27.3 (*C*HCH_2C), 26.3 (CHCH_2*C*), 23.0 (*C*H_2CH_3), 22.5 (CH*C*H_2C), 11.5 (CH_2*C*H_3). **IR** (ATR): 3012 (C-H st), 1630 (C=C st), 1511 (NO_2 st as), 1372 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 207 (72), 168 (M^+-H_2O, 2), 156

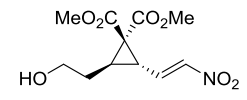
(M^+-C_2H_5, 2), 139 (M^+-NO_2, 2), 113 (M^+-$C_2H_2NO_2$, 2), 107 (32), 105 (34), 93 (35), 91 (84), 81 (28), 80 (28), 79 (100), 78 (33), 77 (69), 67 (41), 65 (41), 57 (48), 55 (53), 53 (44), 51 (42).



(*E*)-2-(2-(2-nitrovinyl)-2-propylcyclopropyl)ethan-1-ol (SI6d). Following the g*eneral procedure K*, **SI6d** (0.68 g, 3.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 2:8) in 97% yield as a yellow oil starting from **3d** (1.10 g, 3.5 mmol), HCl in dioxane (2.20 mL, 8.8 mmol) and MeOH (14 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.20-6.87 (m, 2H, C*H*=C*H*), 3.73-3.62 (m, 2H, SiOCH_2CH_2), 2.05-1.78 (m, 1H, C*H*-CH_2-C), 1.73-1.51 (m, 2H, SiOCH$_2$CH_2), 1.49-1.07 (m, 5H, CH$_2$CH_2CH_3), 0.98-0.66 (4H, CH_2CH$_2$CH$_3$, CHCH_2C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereosimer resonances; d.r.: 1:1.05): 152.3* (*C*H=CH), 148.2 (*C*H=CH), 138.3 (CH=*C*H), 138.5 (CH=*C*H), 62.3 (SiO*C*H$_2$CH$_2$), 38.7 (*C*H$_2$CH$_2$CH$_3$), 32.7* (*C*H$_2$CH$_2$CH$_3$), 32.2 (SiOCH$_2$*C*H$_2$), 31.9* (SiOCH$_2$*C*H$_2$), 27.7 (*C*HCH$_2$C), 27.1* (*C*HCH$_2$C), 25.8 (CHCH$_2$*C*), 25.2* (CHCH$_2$*C*), 23.4 (C*C*H$_2$C), 22.7* (C*C*H$_2$C), 20.4* (CH$_2$*C*H$_2$CH$_3$), 20.0 (CH$_2$*C*H$_2$CH$_3$), 14.3* (CH$_2$CH$_2$*C*H$_3$), 14.2 (CH$_2$CH$_2$*C*H$_3$). **IR** (ATR): 3361 (O-H st), 2934 (C-H st), 2876 (C-H st), 1511 (NO_2 st as). **MS** (EI) m/z (%): 182 (M^+-H_2O, 2), 153 (M^+-NO_2, 3), 135 (18), 127 (M^+-$C_2H_2NO_2$, 2), 109 (29), 107 (22), 105 (20), 93 (69), 91 (57), 81 (42), 79 (100), 77 (57), 71 (18), 69 (39), 67 (81), 65 (20), 55 (69), 57 (39), 53 (26).

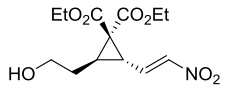


(*E*)-2-(2-(but-3-en-1-yl)-2-(2-nitrovinyl)cyclopropyl)ethan-1-ol (SI6e). Following the *general procedure K*, **SI6e** (0.05 g, 0.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 2:8) in 60% yield as a yellow oil starting from **3e** (0.13 g, 0.4 mmol), HCl in dioxane (0.23 mL, 0.9 mmol) and MeOH (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.20-6.92 (m, 2H, C*H*=C*H*), 5.90-5.67 (m, 1H, CH$_2$CH$_2$C*H*=CH$_2$) 5.13-4.93 (m, 2H, CH$_2$CH$_2$CH=CH_2), 3.72 (dt, *J* = 16.4, 6.4 Hz, 2H, OHCH_2CH$_2$), 2.27-2.12 (m, 2H, CH$_2$CH_2CH=CH$_2$), 1.95-1.84 (m, 1H, C*H*CH$_2$C), 1.77-1.51 (m, 4H, CH_2CH$_2$CH=CH$_2$, OHCH$_2$CH_2), 0.91-0.85 (m, 1H, CHCH_aH$_b$C), 0.79-0.72 (m, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (* denotes minor diastereoisomer resonances; d.r.: 1:0.8) (δ, ppm): 151.6 (*C*H=CH), 147.5 (CH$_2$CH$_2$*C*H=CH$_2$), 138.5* (*C*H=CH), 137.6 (CH=*C*H), 137.5* (CH=*C*H), 136.8* (CH$_2$CH$_2$*C*H=CH$_2$), 115.5 (CH$_2$CH$_2$CH=*C*H$_2$), 115.4* (CH$_2$CH$_2$CH=*C*H$_2$), 62.6 (OH*C*H$_2$CH$_2$), 62.5* (OH*C*H$_2$CH$_2$), 36.0 (*C*H$_2$CH$_2$CH=CH$_2$), 32.8* (*C*H$_2$CH$_2$CH=CH$_2$), 32.0 (OHCH$_2$*C*H$_2$), 31.4* (OHCH$_2$*C*H$_2$), 30.9 (CH$_2$*C*H$_2$CH=CH$_2$), 29.6* (CH$_2$*C*H$_2$CH=CH$_2$), 27.7 (*C*HCH$_2$C), 27.2* (*C*HCH$_2$C), 25.5 (CHCH$_2$*C*), 24.9* (CHCH$_2$*C*), 23.4 (CH*C*H$_2$C), 22.7 (CH*C*H$_2$C). **IR** (ATR): 3386 (O-H st), 2937 (C-H st), 2865 (C-H st), 1511 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 194 (M^+-H_2O), 1), 165 (M^+-NO_2, 1), 199 (21), 139 (M^+-$C^2H^2NO^2$, 1), 105 (68), 93 (40), 92 (24), 91 (100), 83 (23), 81 (29), 80 (20), 79 (91), 78 (24), 77 (73), 67 (35), 65 (25), 55 (58), 53 (27).

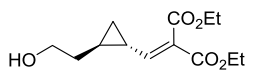


Dimethyl (*E*)-2-(2-hydroxyethyl)-3-(2-nitrovinyl)cyclopropane-1,1-dicarboxylate (SI6f). Following the *general procedure K*, **SI6f** (0.19 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 64% yield as a yellow oil starting from **3f** (0.57 g, 1.1 mmol), HCl in dioxane (0.7 mL, 2.8 mmol), and MeOH (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.28-7.12 (m, 1H, CH=C*H*), 6.97-6.85 (m, 1H, C*H*=CH), 3.80-3.69 (m, 8H, 2 x OCH_3, OHCH_2CH$_2$), 2.61-2.49 (m, 1H, OHCH$_2$CH_aH$_b$), 2.40-2.29 (m, 1H, OHCH$_2$CH$_a$$H_b$), 1.81-1.69 (m, 1H, CHCC*H*), 1.66-1.53 (m, 1H, C*H*CCH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 167.4 (C=O), 167.1 (C=O), 141.1 (CH=*C*H), 138.3 (*C*H=CH), 61.2

($OHCH_2CH_2$), 53.4 (OCH_3), 53.3 (OCH_3), 42.2 ($CHCCH$), 31.8 ($CHCCH$), 30.6 ($OHCH_2CH_2$), 28.2 ($CHCCH$). **IR** (ATR): 3436 (O-H st), 2947 (C-H st), 1730 (C=O st), 1343 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 242 (27), 227 (20), 227 (M^+-NO_2, 3), 214 (M^+-CO_2Me, 20), 213 (29), 201 (M^+-$C_2H_2NO_2$, 4), 195 (31), 194 (48), 183 (50), 181 (28), 167 (45), 163 (66), 157 (M^+-$C_4H_6O_4$, 5), 156 (22), 155 (M^+-2 CO_2Me, 4), 153 (45), 152 (57), 139 (61), 135 (61), 95 (47), 94 (52), 77 (56), 59 (100).



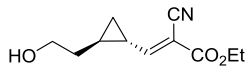
Diethyl (*E*)-2-(2-hydroxyethyl)-3-(2-nitrovinyl)cyclopropane-1,1-dicarboxylate (SI6g). Following the *general procedure K*, **SI6g** (0.11 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 43% yield as a yellow oil starting from **3g** (0.45 g, 0.8 mmol), HCl in dioxane (0.52 mL, 2.1 mmol), and EtOH (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.20 (d, *J* = 13.3 Hz, 1H, CH=C*H*), 6.95 (dd, *J* = 13.3, 10.5 Hz, 1H, C*H*=CH), 4.36-4.12 (m, 4H, OCH_2CH_3), 3.74 (t, *J* = 6.0 Hz, 2H, $OHCH_2CH_2$), 2.61-2.46 (m, 1H, CHCC*H*), 2.38-2.29 (m, 1H, C*H*CCH), 1.84-1.63 (m, 2H, $OHCH_2CH_2$), 1.62-1.54 (br s, 1H, OH), 1.28 (q, *J* = 7.3 Hz, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 167.0 (C=O), 167.0 (C=O), 141.1 (CH=*C*H), 138.5 (*C*H=CH), 62.5 (OCH_2CH_3), 62.4 (OCH_2CH_3), 61.4 ($OHCH_2CH_2$), 42.6 ($CHCCH$), 31.5 ($CHCCH$), 30.5 ($OHCH_2CH_2$), 30.3 ($CHCCH$), 14.3 (OCH_2CH_3), 14.2 (OCH_2CH_3). **IR** (ATR): 3541 (O-H st), 2980 (C-H st), 1726 (C=O st), 1648 (C=C st), 1522 (NO_2 st as), 1353 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 283 (M^+-H_2O, 1), 256 (60), 255 (M^+-NO_2, 26), 228 (M^+-CO_2Et, 2), 207 (45), 167 (43), 163 (67), 155 (M^+-$2CO_2Et$, 32), 138 (43), 137 (84), 135 (54), 125 (48), 121 (55), 110 (36), 108 (33), 107 (38), 97 (30), 96 (31), 95 (48), 94 (59), 83 (38), 81 (56), 79 (100), 77 (83), 67 (57), 66 (47), 55 (44), 53 (63).



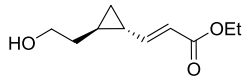
Diethyl 2-((2-(2-hydroxyethyl)cyclopropyl)methylene)malonate (SI6h). Following the *general procedure* K, **SI6h** (0.18 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 65% yield as a yellow oil starting from **3h** (0.53 g, 1.0 mmol), HCl in dioxane (0.67 mL, 2.7 mmol) and EtOH (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.30 (d, *J* = 11.2 Hz, 1H, C*H*=C), 4.20 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.10 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.58 (t, *J* = 6.3 Hz, 2H, $HOCH_2CH_2$), 3.0-2.65 (br s, 1H, OH), 1.71-1.52 (m, 2H, $OHCH_2CH_2$), 1.46-1.35 (m, 1H, C*H*CH_2CH), 1.12-1.09 (m, 7H, OCH_2CH_3, $CHCH_2CH$), 0.87 (t, *J* = 6.8 Hz, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 166.0 (C=O), 164.3 (C=O), 155.5 (*C*H=C), 125.2 (CH=*C*), 62.1 ($OHCH_2CH_2$), 61.2 (OCH_2CH_3), 61.1 (OCH_2CH_3), 36.3 ($OHCH_2CH_2$), 21.2 ($CHCH_2CH$), 20.2 ($CHCH_2CH$), 16.8 ($CHCH_2CH$), 14.2 (OCH_2CH_3), 14.1 (OCH_2CH_3). **IR** (ATR): 3465 (O-H st), 2984 (C-H st), 1724 (C=O st), 1630 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 239 (M^+-H_2O, 3), 210 (14), 184 (57), 183 (M^+-CO_2Et, 17), 156 (100), 128 (66), 110 (84), 98 (M^+-$C_7H_{10}O_4$, 1), 91 (30), 79 (69), 65 (20), 53 (29). **HRMS**: Calculated for $[C_{13}H_{21}O_5]^+$: 257.1389 [$(M+H)^+$]; found: 257.1393.

2-((2-(2-hydroxyethyl)cyclopropyl)methylene)malononitrile (SI6i). Following the *general procedure K*, **SI6i** (0.96 g, 5.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 68% yield as a yellow oil starting from **3i** (0.21 g, 0.5 mmol), HCl in dioxane (0.32 mL, 1.3 mmol) and MeOH (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:7.8): 6.99* (d, *J* = 11.7 Hz, 1H, CH=C), 6.70 (d, *J* = 11.3 Hz, 1H, CH=C), 3.66 (t, *J* = 5.9 Hz, 2H, $OHCH_2CH_2$), 2.45-2.26 (br s, 1H, OH), 1.90 (ddt, *J* = 11.5, 7.9, 3.9 Hz, 1H, C*H*CH_2CH), 1.73-1.46 (m, 3H, $OHCH_2CH_2$,

$CHCH_2CH$), 1.28 (dddd, *J* = 19.1, 14.8, 9.1, 5.5 Hz, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 173.8 (*C*H=C), 112.8 (CN), 111.7 (CN), 83.8 (CH=*C*), 61.4 ($OHCH_2CH_2$), 35.7 ($OHCH_2CH_2$), 24.8 ($CHCH_2CH$), 24.6 ($CHCH_2CH$), 19.7 ($CHCH_2CH$). **IR** (ATR): 3386 (O-H st), 2230 (C-N st), 1591 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 162 (M^+, 1), 145 (M^+-H_2O, 3), 141 (100), 131 (79), 118 (31), 105 (86), 98 (M^+-C_3N_2, 1), 77 (62), 65 (28), 57 (23), 51 (27). **HRMS**: Calculated for $[C_9H_9NO_2]^-$: 161.0715 $[(M-H)^-]$; found: 161.0716.

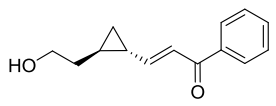


Ethyl (*Z*)-2-cyano-3-(2-(2-hydroxyethyl)cyclopropyl)acrylate (SI6j). Following the *general procedure* K, **SI6j** (0.42 g, 2.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 90% yield as a yellow oil starting from **3j** (1.00 g, 2.2 mmol), HCl in dioxane (1.34 mL, 5.6 mmol) and EtOH (4.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.93 (d, *J* = 11.4 Hz, 1H, CH=C), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.55 (t, *J* = 6.2 Hz, 2H, $OHCH_2CH_2$), 3.35-3.05 (br s, 1H, OH), 1.79-1.70 (m, 1H, $CHCH_2CH$), 1.57-1.46 (m, 2H, $OHCH_2CH_2$), 1.44-1.35 (m, 1H, $CHCH_2CH$), 1.18 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.13-1.06 (m, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 168.1 (*C*H=C), 161.5 (C=O), 114.4 (CN), 104.7 (CH=*C*), 61.8 ($OHCH_2CH_2$), 61.3 (OCH_2CH_3), 35.7 ($OHCH_2CH_2$), 23.3 ($CHCH_2CH$), 23.1 ($CHCH_2CH$), 18.4 ($CHCH_2CH$), 14.0 (OCH_2CH_3). **IR** (ATR): 3453 (O-H st), 2972 (C-H st), 2252 (C-N st), 1724 (C=O st), 1605 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 209 (M^+, 8), 178 (24), 163 (26), 146 (49), 136 (M^+-CO_2Et, 23), 133 (84), 119 (94), 106 (100), 91 (62), 77 (82), 67 (34), 52 (45). **HRMS**: Calculated for $[C_{11}H_{16}NO_3]^+$: 210.1130 $[(M+H)^+]$; found: 210.1136.



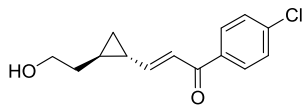
ethyl (*E*)-3-((1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl)acrylate (SI6k). Following the *general procedure K*, **SI6k** (0.12 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 64% yield as yellow oil starting from **3k** (0.44 g, 1.0 mmol), HCl in dioxane (0.66 mL, 2.7 mmol) and EtOH (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.46 (dd, *J* = 15.4, 10.0 Hz, 1H, C*H*=CH), 5.83 (d, *J* = 15.4 Hz, 1H, CH=C*H*), 4.21-4.12 (m, 2H, OCH_2CH_3), 3.71 (t, *J* = 6.5 Hz, 2H, $SiOCH_2CH_2$), 1.69-1.62 (br s, 1H, OH), 1.58 (q, *J* = 6.6 Hz, 2H, OCH_2CH_2), 1.36 (ddd, *J* = 9.8, 8.2, 4.3 Hz, 1H, $CHCH_2CH$), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.08 (dddd, *J* = 13.3, 8.3, 6.7, 4.0 Hz, 1H, $CHCH_2CH$), 0.90-0.77 (m, 2H, $CHCH_2CH$).

General procedure L: To a solution of **3l-z** (1.5 mmol, 1.0 eq) in THF (15 mL, 0.1 *M*), TBAF (1 *M* in THF, 1.6 mmol, 1.1 eq) was added and the reaction was stirred at room temperature for 1 hour. When the reaction was finished, the solvent was removed and the crude was then purified by flash column chromatography to afford pure **SI6l-z**.

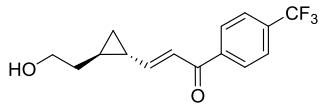


(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-phenylprop-2-en-1-one (SI6l). Following the *general procedure L*, **SI6l** (0.11 g, 0.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 74% yield as a yellow oil starting from **3l** (0.30 g, 0.7 mmol), TBAF (0.73 mL, 0.7 mmol) and THF (7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.96-7.88 (m, 2H, C_{arom}-H),

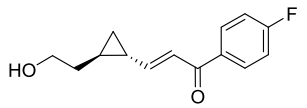
7.76-7.30 (m, 3H, C_{arom}-H), 6.97 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.59 (dd, *J* = 15.1, 10.1 Hz, 1H, C*H*=CH), 3.71 (t, *J* = 6.5 Hz, 2H, OHCH_2CH$_2$), 2.35-2.08 (br s, 1H, OH), 1.61 (q, *J* = 6.8 Hz, 2H, OHCH$_2$CH_2), 1.56-1.43 (m, 1H, CHCH$_2$C*H*), 1.21-1.12 (m, 1H, C*H*CH$_2$CH), 0.97-0.81 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 190.1 (C=O), 154.5 (CH=*C*H), 138.2 (C_{arom}-C), 132.6 (C_{arom}-H), 129.6 (C_{arom}-H), 128.6 (C_{arom}-H), 128.5 (C_{arom}-H), 127.7 (C_{arom}-H), 122.7 (*C*H=CH), 62.4 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 22.8 (CHCH$_2$*C*H), 20.7 (*C*HCH$_2$CH), 16.2 (CH*C*H$_2$CH). **IR** (ATR): 3453 (O-H st), 1738 (C=O st), 1655 (C=C st) cm^{-1}.



(*E*)-1-(4-chlorophenyl)-3-(2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6m). Following the *general procedure L*, **SI6m** (0.26 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 73% yield as a yellow oil starting from **3m** (0.70 g, 1.4 mmol), TBAF (1.50 mL, 1.5 mmol) and THF (14 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.90-7.83 (m, 2H, C_{arom}-H), 7.46-7.40 (m, 2H, C_{arom}-H), 6.94 (d, *J* = 15.1 Hz, CH=C*H*), 6.62 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.74 (t, *J* = 6.4 Hz, 2H, OHCH_2CH$_2$), 1.68-1.57 (m, 2H, OHCH$_2$CH_2), 1.57-1.46 (m, 2H, CHCH$_2$C*H*, OH), 1.27-1.15 (m, 1H, C*H*CH$_2$CH), 1.01-0.89 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.6 (C=O), 155.0 (*C*H=CH), 139.0 (C_{arom}-C), 136.6 (C_{arom}-C), 129.9 (C_{arom}-H), 128.9 (C_{arom}-H), 122.3 (CH=*C*H), 62.6 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 22.9 (CHCH$_2$*C*H), 20.8 (*C*HCH$_2$CH), 16.4 (CH*C*H$_2$CH). **IR** (ATR): 3453 (O-H st), 2972 (C-H st), 1738 (C=O st) cm^{-1}.

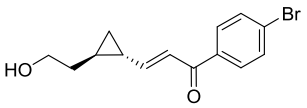


(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (SI6n). Following the *general procedure L*, **SI6n** (0.02 g, 0.06 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 67% yield as a yellow oil starting from **3n** (0.05 g, 0.1 mmol), TBAF (0.11 mL, 0.1 mmol) and THF (1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.00 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.72 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 6.95 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.64 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.75 (t, *J* = 6.4 Hz, 2H, OHCH_2CH$_2$), 1.73-1.46 (m, 4H, OHCH$_2$CH_2, CHCH$_2$C*H*, OH), 1.28-1.19 (m, 1H, C*H*CH$_2$CH), 1.04-0.90 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.0 (C=O), 156.0 (*C*H=CH), 141.2 (C_{arom}-C), 137.7 (q, J_{CF} = 271.0 Hz, CF_3), 128.8 (C_{arom}-H), 125.7 (q, $^{3}J_{CF}$ = 3.9 Hz, C_{arom}-H), 122.5 (CH=*C*H), 62.5 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$CH$_2$), 23.0 (CHCH$_2$*C*H), 21.1 (CH*C*H$_2$CH), 16.6 (*C*HCH$_2$CH). **IR** (ATR): 3461 (O-H st), 2972 (C-H st), 1738 (C=O st), 1368 (C-F st), 776 (CF_3) cm^{-1}. **MS** (EI) m/z (%): 284 (M^{+}. 2), 281 (27), 265 (18), 253 (17), 225 (65), 215 (M^{+}-CF_3, 2), 212 (29), 209 (21), 208 (19), 207 (100), 199 (29), 193 (16), 173 (76), 145 (64), 78 (18), 77 (20).

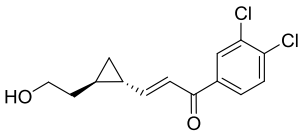


(*E*)-1-(4-fluorophenyl)-3-(2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6o). Following the *general procedure L*, **SI6o** (0.17 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 64% yield as a yellow oil starting from **3o** (0.53 g, 1.1 mmol), TBAF (1.24 mL, 1.2 mmol) and THF (11 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.96-7.87 (m, 2H, C_{arom}-H), 7.14-7.03 (m, 2H, C_{arom}-H), 6.92 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.69 (t, *J* = 6.5 Hz, 2H, OHCH_2CH$_2$), 2.39-2.22 (br s, 1H, OH), 1.66-1.54 (m, 2H, OHCH$_2$CH_2), 1.53-1.42 (m, 1H, CHCH$_2$C*H*), 1.23-1.12 (m, 1H, C*H*CH$_2$CH), 0.96-0.84 (m, 2H, CHCH_2CH).

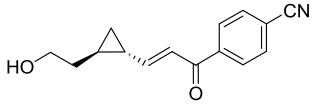
^{13}C NMR (75.4 MHz, $CDCl_3$) (δ, ppm): 188.4 (C=O), 165.4 (d, $^1J_{C\text{-}F}$ = 254.0 Hz, CCHCHCF), 154.9 (*C*H=CH), 131.0 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, C*C*HCHCF), 122.1 (CH=*C*H), 115.6 (d, $^2J_{C\text{-}F}$ = 21.8 Hz, CCH*C*HCF), 62.3 (OH*C*H_2CH$_2$), 36.5 (OHCH$_2$*C*H$_2$), 2.8 (CHCH$_2$*C*H), 20.8 (*C*HCH$_2$CH), 16.3 (CH*C*H$_2$CH). **IR** (ATR): 3411 (O-H st), 1659 (C=O st), 1601 (C=C st), 1228 (C-F st) cm^{-1}.



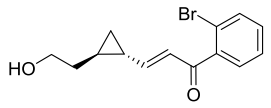
(*E*)-1-(4-bromophenyl)-3-(2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6p). Following the *general procedure L*, **SI6p** (0.25 g, 0.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 70% yield as a yellow oil starting from **3p** (0.64 g, 1.2 mmol), TBAF (1.30 mL, 1.3 mmol) and THF (12 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.81-7.77 (m, 2H, C$_{arom}$-H), 7.59-7.56 (m, 2H, C$_{arom}$-H), 6.93 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.61 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.74 (t, *J* = 6.3 Hz, 2H, OH*C*H_2CH$_2$), 1.67-1.58 (m, 2H, OHCH$_2$CH_2), 1.56- 1.47 (m, 2H, C*H*CH$_2$C*H*), 1.24-1.17 (br s, 1H, OH), 1.01-0.88 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.8 (C=O), 155.1 (*C*H=CH), 137.0 (C$_{arom}$-C), 131.9 (C$_{arom}$-H), 130.0 (C$_{arom}$-H), 127.7 (C$_{arom}$-C), 122.3 (CH=*C*H), 62.6 (OH*C*H_2CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 22.9 (CHCH$_2$*C*H), 20.8 (*C*HCH$_2$CH), 16.4 (CH*C*H$_2$CH). **IR** (ATR): 3465 (O-H st), 1741 (C=O st), 765 (C-Br st) cm^{-1}.



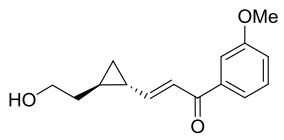
(*E*)-1-(3,4-dichlorophenyl)-3-(2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6q). Following the *general procedure L*, **SI6q** (0.15 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 78% yield as a yellow oil starting from **3q** (0.41 g, 0.8 mmol), TBAF (0.87 mL, 0.9 mmol) and THF (8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99 (d, *J* = 2.0 Hz, 1H, C$_{arom}$-H), 7.74 (dd, *J* = 8.3, 2.0 Hz, 1H, C$_{arom}$-H), 7.52 (d, *J* = 8.3 Hz, 1H, C$_{arom}$-H), 6.90 (d, *J* = 15.0 Hz, 1H, CH=C*H*), 6.63 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 3.73 (t, *J* = 6.4 Hz, 2H, OH*C*H_2CH$_2$), 1.73 (br s, 1H, OH), 1.67-1.57 (m, 2H, OHCH$_2$CH_2), 1.55-1.48 (m, 1H, CHCH$_2$C*H*), 1.27-1.18 (m, 1H, C*H*CH$_2$CH), 1.02-0.89 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 187.3 (C=O), 156.0 (*C*H=CH), 137.8 (C$_{arom}$-C), 137.1 (C$_{arom}$-C), 133.2 (C$_{arom}$-C), 130.7 (CH=*C*H), 130.5 (C$_{arom}$-H), 127.5 (C$_{arom}$-H), 121.7 (C$_{arom}$-H), 62.5 (OH*C*H$_2$CH$_2$), 36.5 (OHCH$_2$*C*H$_2$), 23.0 (CHCH$_2$*C*H), 21.1 (*C*HCH$_2$CH), 16.6 (CH*C*H$_2$CH). **IR** (ATR): 3540 (O-H st), 1738 (C=O st) cm^{-1}.



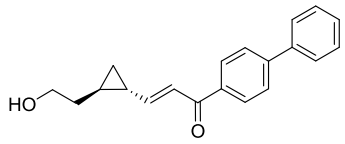
(*E*)-4-(3-(2-(2-hydroxyethyl)cyclopropyl)acryloyl)benzonitrile (SI6r). Following the *general procedure L*, **SI6r** (0.10 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 51% yield as a yellow oil starting from **3r** (0.40 g, 0.8 mmol), TBAF (0.91 mL, 0.9 mmol) and THF (8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.01-7.95 (m, 2H, C$_{arom}$-H), 7.78-7.73 (m, 2H, C$_{arom}$-H), 6.92 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.64 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.73 (t, *J* = 6.4 Hz, 2H, OH*C*H_2CH$_2$), 1.69-1.49 (m, 4H, OHCH$_2$CH_2, CHCH$_2$C*H*, OH), 1.31-1.17 (m, 1H, C*H*CH$_2$CH), 1.04-0.91 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.5 (C=O), 156.7 (*C*H=CH), 141.6 (C$_{arom}$-C), 132.5 (C$_{arom}$-H), 128.9 (C$_{arom}$-H), 122.1 (CH=*C*H), 118.2 (CN), 115.8 (C$_{arom}$-C), 62.5 (OH*C*H$_2$CH$_2$), 36.5 (OHCH$_2$*C*H$_2$), 23.1 (CHCH$_2$*C*H), 21.2 (*C*HCH$_2$CH), 16.7 (CH*C*H$_2$CH). **IR** (ATR): 3501 (O-H st), 3009 (C-H st), 1741 (C=O st) cm^{-1}.



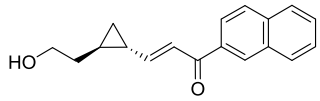
(*E*)-1-(2-bromophenyl)-3-((1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6s). Following the *general procedure L*, **SI6s** (0.18 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 42% yield as a yellow oil starting from **3s** (0.78 g, 1.5 mmol), TBAF (1.61 mL, 1.6 mmol) and THF (15 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.58-7.55 (m, 1H, C_{arom}-H), 7.35-7.31 (m, 1H, C_{arom}-H), 7.30-7.24 (m, 2H, C_{arom}-H), 6.50-6.46 (m, 2H, CH=C*H*), 6.24-6.18 (m, 1H, C*H*=CH), 3.71 (m, 2H, OHCH_2CH$_2$), 1.95-1.71 (br s, 1H, OH), 1.67-1.50 (m, 2H, OHCH$_2$CH_2), 1.49-1.42 (m, 1H, CHCH$_2$C*H*), 1.15-1.08 (m, 1H, C*H*CH$_2$CH), 0.92-0.85 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 194.3 (C=O), 157.3 (*C*H=CH), 141.2 (C_{arom}-C), 133.4 (C_{arom}-H), 131.1 (C_{arom}-H), 129.0 (C_{arom}-H), 127.3 (C_{arom}-H), 127.1 (CH=*C*H), 119.4 (C_{arom}-C), 62.4 (OH*C*H$_2$CH$_2$), 36.5 (OHCH$_2$*C*H$_2$), 22.7 (CHCH$_2$*C*H), 21.1 (*C*HCH$_2$CH), 16.6 (CH*C*H$_2$CH). **MS** (EI) m/z (%): 237 (25), 235 (25), 224 (28), 185 (59), 183 (69), 182 (M^+-C_7H_4O, 4), 157 (50), 155 (29), 115 (40), 111 (M^+-C_7H_4BrO, 4), 91 (36), 81 (30), 79 (29), 77 (89), 76 (52), 75 (51), 74 (40), 65 (26), 63 (35), 53 (45), 51 (81), 50 (100).



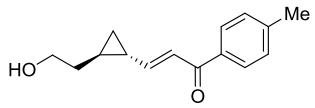
(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-(3-methoxyphenyl)prop-2-en-1-one (SI6t). Following the *general procedure L*, **SI6t** (0.18 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 53% yield as a yellow oil starting from **3t** (0.69 g, 1.4 mmol), TBAF (1.55 mL, 1.5 mmol) and THF (14 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.52-7.41 (m, 2H, C_{arom}-H), 7.34 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.07 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H, C_{arom}-H), 6.95 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.59 (dd, *J* = 15.1, 10.1 Hz, 1H, C*H*=CH), 3.84 (s, 3H, OCH_3), 3.71 (t, *J* = 6.4 Hz, 2H, OHCH_2CH$_2$), 1.96 (br s, 1H, OH), 1.66-1.54 (m, 2H, OHCH$_2$CH_2), 1.53-1.46 (m, 1H, CHCH$_2$C*H*), 1.25-1.11 (m, 1H, C*H*CH$_2$CH), 0.97-0.84 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.7 (C=O), 159.9 (C_{arom}-C), 154.5 (*C*H=CH), 139.6 (C_{arom}-C), 129.5 (CH=*C*H), 122.7 (C_{arom}-H), 121.0 (C_{arom}-H), 119.1 (C_{arom}-H), 112.9 (C_{arom}-H), 62.5 (OH*C*H$_2$CH$_2$), 55.5 (OCH_3), 36.6 (OHCH$_2$*C*H$_2$), 22.8 (CHCH$_2$*C*H), 20.7 (*C*HCH$_2$CH), 16.2 (CH*C*H$_2$CH). **IR** (ATR): 3451 (O-H st), 3016 (C-H st), 1734 (C=O st) cm^{-1}.



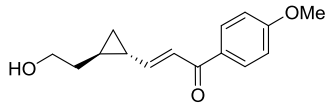
(*E*)-1-([1,1'-biphenyl]-4-yl)-3-(2-(2-hydroxyethyl)cyclopropyl)prop-2-en-1-one (SI6u). Following the *general procedure L*, **SI6u** (0.52 g, 1.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 57% yield as a yellow oil starting from **3u** (1.64 g, 3.1 mmol), TBAF (3.41 mL, 3.4 mmol) and THF (31 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) 8.03-7.98 (m 2H, C_{arom}-H), 7.68-7.66 (m, 2H, C_{arom}-H), 7.64-7.60 (m, 2H, C_{arom}-H), 7.46 (dd, *J* = 8.4, 6.8 Hz, 2H, C_{arom}-H), 7.42-7.36 (m, 1H, C_{arom}-H), 7.03 (d, *J* = 15.0 Hz, 1H, CH=C*H*), 6.65 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.74 (t, *J* = 6.4 Hz, 2H, OHCH_2CH$_2$), 2.21-1.99 (br s, 1H, OH), 1.69-1.58 (m, 2H, OHCH$_2$CH_2), 1.54 (ddt, *J* = 10.1, 8.3, 4.3 Hz, 1H, CHCH$_2$C*H*), 1.24-1.19 (m, 1H, C*H*CH$_2$CH), 0.97 (dt, *J* = 8.9, 4.7 Hz, 1H, CHCH_aH$_b$CH), 0.91 (ddd, *J* = 8.2, 6.2, 4.8 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.5 (C=O), 154.4 (*C*H=CH), 145.3 (C_{arom}-C), 140.1 (C_{arom}-C), 136.9 (C_{arom}-C), 129.1 (C_{arom}-H), 129.0 (C_{arom}-H), 128.2 (CH=*C*H), 127.3 (C_{arom}-H), 122.6 (C_{arom}-H), 62.5 (OH*C*H$_2$CH$_2$), 38.6 (OHCH$_2$*C*H$_2$), 22.8 (CHCH$_2$*C*H), 20.7 (*C*HCH$_2$CH), 16.3 (CH*C*H$_2$CH). **IR** (ATR): 3489 (O-H st), 3016 (C-H st), 1738 (C=O st) cm^{-1}.



(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-(naphthalen-2-yl)prop-2-en-1-one (SI6v). Following the *general procedure L*, **SI6v** (0.23 g, 0.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 66% yield as a yellow oil starting from **3v** (0.63 g, 1.3 mmol), TBAF (1.44 mL, 1.4 mmol) and THF (13 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.44 (d, *J* = 1.7 Hz, 1H, C_{arom}-H), 8.06-7.83 (m, 4H, C_{arom}-H), 7.55 (pd, *J* = 7.1, 1.5 Hz, 2H, C_{arom}-H), 7.15 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.67 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.74 (t, *J* = 6.4 Hz, 2H, OHC*H*$_2$CH$_2$), 1.95-1.78 (br s, 1H, OH), 1.71-1.51 (m, 3H, OHCH$_2$C*H*$_2$, CHCH$_2$C*H*), 1.30-1.14 (m, 1H, C*H*CH$_2$CH), 1.03-0.85 (m, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.8 (C=O), 154.4 (*C*H=CH), 135.5 (C_{arom}-C), 135.4 (C_{arom}-C), 132.6 (C_{arom}-C), 129.8 (C_{arom}-H), 129.5 (C_{arom}-H), 128.5 (C_{arom}-H), 128.3 (C_{arom}-H), 127.9 (C_{arom}-H), 126.8 (C_{arom}-H), 124.6 (C_{arom}-H), 122.7 (CH=*C*H), 62.5 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 22.9 (CHCH$_2$*C*H), 20.7 (*C*HCH$_2$CH), 16.3 (CH*C*H$_2$CH). **IR** (ATR): 3451 (O-H st), 3009 (C-H t), 1738 (C=O st), 1655 (=C st) cm^{-1}.

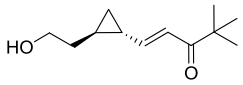


(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-(*p*-tolyl)prop-2-en-1-one (SI6w). Following the *general procedure L*, **SI6w** (0.22 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 62% yield as a yellow oil starting from **3w** (0.70 g, 1.5 mmol), TBAF (1.60 mL, 1.6 mmol) and THF (15 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.88-7.79 (m, 2H, C_{arom}-H), 7.29-7.21 (m, 2H, C_{arom}-H), 6.98 (d, *J* = 15.0, 1H, CH=C*H*), 6.58 (dd, *J* = 15.1, 10.2 Hz, 1H, C*H*=CH), 3.72 (t, *J* = 6.5 Hz, 2H, OH-C*H*$_2$-CH$_2$), 2.40 (s, 3H, CH$_3$), 1.95-1.82 (br s, 1H, OH), 1.65-1.56 (m, 2H, OHCH$_2$C*H*$_2$), 1.53-1.46 (m, 1H, CHCH$_2$C*H*), 1.23-1.12 (m, 1H, C*H*CH$_2$CH), 0.98-0.84 (m, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 189.6 (C=O), 153.9 (*C*H=CH), 143.4 (C_{arom}-C), 135.6 (C_{arom}-C), 129.3 (C_{arom}-H), 128.6 (C_{arom}-H), 122.7 (CH=*C*H), 62.5 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 22.7 (CHCH$_2$*C*H), 21.7 (CH$_3$), 20.6 (*C*HCH$_2$CH), 16.1 (CH*C*H$_2$CH). **IR** (ATR): 3465 (O-H st), 2969 (C-H st), 1741 (C=O st) cm^{-1}.



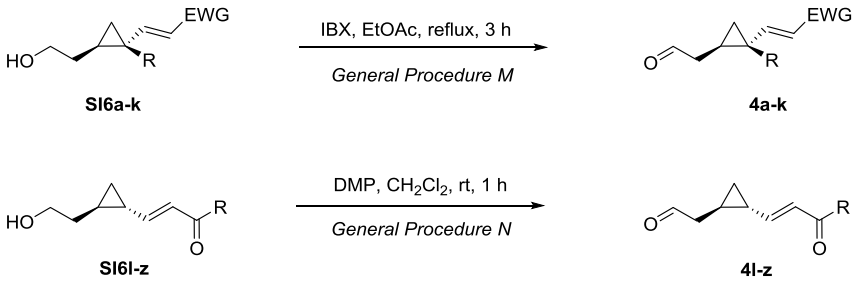
(*E*)-3-(2-(2-hydroxyethyl)cyclopropyl)-1-(4-methoxyphenyl)prop-2-en-1-one (SI6x). Following the *general procedure L*, **SI6x** (0.25 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 77% yield as a yellow oil starting from **3x** (0.61 g, 1.3 mmol), TBAF (1.40 mL, 1.4 mmol) and THF (13 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.99-7.90 (m, 2H, C_{arom}-H), 7.01-6.91 (m, 3H, C_{arom}-H, CH=C*H*), 6.58 (dd, *J* = 15.0, 10.1 Hz, 1H, C*H*=CH), 3.86 (s, 3H, OCH$_3$), 3.73 (t, *J* = 6.4 Hz, 2H, OHC*H*$_2$CH$_2$), 1.72-1.88 (br s, 1H, OH), 1.65-1.57 (m, 2H, OHCH$_2$C*H*$_2$), 1.56-1.44 (m, 1H, CHCH$_2$C*H*), 1.22-1.12 (m, 1H, C*H*CH$_2$CH), 1.00-0.82 (m, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 188.3 (C=O), 163.3 (C_{arom}-C), 153.3 (*C*H=CH), 131.0 (C_{arom}-C), 130.8 (C_{arom}-H), 122.4 (CH=*C*H), 113.8 (C_{arom}-H), 62.6 (OH*C*H$_2$CH$_2$), 55.6 (OCH$_3$), 36.6 (OHCH$_2$*C*H$_2$), 22.7 (CHCH$_2$*C*H), 20.5 (*C*HCH$_2$CH), 16.1 (CH*C*H$_2$CH). **IR** (ATR): 3443 (O-H st), 2930 (C-H st), 1741 (C=O st), 1605 (C=C st) cm^{-1}.

((*E*)-4-(2-(2-hydroxyethyl)cyclopropyl)but-3-en-2-one (SI6y). Following the *general procedure L*, **SI6y** (0.12 g, 0.8 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 87% yield as a yellow oil starting from **3y** (0.34 g, 0.9 mmol), TBAF (0.96 mL, 0.9 mmol) and THF (9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.32 (dd, *J* = 15.7, 9.6 Hz, 1H, C*H*=CH), 6.14 (d, *J* = 15.7 Hz, 1H, CH=C*H*), 3.72 (t, *J* = 6.4 Hz, 2H, SiOCH_2CH$_2$), 2.19 (s, 3H, CH_3), 1.66-1.56 (m, 2H, SiOCH$_2$CH_2), 1.42-1.33 (m, 1H, CHCH$_2$C*H*), 1.18-1.07 (m, 1H, C*H*CH$_2$CH), 0.92-0.85 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 197.9 (C=O), 152.6 (*C*H=CH), 128.2 (CH=*C*H), 62.5 (OH*C*H$_2$CH$_2$), 36.6 (OHCH$_2$*C*H$_2$), 27.1 (CH_3), 22.0 (CHCH$_2$*C*H), 20.4 (*C*HCH$_2$CH), 16.0 (CH*C*H$_2$CH). **IR** (ATR): 3451 (O-H st), 2937 (C-H st), 1738 (C=O st), 1655 (C=C st) cm^{-1}.

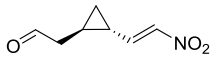


(*E*)-1-((1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl)-4,4-dimethylpent-1-en-3-one (SI6z). Following the *general procedure L*, **SI6z** (0.11 g, 0.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 73% yield as a yellow oil starting from **3z** (0.32 g, 0.7 mmol), TBAF (0.81 mL, 0.8 mmol) and THF (7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.56 (dd, *J* = 15.0, 1.2 Hz, 1H, CH=C*H*), 6.42 (ddd, *J* = 15.0, 9.8, 1.2 Hz, 1H, C*H*=CH), 3.70 (t, *J* = 6.5 Hz, 2H, SiOCH_2CH$_2$), 1.79-1.68 (br s, 1H, OH), 1.69-1.47 (m, 2H, SiOCH$_2$CH_2), 1.39 (ddt, *J* = 12.9, 8.4, 4.0 Hz, 1H, CHCH$_2$C*H*), 1.13 (s, 9H, 3 x CH_3), 1.11-1.03 (m, 1H, C*H*CH$_2$CH), 0.90-0.77 (m, 2H, CHCH_2CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.9 (C=O), 152.0 (*C*H=CH), 121.3 (CH=*C*H), 62.6 (OH*C*H$_2$CH$_2$), 42.8 (*C*(CH$_3$)$_3$), 36.6 (OHCH$_2$*C*H$_2$), 26.5 (3 x CH_3), 22.3 (CHCH$_2$*C*H), 20.2 (*C*HCH$_2$CH), 15.8 (CH*C*H$_2$CH).

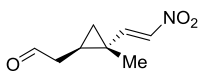
2.1.8. Synthesis of 4a-z



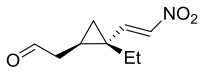
General procedure M: To a solution of the corresponding alcohol **SI6a-k** (1.5 mmol, 1.0 eq) in EtOAc (15 mL, 0.1 *M*), IBX (3.0 mmol, 2.0 eq) was added in one portion and the reaction mixture was heated to reflux for 3 hours. Once the reaction was finished, it was filtered by celite® and concentrated in vacuo. The crude was dissolved in Et_2O (20 mL) and it was washed with saturated $NaHCO_3$ solution (3 x 20 mL). Organic extract were dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **4a-k**.



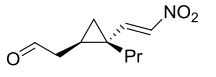
***trans*-(*E*)-2-(2-(2-nitrovinyl)cyclopropyl)acetaldehyde (4a).** Following the *general procedure M*, **4a** (0.33 g, 2.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 70% yield as a yellow solid starting from **SI6a** (0.48 g, 3.1 mmol), IBX (1.70 g, 6.1 mmol) and EtOAc (30 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (s, 1H, CHO), 7.11 (d, *J* = 13.2 Hz, 1H, CH=C*H*), 6.83 (dd, *J* = 13.2, 10.2 Hz, 1H, C*H*=CH), 2.53 (dt, *J* = 6.7, 1.6 Hz, 2H, CHOCH_2), 1.51-1.42 (m, 2H, C*H*CH$_2$C*H*), 1.12 (dt, *J* = 8.6, 5.3 Hz, 1H, CHCH_aH$_b$CH), 1.05 (dt, *J* = 8.0, 5.7 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 146.5 (CH=*C*H), 137.9 (*C*H=CH), 47.1 (CHO*C*H$_2$), 18.3 (CHCH$_2$*C*H), 17.0 (*C*HCH$_2$CH), 16.0 (CH*C*H$_2$CH). **IR** (ATR): 2855 (C-H st), 1713 (C=O st), 1637 (C=C st), 1511 (NO_2 st as), 1393 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 109 (M$^+$-NO_2, 9), 108 (24), 81 (31), 80 (23), 79 (100), 78 (24), 77 (67), 69 (21), 67 (18), 66 (39), 65 (28), 55 (24), 53 (42), 52 (21), 51 (30). **HRMS**: Calculated for [$C_7H_8NO_3$]$^-$: 154.0504 [(M-H)$^-$]; found: 154.0509. **m.p**. (CH_2Cl_2) = 34-37°C.



(*E*)-2-(2-methyl-2-(2-nitrovinyl)cyclopropyl)acetaldehyde (4b). Following the *general procedure M*, **4b** (0.66 g, 0.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 57% yield as a yellow oil starting from **SI6b** (0.10 g, 0.6 mmol), IBX (0.33 g, 1.2 mmol) and EtOAc (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.80 (s, 1H, CHO), 6.98 (d, *J* = 13.4 Hz, 1H, CH=C*H*), 6.85 (d, *J* = 13.4 Hz, 1H, C*H*=CH), 2.75-2.51 (m, 2H, CHOCH_2), 1.59-1.45 (m, 1H, C*H*CH$_2$C), 1.29 (dd, *J* = 9.2, 5.2 Hz, 1H, CHCH_aH$_b$C), 1.20 (s, 3H, CH_3), 0.77 (t, *J* = 5.9 Hz, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.1 (CHO), 152.1 (CH=*C*H), 137.0 (*C*H=CH), 43.3 (CHO*C*H$_2$), 22.9 (CH*C*H$_2$C), 21.6 (*C*HCH$_2$C), 20.2 (CHCH$_2$*C*), 15.5 (CH_3). **IR** (ATR): 2965 (C-H st), 1734 (C=O st), 1622 (C=C st), 1372 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 214 (21), 213 (100), 183 (34), 154 (M$^+$-CH_3, 1), 78 (8). **m.p.** (CH_2Cl_2) = 50-53°C.

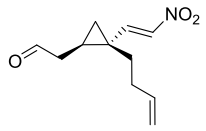


(*E*)-2-(2-ethyl-2-(2-nitrovinyl)cyclopropyl)acetaldehyde (4c). Following the *general procedure M*, **4c** (0.02 g, 0.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 70% yield as a yellow oil starting from **SI6c** (0.03 g, 0.2 mmol), IBX (0.11 g, 0.4 mmol) and EtOAc (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.82 (t, *J* = 1.4 Hz, 1H, CHO), 6.97 (s, 2H, C*H*=C*H*), 2.75-2.51 (m, 2H, CHOCH_2), 1.30-1.20 (m, 3H, CH_2CH$_3$, C*H*CH$_2$C), 1.01 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3), 0.86 (d, *J* = 7.5 Hz, 1H, CHCH_aH$_b$C), 0.73 (t, *J* = 6.0 Hz, 1H, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.0 (CHO), 150.0 (*C*H=CH), 100.1 (CH=*C*H), 43.2 (CHO*C*H$_2$), 25.7 (CHCH$_2$*C*), 23.4 (*C*H$_2$CH$_3$), 22.6 (*C*HCH$_2$C), 21.8 (CH*C*H$_2$C), 11.4 (CH$_2$*C*H$_3$). **IR** (ATR): 2922 (C-H st), 1734 (C=O), 1375 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for [$C_9H_{12}NO_3$]$^-$: 182.0817 [(M-H)$^-$]; found: 182.0836.

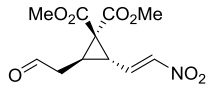


(*E*)-2-(2-(2-nitrovinyl)-2-propylcyclopropyl)acetaldehyde (4d) Following the *general procedure M*, **4d** (0.40 g, 1.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 65% yield as a brown oil starting from **SI6d** (0.60 g, 3.0 mmol), IBX (1.68 g, 6.0 mmol) and EtOAc (30 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:0.7): 9.75 (dd, *J* = 1.5 Hz, 1H, CHO), 9.70* (t, *J* = 1.4 Hz, 1H, CHO), 7.07-6.82 (m, 2H, C*H*=C*H*), 2.73-2.40 (m, 2H, CHOCH_2), 1.56-1.29 (m, 5H, CH_2CH_2CH$_3$, C*H*CH$_2$C), 1.29-1.11 (m, 1H, CHCH_aH$_b$C), 0.95-0.67 (m, 4H, CH$_2$CH$_2$CH_3, CHCH$_a$$H_b$C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.4 (CHO), 200.2* (CHO), 150.6 (*C*H=CH), 145.4* (*C*H=CH),

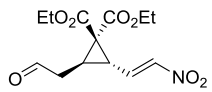
138.9 (CH=*C*H), 137.0 (CH=*C*H), 43.6 (CHO*C*H_2), 42.9* (CHO*C*H_2), 38.5 (*C*$H_2CH_2CH_3$), 32.3* (*C*$H_2CH_2CH_3$), 25.1 ($CHCH_2$*C*), 24.5* ($CHCH_2$*C*), 22.8 (*C*HCH_2C), 22.4* (*C*HCH_2C), 21.9 (CH*C*H_2C), 21.7* (CH*C*H_2C), 20.1 (CH_2*C*H_2CH_3), 19.6* (CH_2*C*H_2CH_3), 14.1 (CH_2CH_2*C*H_3), 14.0* (CH_2CH_2*C*H_3). **IR** (ATR): 2965 (C-H st), 1734 (C=O st), 1368 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 167 (100), 166 (20), 165 (60), 152 (37), 151 (M^+-NO_2, 22),91 (51). **HRMS**: Calculated for $[C_{10}H_{15}NO_3Na]^+$: 220.0950 [$(M+Na)^+$]; found: 220.0948.



(*E*)-2-(2-(but-3-en-1-yl)-2-(2-nitrovinyl)cyclopropyl)acetaldehyde (4e). Following the *general procedure M*, **4e** (0.03 g, 0.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 50% yield as a brown oil starting from **SI6e** (0.05 g, 0.2 mmol), IBX (0.13 g, 0.4 mmol) and EtOAc (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes minor diastereoisomer resonances; d.r.: 1:1): 9.76 (s, 1H, CHO), 7.07-6.88 (m, 2H, C*H*=C*H*), 5.84-5.68 (m, 1H, CH_2CH_2C*H*=CH_2), 5.07-4.97 (m, 2H, CH_2CH_2CH=CH_2), 2.69-2.51 (m, 2H, CHOCH_2), 2.37-2.06 (m, 4H, CH_2CH_2CH=CH_2), 1.77-1.48 (m, 3H, C*H*CH_2C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 199.6* (CHO), 150.0 (*C*H=CH), 145.8* (*C*H=CH), 139.4 (CH_2CH_2*C*H=CH_2), 139.4* (CH_2CH_2*C*H=CH_2), 119.5 (CH_2CH_2CH=*C*H_2), 115.7* (CH=*C*H), 115.5 (CH=*C*H), 94.6* (CH_2CH_2CH=*C*H_2), 43.9 (CHO*C*H_2), 43.3* (CHO*C*H_2), 36.8* (*C*H_2CH_2CH=CH_2), 36.0 (*C*H_2CH_2CH=CH_2), 31.2* (CH_2*C*H_2CH=CH_2), 30.8 (CH_2*C*H_2CH=CH_2), 25.0 ($CHCH_2$*C*), 24.4* ($CHCH_2$*C*), 22.9 (CH*C*H_2C), 22.5* (CH*C*H_2C), 22.1 (*C*HCH_2C), 21.9* (*C*HCH_2C). **IR** (ATR): 2930 (C-H st), 2868 (C-H st), 1724 (C=O st), 1511 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 151 (M^+-NO_2, 22), 150 (21), 121 (29), 109 (18), 108 (20), 107 (100), 105 (18), 93 (25), 91 (66), 81 (44), 79 (99), 78 (20), 77 (57), 67 (31), 65 (18).

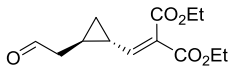


Dimethyl (*E*)-2-(2-nitrovinyl)-3-(2-oxoethyl)cyclopropane-1,1-dicarboxylate (4f). Following the *general procedure M*, **4f** (0.12 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 50% yield as a yellow oil starting from **SI6f** (0.25 g, 0.9 mmol), IBX (0.50 g, 1.8 mmol) and EtOAc (9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.71 (s, 1H, CHO), 7.19 (d, *J* = 13.3 Hz, 1H, CH=C*H*), 6.95-6.84 (m, 1H, C*H*=CH), 3.76 (app d, *J* = 2.6 Hz, 6H, 2 x OCH_3), 2.78-2.62 (m, 2H, CHOCH_2), 2.55-2.47 (m, 2H, C*H*CC*H*). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 198.2 (CHO), 167.0 (C=O), 166.7 (C=O), 141.7 (CH=*C*H), 137.2 (*C*H=CH), 53.5 (OCH_3), 53.4 (OCH_3), 41.5 (CHO*C*H_2), 41.1 (CH*C*CH), 30.2 (CHC*C*H), 27.2 (*C*HCCH). **IR** (ATR): 2959 (C-H st), 1726 (C=C st), 1436 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 271 (M^+, 1), 242 (M^+-CHO, 6), 225 (M^+-NO_2, 6), 212 (M^+-CO_2Me, 7), 153 (M^+-2 x CO_2Me, 8), 151 (15), 105 (17), 77 (71), 59 (100), 53 (24), 51 (45).

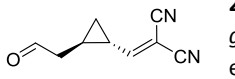


Diethyl (*E*)-2-(2-nitrovinyl)-3-(2-oxoethyl)cyclopropane-1,1-dicarboxylate (4g). Following the *general procedure M*, **4g** (0.09 g, 0.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 80% yield as a yellow oil starting from **SI6g** (0.11 g, 0.4 mmol), IBX (0.20 g, 0.7 mmol) and EtOAc (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.73 (s, 1H, CHO), 7.23-7.17 (m, 1H, CH=C*H*), 6.99-6.86 (m, 1H, C*H*=CH), 4.35-4.08 (m, 4H, OC$H_2$$CH_3$), 2.70-2.67 (m, 1H, CHCC*H*), 2.66-2.62 (C*H*CCH), 2.54-2.47 (m, 2H, CHOCH_2), 1.30-1.22 (m, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 198.2 (CHO), 166.6 (C=O), 166.3 (C=O), 141.6 (CH=*C*H), 137.4 (*C*H=CH), 62.6 (O*C*H_2CH_3), 41.5 (CHO*C*H_2),

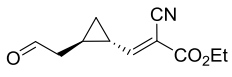
41.5 (CH*C*CH), 30.0 (CHC*C*H), 26.9 (*C*HCCH), 14.1 (OCH_2CH_3). **IR** (ATR): 2982 (C-H st), 1725 (C=O st), 1525 (NO_2 st as), 1350 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 285 (39), 253 (M^+-NO_2, 3), 226 (M^+-CO_2Et, 8), 181 (17), 179 (16), 165 (28), 153 (M^+-2 x CO_2Et 26), 151 (29), 137 (33), 135 (45), 134 (19), 123 (43), 109 (37), 107 (100), 105 (19), 103 (17), 95 (22), 81 (28), 79 (59), 78 (20), 77 (52), 67 (17), 65 (18), 55 (18), 53 (29), 51 (16). **HRMS**: Calculated for $[C_{13}H_{16}NO_7]^+$: 298.0927 [$(M-H)^-$]; found: 298.0927.



Diethyl 2-((2-(2-oxoethyl)cyclopropyl)methylene)malonate (4h). Following the *general procedure M*, **4h** (0.10 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 69% yield as a yellow oil starting from **SI6h** (0.15 g, 0.6 mmol), IBX (0.33 g, 1.2 mmol) and EtOAc (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.71 (s, 1H, CHO), 6.34 (d, *J* = 11.1 Hz, 1H, CH=C), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.15 (d, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.42 (qdd, *J* = 17.6, 7.0, 1.7 Hz, 2H, $CHOCH_2$), 1.81 (ddt, *J* = 12.0, 8.5, 4.4 Hz, 1H, $CHCH_2CH$), 1.38 (ddd, *J* = 10.5, 8.5, 5.3 Hz, 1H, $CHCH_2CH$), 1.24 (dt, *J* = 14.3, 7.1 Hz, 6H, OCH_2CH_3), 0.99 (ddt, *J* = 19.5, 8.1, 5.2 Hz, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.4 (CHO), 165.5 (C=O), 164.2 (C=O), 153.8 (*C*H=C), 126.1 (CH=*C*), 61.2 (OCH_2CH_3), 61.1 (OCH_2CH_3), 47.0 ($CHOCH_2$), 19.7 ($CHCH_2CH$), 16.9 ($CHCH_2CH$), 16.3 ($CHCH_2CH$), 14.1 (OCH_2CH_3), 14.0 (OCH_2CH_3). **IR** (ATR): 3012 (C-H st), 1741 (C=O st), 1620 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 254 (M^+, 1), 225 (M^+-CHO, 1), 181 (M^+-CO_2Et, 15), 162 (47), 136 (17), 110 (92), 108 (M^+-2 x CO_2Et, 17), 79 (100), 53 (35). **HRMS**: Calculated for $[C_{13}H_{19}O_5]^+$: 255.1233 [$(M+H)^+$]; found: 255.1235.

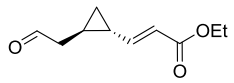


2-((2-(2-oxoethyl)cyclopropyl)methylene)malononitrile (4i). Following the *general procedure M*, **4i** (0.02 g, 0.07 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 21% yield as a yellow solid starting from **SI6i** (0.06 g, 0.3 mmol), IBX (0.2 g, 0.7 mmol) and EtOAc (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.72 (s, 1H, CHO), 6.72 (d, *J* = 11.2 Hz, 1H, CH=C), 2.59 (d, *J* = 6.8 Hz, 2H, $CHOCH_2$), 1.97-1.83 (m, 1H, $CHCH_2CH$), 1.79-1.66 ($CHCH_2CH$), 1.36-1.23 (m, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.4 (CHO), 172.4 (*C*H=C), 112.5 (CN), 111.4 (CN), 85.0 (CH=*C*), 46.3 ($CHOCH_2$), 23.8 ($CHCH_2CH$), 19.8 ($CHCH_2CH$), 18.5 ($CHCH_2CH$). **IR** (ATR): 2233 (C-N st), 1720 (C=O st), 1595 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 160 (M^+, 1), 142 (57), 133 (36), 115 (56), 104 (89), 91 (100), 77 (38), 67 (31), 51 (31). **HRMS**: Calculated for $[C_9H_7N_2O]^-$: 159.0560 [$(M-H)^-$]; found: 159.0558.



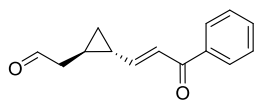
Ethyl (*Z*)-2-cyano-3-(2-(2-oxoethyl)cyclopropyl)acrylate (4j). Following the *general procedure M*, **4j** (0.18 g, 0.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 3:7) in 74% yield as a yellow oil starting from **SI6j** (0.25 g, 1.2 mmol), IBX (0.67 g, 2.4 mmol) and EtOAc (12 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.69 (s, 1H, CHO), 6.97 (d, *J* = 11.3 Hz, 1H, CH=C), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.63-2.42 (m, 2H, $CHOCH_2$), 1.83 (ddt, *J* = 12.0, 8.3, 4.3 Hz, 1H, $CHCH_2CH$), 1.66-1.51 (m, 1H, $CHCH_2CH$), 1.30-1.11 (m, 5H, OCH_2CH_3, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.7 (CHO), 166.4 (*C*H=C), 161.3 (C=O), 114.3 (CN), 106.0 (CH=*C*), 62.0 (OCH_2CH_3), 46.5 ($CHOCH_2$), 22.5 ($CHCH_2CH$), 18.6 ($CHCH_2CH$), 17.4 ($CHCH_2CH$), 14.0 (OCH_2CH_3). **IR** (ATR): 2987 (C-H st), 2362 (C-N st), 1720 (C=O st), 1609 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 391 (31), 390 (100), 207 (M^+, 3), 199 (30), 183

(15), 181 (M^+-CN, 14), 178 (M^+-CHO, 1), 135 (11), 134 (M^+-CO_2Et, 1). **HRMS**: Calculated for $[C_{11}H_{13}NO_3Na]^+$: 230.0793 [$(M+Na)^+$]; found: 230.0792.

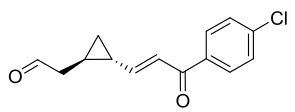


Ethyl (*E*)-3-((1*S*,2*R*)-2-(2-oxoethyl)cyclopropyl)acrylate (4k). Following the *general procedure M*, **4k** (0.30 g, 1.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 69% yield as a yellow oil starting from **SI6k** (0.43 g, 2.3 mmol), IBX (1.30 g, 4.6 mmol) and EtOAc (23 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.75 (s, 1H, CHO), 6.45 (dd, *J* = 15.5, 9.8 Hz, 1H, C*H*=CH), 5.82 (d, *J* = 15.4 Hz, 1H, CH=C*H*), 4.38-4.06 (m, 2H, OCH_2CH$_3$), 2.42 (td, *J* = 7.3, 1.8 Hz, 2H, CHOCH_2), 1.45-1.36 (m, 1H, CHCH$_2$C*H*), 1.25-1.20 (m, 3H, OCH$_2$CH_3), 0.95 (dd, *J* = 8.6, 5.5 Hz, 1H, C*H*CH$_2$CH), 0.84 (ddd, *J* = 8.3, 5.7, 4.6 Hz, 2H, CHCH_2CH).

General procedure N: To a solution of the corresponding alcohol **SI6l-z** (1.5 mmol, 1.0 eq) in CH_2Cl_2 (6 mL, 0.24 *M*), Dess-Martin periodinane (2.2 mmol, 1.5 eq) was added and the reaction was stirred at the same temperature for 1 hour. When the reaction was finished, the solvent was removed and the crude was then purified by flash column chromatography to afford pure **4l-z**.

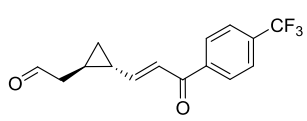


(*E*)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)cyclopropyl)acetaldehyde (4l). Following the *general procedure N*, **4l** (0.09 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 84% yield as a yellow oil starting from **SI6l** (0.11 g, 0.5 mmol), Dess-Martin periodinane (0.31 g, 0.7 mmol) and CH_2Cl_2 (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.73 (s, 1H, CHO), 7.88 (dq, *J* = 8.8, 2.1 Hz, 2H, C_{arom}-H), 7.54-7.34 (m, 3H, C_{arom}-H), 6.96 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.52-2.34 (m, 2H, CHOCH_2), 1.58-1.45 (m, 1H, CHCH$_2$C*H*), 1.41-1.30 (m, 1H, C*H*CH$_2$CH), 1.04-0.96 (m, 1H, CHCH_aH$_b$CH), 0.92-0.84 (m, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 189.8 (C=O), 152.8 (CH=*C*H), 137.9 (C_{arom}-C), 132.6 (C_{arom}-H), 128.5 (C_{arom}-H), 128.4 (C_{arom}-H), 123.4 (*C*H=CH), 47.1 (CHO*C*H$_2$), 22.1 (*C*HCH$_2$CH), 16.4 (CHCH$_2$*C*H), 15.6 (CH*C*H$_2$CH). **IR** (ATR): 3012 (C-H st), 1730 (C=O st), 1666 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 281 (22), 214 (M^+, 1), 208 (22), 207 (93), 106 (28), 105 (90), 96 (15), 94 (16), 83 (16), 79 (24), 78 (72), 77 (100), 73 (16), 52 (27), 51 (57). **HRMS**: Calculated for $[C_{14}H_{15}O_2]^+$: 215.1072 [$(M+H)^+$]; found: 215.1081.

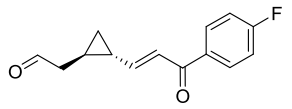


(*E*)-2-(2-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4m) Following the *general procedure N*, **4m** (0.16 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 60% yield as a yellow oil starting from **SI6m** (0.26 g, 1.0 mmol), Dess-Martin periodinane (0.67 g, 1.6 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.74 (t, *J* = 1.7 Hz, 1H, CHO), 7.85-7.78 (m, 2H, C_{arom}-H), 7.42-7.34 (m, 2H, C_{arom}-H), 6.91 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.53-2.34 (m, 2H, CHOCH_2), 1.56-1.47 (m, 1H, CHCH$_2$C*H*), 1.43-1.32 (m, 1H, C*H*CH$_2$CH), 1.02 (dt, *J* =

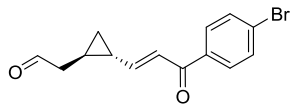
8.7, 4.9 Hz, 1H, CHC$H_a$$H_b$CH), 0.91 (dt, *J* = 8.3, 5.6 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.6 (CHO), 188.3 (C=O), 153.3 (*C*H=CH), 138.9 (C_{arom}-C), 136.2 (C_{arom}-C), 129.8 (C_{arom}-H), 128.8 (C_{arom}-H), 122.8 (CH=*C*H), 47.2 (CHO*C*H$_2$), 22.3 (CHCH$_2$*C*H), 16.5 (*C*HCH$_2$CH), 15.7 (CH*C*H$_2$CH). **IR** (ATR): 3019 (C-H st), 1724 (C=O st), 1666 (C=C st), 1088 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 248 (M^+, 3), 219 (M^+-CHO, 1), 141 (34), 139 (100), 137 (M^+-C_6H_4Cl, 1), 111 (42), 109 (M^+-C_7H_4OCl, 10), 94 (50), 81 (15), 75 (18). **HRMS**: Calculated for $[C_{14}H_{13}N_3O_2ClNa]^+$: 271.0502 [(M+Na)$^+$]; found: 271.0507.



(*E*)-2-(2-(3-oxo-3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)cyclopropyl)acetaldehyde (4n). Following the *general procedure N*, **4n** (0.06 g, 0.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 69% yield as a yellow oil starting from **SI6n** (0.08 g, 0.3 mmol), Dess-Martin periodinane (0.18 g, 0.4 mmol) and CH_2Cl_2 (1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.7 Hz, 1H, CHO), 7.99 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.70 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.96 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.63 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.49 (dt, *J* = 6.9, 1.9 Hz, 2H, CHOC*H*$_2$), 1.57 (ddt, *J* = 10.0, 8.5, 4.4 Hz, 1H, CHCH$_2$C*H*), 1.52-1.37 (m, 1H, C*H*CH$_2$CH), 1.08 (dt, *J* = 8.6, 4.9 Hz, 1H, CHC$H_a$$H_b$CH), 1.02-0.92 (m, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.6 (CHO), 188.9 (C=O), 154.3 (*C*H=CH), 140.9 (C_{arom}-C), 135.0 (q, J_{CF} = 275.0 Hz, CF_3), 131.9 (C_{arom}-C), 128.8 (C_{arom}-H), 125.7 (q, $^3J_{CF}$ = 3.6 Hz, C_{arom}-CF_3), 123.2 (CH=*C*H), 47.3 (CHO*C*H$_2$), 22.5 (CHCH$_2$*C*H), 16.8 (*C*HCH$_2$CH), 16.0 (CH*C*H$_2$CH). **IR** (ATR): 2972 (C-H st), 1741 (C=O st), 1368 (C-F st), 776 (CF_3) cm^{-1}. **HRMS**: Calculated for $[C_{15}H_{14}O_2F_3]^+$: 283.0946 [M^+]; found: 283.0948.

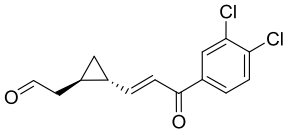


(*E*)-2-(2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4o). Following the *general procedure N*, **4o** (0.12 g, 0.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 72% yield as a yellow oil starting from **SI6o** (0.17 g, 0.7 mmol), Dess-Martin periodinane (0.46 g, 1.1 mmol) and CH_2Cl_2 (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (t, *J* = 1.7 Hz, 1H, CHO), 8.00-7.90 (m, 2H, C_{arom}-H), 7.18-7.08 (m, 2H, C_{arom}-H), 6.98 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.61 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.56-2.38 (m, 2H, CHOC*H*$_2$), 1.62-1.51 (m, 1H, CHCH$_2$C*H*), 1.47-1.36 (m, 1H, C*H*CH$_2$CH), 1.10-1.04 (m, 1H, CHC$H_a$$H_b$CH), 0.99-0.92 (m, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.7 (CHO), 188.1 (C=O), 165.6 (d, $^1J_{C\text{-}F}$ = 254.0 Hz, CCHCH*C*F), 152.9 (*C*H=CH), 134.4 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, *C*CHCHCF), 131.1 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, C*C*HCHCF), 123.1 (CH=*C*H), 115.9 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, CCH*C*HCF), 47.4 (CHO*C*H$_2$), 22.4 (CHCH$_2$*C*H), 16.6 (*C*HCH$_2$CH), 15.8 (CH*C*H$_2$CH). **IR** (ATR): 3016 (C-H st), 1738 (C=O st), 1605 (C=C st), 1368 (C-F st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{13}O_2FNa]^+$: 255.0797[(M+Na)$^+$]; found: 255.0801.

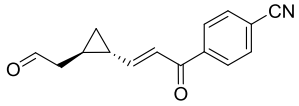


(*E*)-2-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4p). Following the *general procedure N*, **4p** (0.16 g, 0.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 66% yield as a yellow oil starting from **SI6p** (0.25 g, 0.8 mmol), Dess-Martin periodinane (0.53 g, 1.3 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.73 (s, 1H, CHO), 7.78-7.70 (m, 2H, C_{arom}-H), 7.59-7.50 (m, 2H, C_{arom}-H), 6.91 (d, *J* = 17.5 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.53-2.35 (m, 2H, CHOC*H*$_2$), 1.57-1.47 (m, 1H, CHCH$_2$C*H*), 1.44-1.32 (m, 1H, C*H*CH$_2$CH), 1.02 (dt, *J* = 8.3, 4.9 Hz, 1H, CHC$H_a$$H_b$CH), 0.91

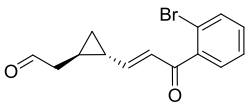
(dt, *J* = 7.9, 5.5 Hz, 1H, $CHCH_aH_bCH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.6 (CHO), 188.5 (C=O), 153.4 (*C*H=CH), 136.7 (C_{arom}-C), 131.8 (C_{arom}-H), 129.9 (C_{arom}-H), 127.6 (C_{arom}-C), 122.8 (CH=*C*H), 47.2 ($CHOCH_2$), 22.3 ($CHCH_2CH$), 16.5 ($CHCH_2CH$), 15.7 ($CHCH_2CH$). **IR** (ATR): 3012 (C-H st), 1734 (C=O st), 1666 (C=C st), 1070 (C-Br st), 1001 (C-Br st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{13}O_2BrNa]^+$: 314.0997 $[(M+Na)^+]$; found: 314.9998.



(*E*)-2-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4q). Following the *general procedure N*, **4q** (0.16 g, 0.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 66% yield as a yellow oil starting from **SI6q** (0.25 g, 0.8 mmol), Dess-Martin periodinane (0.53 g, 1.3 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.73 (s, 1H, CHO), 7.78-7.70 (m, 2H, C_{arom}-H), 7.59-7.50 (m, 2H, C_{arom}-H), 6.91 (d, *J* = 17.5 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.53-2.35 (m, 2H, $CHOCH_2$), 1.57-1.47 (m, 1H, $CHCH_2CH$), 1.44-1.32 (m, 1H, $CHCH_2CH$), 1.02 (dt, *J* = 8.3, 4.9 Hz, $CHCH_aH_bCH$), 0.91 (dt, *J* = 7.9, 5.5 Hz, 1H, $CHCH_aH_bCH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.6 (CHO), 188.5 (C=O), 153.4 (*C*H=CH), 136.7 (C_{arom}-C), 131.8 (C_{arom}-H), 129.9 (C_{arom}-H), 127.6 (C_{arom}-C), 122.8 (CH=*C*H), 47.2 ($CHOCH_2$), 22.3 ($CHCH_2CH$), 16.5 ($CHCH_2CH$), 15.7 ($CHCH_2CH$). **IR** (ATR): 3012 (C-H st), 1734 (C=O st), 1666 (C=C st), 1070 (C-Cl st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{13}O_2BrNa]^+$: 314.0997 $[(M+Na)^+]$; found: 314.9998.

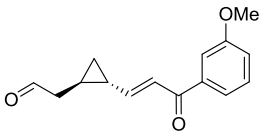


(*E*)-4-(3-(2-(2-oxoethyl)cyclopropyl)acryloyl)benzonitrile (4r). Following the *general procedure N*, **4r** (0.08 g, 0.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 77% yield as a yellow oil starting from **SI6r** (0.10 g, 0.4 mmol), Dess-Martin periodinane (0.27 g, 0.6 mmol) and CH_2Cl_2 (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.6 Hz, 1H, CHO), 8.01-7.92 (m, 2H, C_{arom}-H), 7.78-7.72 (m, 2H, C_{arom}-H), 6.94 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.64 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.50 (dd, *J* = 7.0, 1.6 Hz, 2H, $CHOCH_2$), 1.61-1.52 (m, 1H, $CHCH_2CH$), 1.50-1.37 (m, 1H, $CHCH_2CH$), 1.09 (dt, *J* = 8.7, 4.9 Hz, 1H, $CHCH_aH_bCH$), 0.98 (dt, *J* = 8.2, 5.6 Hz, 1H, $CHCH_aH_bCH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.5 (CHO), 188.3 (C=O), 155.0 (*C*H=CH), 14.4 (C_{arom}-C), 132.5 (C_{arom}-H), 128.8 (C_{arom}-H), 122.8 (CH=*C*H), 118.1 (CN), 115.8 (C_{arom}-C), 47.3 ($CHOCH_2$), 22.6 ($CHCH_2CH$), 16.9 ($CHCH_2CH$), 16.1 ($CHCH_2CH$). **IR** (ATR): 1734 (C=O st), 1616 (C=C st) cm^{-1}. **HRMS**: Calculated for $[C_{15}H_{14}NO_2]^+$: 240.1025$[(M+H)^+]$; found: 240.1821.

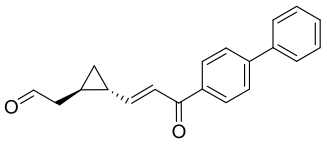


2-((1*R*,2*S*)-2-((*E*)-3-(2-bromophenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4s). Following the *general procedure N*, **4s** (0.13 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 30% yield as a yellow oil starting from **SI6s** (0.18 g, 1.5 mmol), Dess-Martin periodinane (0.93 g, 2.2 mmol) and CH_2Cl_2 (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.71 (t, *J* = 1.7 Hz, 1H, CHO), 7.53-7.51 (m, 1H, C_{arom}-H), 7.32-7.20 (m, 3H, C_{arom}-H), 6.46 (dd, *J* = 15.6, 1.4 Hz, 1H, CH=C*H*), 6.18 (ddd, *J* = 15.6, 9.9, 2.8 Hz, 1H, C*H*=CH), 2.50-2.27 (m, 2H, $CHOCH_2$), 1.53-1.43 (m, 1H, $CHCH_2CH$), 1.34-1.29 (m, 1H, $CHCH_2CH$), 0.98-0.86 (m, 2H, $CHCH_2CH$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 200.6 (CHO), 194.1 (C=O), 155.5 (*C*H=CH), 141.0 (C_{arom}-C), 133.4

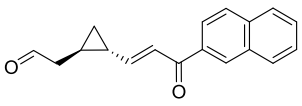
(C_{arom}-H), 131.2 (C_{arom}-H), 129.0 (C_{arom}-H), 127.8 (C_{arom}-H), 127.3 (CH=*C*H), 119.3 (C_{arom}-C), 47.2 (CHO*C*H_2), 22.1 (CHCH$_2$*C*H), 16.8 (*C*HCH$_2$CH), 16.0 (CH*C*H$_2$CH). **MS** (EI) m/z (%): 185 (48), 183 (64), 182 (M^+-C_7H_9O, 2), 157 (40), 155 (40), 109 (M^+-C_7H_4BrO, 3), 105 (19), 94 (53), 81 (40), 78 (19), 77 (100), 76 (60), 75 (59), 74 (51), 66 (21), 65 (24), 63 (35), 53 (24), 52 (26), 51 (68), 50 (82).



(*E*)-2-(2-(3-(3-methoxyphenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4t). Following the *general procedure N*, **4t** (0.17 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 97% yield as a yellow oil starting from **SI6t** (0.18 g, 0.7 mmol), Dess-Martin periodinane (0.47 g, 1.1 mmol) and CH_2Cl_2 (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (t, *J* = 1.8 Hz, 1H, CHO), 7.51-7.41 (m, 2H, C_{arom}-H), 7.34 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.07 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, C_{arom}-H), 6.96 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.59 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 3.83 (s, 3H, OCH_3), 2.56-2.36 (m, 2H, CHOCH_2), 1.59-1.50 (m, 1H, CHCH$_2$C*H*), 1.46-1.35 (m, 1H, C*H*CH$_2$CH), 1.05 (dt, *J* = 8.6, 4.9 Hz, 1H, CHCH_aH$_b$CH), 0.92 (ddd, *J* = 8.2, 6.0, 5.0 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 189.5 (C=O), 159.9 (C_{arom}-C), 152.7 (*C*H=CH), 139.4 (C_{arom}-C), 129.6 (CH=*C*H), 123.5 (C_{arom}-H), 121.0 (C_{arom}-H), 119.2 (C_{arom}-H), 112.8 (C_{arom}-H), 55.5 (OCH_3), 47.3 (CHO*C*H_2), 22.3 (CHCH$_2$*C*H), 16.5 (*C*HCH$_2$CH), 15.7 (CH*C*H$_2$CH). **IR** (ATR): 3009 (C-H st), 1738 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{15}H_{17}O_3]^+$: 245.1178[(M+H)$^+$]; found: 245.1182.

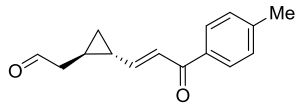


(*E*)-2-(2-(3-([1,1'-biphenyl]-4-yl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4u) Following the *general procedure N*, **4u** (0.20 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 39% yield as a yellow oil starting from **SI6u** (0.52 g, 1.8 mmol), Dess-Martin periodinane (1.13 g, 2.7 mmol) and CH_2Cl_2 (7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.81 (t, *J* = 1.8 Hz, 1H, CHO), 8.04-7.99 (m, 2H, C_{arom}-H), 7.70-7.66 (m, 2H, C_{arom}-H), 7.66-7.62 (m, 2H, C_{arom}-H), 7.47 (dd, *J* = 8.4, 6.8 Hz, 2H, C_{arom}-H), 7.44-7.37 (m, 1H, C_{arom}-H), 7.06 (d, *J* = 15.1 Hz, CH=C*H*), 6.65 (dd, *J* = 15.1, 10.0 Hz, 1H, C*H*=CH), 2.58-2.41 (m, 2H, CHOCH_2), 1.59 (ddd, *J* = 9.9, 8.4, 4.4 Hz, 1H, CHCH$_2$C*H*), 1.44 (dqd, *J* = 8.7, 6.8, 4.0 Hz, 1H, C*H*CH$_2$CH), 1.09 (dd, *J* = 8.7, 4.9 Hz, 1H, CHCH_aH$_b$CH), 0.97 (dt, *J* = 8.3, 5.6 Hz, 1H, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 189.3 (C=O), 152.6 (*C*H=CH), 145.5 (C_{arom}-C), 140.1 (C_{arom}-C), 136.8 (C_{arom}-C), 129.2 (C_{arom}-H), 129.1 (C_{arom}-H), 128.3 (CH=*C*H), 127.4 (C_{arom}-H), 123.6 (C_{arom}-H), 47.4 (CHO*C*H_2), 22.4 (CHCH$_2$*C*H), 16.6 (*C*HCH$_2$CH), 15.8 (CH*C*H$_2$CH). **IR** (ATR): 1727 (C=O st), 1655 (C=C st) cm^{-1}. **HRMS**: Calculated for $[C_{20}H_{18}O_2Na]^+$: 313.1205 [M+Na]$^+$; found: 313.1207.

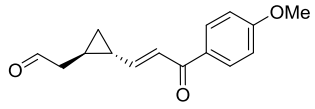


(*E*)-2-(2-(3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4v). Following the *general procedure N*, **4v** (0.19 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 82% yield as a yellow oil starting from **SI6v** (0.23 g, 0.8 mmol), Dess-Martin periodinane (0.55 g, 1.3 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (t, *J* = 1.8 Hz, 1H, CHO), 8.44 (d, *J* = 1.7 Hz, 1H, C_{arom}-H), 8.06-7.81 (m, 4H, C_{arom}-H), 7.64-7.49 (m, 2H, C_{arom}-H), 7.17 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.67 (dd, *J* =

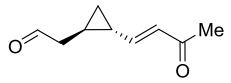
15.1, 10.0 Hz, 1H, C*H*=CH), 2.60-2.37 (m, 2H, CHOCH_2), 1.66-1.56 (m, 1H, CHCH_2C*H*), 1.48-1.37 (m, 1H, C*H*CH_2CH), 1.16-1.03 (m, 1H, CHC$H_a$$H_b$CH), 1.02-0.92 (m, 1H, CHC$H_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 189.5 (C=O), 152.6 (*C*H=CH), 135.5 (C_{arom}-C), 135.4 (C_{arom}-C), 132.6 (C_{arom}-C), 129.9 (CH=*C*H), 129.5 (C_{arom}-H), 128.5 (C_{arom}-H), 128.4 (C_{arom}-H), 127.9 (C_{arom}-H), 126.8 (C_{arom}-H), 124.5 (C_{arom}-H), 123.5 (C_{arom}-H), 47.4 (CHO*C*H_2), 22.3 (CHCH_2*C*H), 16.5 (*C*HCH_2CH), 15.8 (CH*C*H_2CH). **IR** (ATR): 1724 (C=O st), 1656 (C=C st) cm^{-1}. **HRMS**: Calculated for $[C_{18}H_{17}O_2]^+$: 265.1229[$(M+H)^+$]; found: 265.1234.



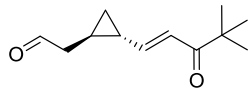
(*E*)-2-(2-(3-oxo-3-(p-tolyl)prop-1-en-1-yl)cyclopropyl)acetaldehyde (4w). Following the *general procedure N*, **4w** (0.18 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 76% yield as a yellow oil starting from **SI6w** (0.25 g, 1.0 mmol), Dess-Martin periodinane (0.64 g, 1.5 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.73 (t, *J* = 1.8 Hz, 1H, CHO), 7.84-7.76 (m, 2H, C_{arom}-H), 7.27-7.16 (m, 2H, C_{arom}-H), 6.97 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.57 (dd, *J* = 15.1, 9.9 Hz, 1H, C*H*=CH), 2.48-2.29 (m, 5H, CH_3, CHOCH_2), 1.57-1.45 (m, 1H, CHCH_2C*H*), 1.45-1.28 (m, 1H, C*H*CH_2CH), 1.01 (dt, *J* = 8.6, 4.9 Hz, 1H, CHC$H_a$$H_b$CH), 0.90 (dq, *J* = 8.4, 6.2, 5.2 Hz, 1H, CHC$H_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.9 (CHO), 189.3 (C=O), 152.3 (*C*H=CH), 143.4 (C_{arom}-C), 135.3 (C_{arom}-C), 129.2 (C_{arom}-H), 128.5 (C_{arom}-H), 123.3 (CH=*C*H), 47.2 (CHO*C*H_2), 22.1 (CHCH_2*C*H), 21.6 (CH_3), 16.3 (*C*HCH_2CH), 15.6 (CH*C*H_2CH). **IR** (ATR): 1724 (C=O st), 1666 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 228 (M^+, 3), 119 (100), 109 (M^+-C_8H_7O, 1), 94 (28), 91 (42), 65 (16). **HRMS**: Calculated for $[C_{15}H_{16}O_2Na]^+$: 251.1048 [$(M+Na)^+$]; found: 251.1049.



(*E*)-2-(2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)cyclopropyl)acetaldehyde (4x). Following the *general procedure N*, **4x** (0.18 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 76% yield as a yellow oil starting from **SI6x** (0.25 g, 1.0 mmol), Dess-Martin periodinane (0.64 g, 1.5 mmol) and CH_2Cl_2 (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.71 (t, *J* = 1.8 Hz, 1H, CHO), 7.90-7.81 (m, 2H, C_{arom}-H), 6.96 (d, *J* = 15.0 Hz, 1H, CH=C*H*), 6.90-6.84 (m, 2H, C_{arom}-H), 6.53 (dd, *J* = 15.0, 9.9 Hz, 1H, C*H*=CH), 3.78 (s, 3H, OCH_3), 2.50-2.29 (m, 2H, CHOCH_2), 1.54-1.41 (m, 1H, CHCH_2C*H*), 1.36-1.29 (m, 1H, C*H*CH_2CH), 0.98 (dt, *J* = 8.6, 4.8 Hz, 1H, CHC$H_a$$H_b$CH), 0.85 (dt, *J* = 8.3, 5.5 Hz, CHC$H_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 187.9 (C=O), 163.2 (C_{arom}-C), 151.6 (*C*H=CH), 130.6 (C_{arom}-H), 122.9 (CH=*C*H), 113.7 (C_{arom}-H), 55.4 (OCH_3), 47.1 (CHO*C*H_2), 22.0 (CHCH_2*C*H), 16.2 (*C*HCH_2CH), 15.4 (CH*C*H_2CH). **IR** (ATR): 3012 (C-H st), 1730 (C=O st), 1605 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 244 (M^+, 2), 137 (M^+-C_7H_7O, 1), 109 (M^+-$C_8H_7O_2$, 1), 94 (25), 77 (22). **HRMS**: Calculated for $[C_{15}H_{17}O_3]^+$: 245.1178 [$(M+H)^+$]; found: 248.1178.

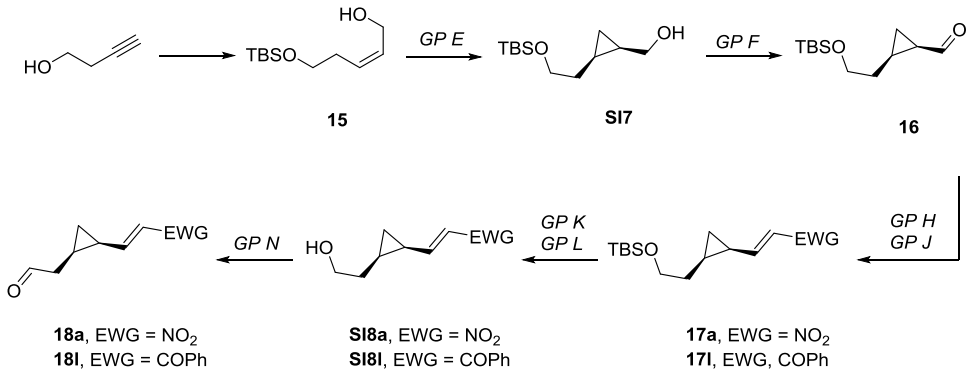


(*E*)-2-(2-(3-oxobut-1-en-1-yl)cyclopropyl)acetaldehyde (4y). Following the *general procedure N*, **4y** (0.09 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 82% yield as a yellow oil starting from **SI6y** (0.12 g, 0.8 mmol), Dess-Martin periodinane (0.48 g, 1.1 mmol) and CH_2Cl_2 (3 mL).**^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.75 (t, *J* = 1.7 Hz, 1H, CHO), 6.31 (dd, *J* = 15.7, 9.4 Hz, 1H, C*H*=CH), 6.13 (d, *J* = 15.7 Hz, 1H, CH=C*H*), 2.52-2.34 (m, 2H, CHOCH_2), 2.17 (s, 3H, CH_3), 1.47-1.26 (m, 2H, C*H*CH_2C*H*), 0.97 (dt, *J* = 8.6, 5.0 Hz, 1H, CHC$H_a$$H_b$CH), 0.88 (ddd, *J* = 8.2, 6.1, 5.1 Hz, 1H, CHC$H_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.8 (CHO), 197.9 (C=O), 151.1 (*C*H=CH), 128.8 (CH=*C*H), 47.3 (CHO*C*H_2), 21.1 (CH_3), 21.5 (CHCH_2*C*H), 16.2 (*C*HCH_2CH), 15.4 (CH*C*H_2CH). **IR** (ATR): 2972 (C-H st), 1738 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{11}H_{15}O_4]^+$: 3211.0970 [(M-H)$^-$]; found: 211.0974.

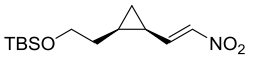


2-((1*R*,2*S*)-2-((*E*)-4,4-dimethyl-3-oxopent-1-en-1-yl)cyclopropyl)acetaldehyde (4z). Following the *general procedure N*, **4z** (0.04 g, 0.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 36% yield as a yellow oil starting from **SI6z** (0.10 g, 0.5 mmol), Dess-Martin periodinane (0.34 g,0.8 mmol) and CH_2Cl_2 (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.72 (t, *J* = 2.0 Hz, 1H, CHO), 6.59-6.51 (m, 1H, CH=C*H*), 6.46-6.33 (m, 1H, C*H*=CH), 2.51-2.27 (m, 2H, CHOCH_2), 1.48-1.36 (m, 1H, CHCH_2C*H*), 1.34-1.23 (m, 1H, C*H*CH_2CH), 1.11-1.08 (m, 9H, 3 x CH_3), 0.96-0.90 (m, 1H, CHC$H_a$$H_b$CH), 0.88-0.79 (m, 1H, CHC$H_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.5 (CHO), 200.9 (C=O), 150.3 (*C*H=CH), 122.1 (CH=*C*H), 47.3 (CHO*C*H_2), 42.7 (*C*(CH_3)$_3$), 26.3 (3 x CH_3), 21.8 (CHCH_2*C*H), 16.0 (*C*HCH_2CH), 15.3 (CH*C*H_2CH). **MS** (EI) m/z (%): 202 (18), 201 (100), 109 (M^+-C_5H_9O, 1), 85 (M^+-C_7H_9O, 2).

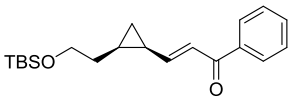
2.1.9. Synthesis of *cis*-cyclopropanes 18a and 18l



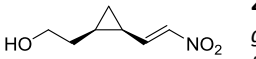
15 was reported compound and it was prepared following the procedure described in the literature. Spectroscopic data were consistent with those reported in the literature.[16] For the preparation of **SI7** and **16**, the same methodology previously described was followed. Spectroscopic data were consistent with those reported in the literature.[16]



***tert*-butyldimethyl(2-((1*R*,2*R*)-2-((*E*)-2-nitrovinyl)cyclopropyl)ethoxy)silane (17a).** Following the *general procedure H*, **17a** (1.00 g, 3.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 70% yield as a yellow oil starting from **16** (1.20 g, 5.3 mmol), nitromethane (0.57 mL, 10.5 mmol), piperidine (0.21 mL, 2.1 mmol), M.S. and CH_2Cl_2 (26 mL).**^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.10 (dq, *J* = 13.1, 1.4 Hz, 1H, CH=C*H*), 7.00 (tt, *J* = 11.4, 1.4 Hz, 1H, C*H*=CH), 3.64 (t, *J* = 6.0 Hz, 2H, SiOCH_2CH$_2$), 1.71-1.57 (m, 3H, SiOCH$_2$CH_2, CHCH$_2$C*H*), 1.49 (tt, *J* = 8.6, 6.8 Hz, 1H, C*H*CH$_2$CH), 1.32-1.25 (m, 1H, CHCH_aH$_b$CH), 0.85 (s, 9H, 3 x CH_3), 0.70-0.64 (m, 1H, CHCH$_a$$H_b$CH), 0.001 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 146.0 (*C*H=CH), 138.3 (CH=*C*H), 62.6 (SiO*C*H$_2$CH$_2$), 32.7 (SiOCH$_2$*C*H$_2$), 25.9 (3 x CH_3), 19.9 (CHCH$_2$*C*H), 18.3 (Si*C*(CH$_3$)$_3$), 16.4 (CH*C*H$_2$CH), 16.2 (*C*HCH$_2$CH), -5.4 (2 x CH_3). **IR** (ATR): 2930 (C-H st), 1734 (C=O st), 1518 (NO_2 st as), 1343 (NO_2 st sim) cm^{-1}.



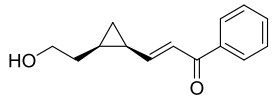
(*E*)-3-((1*R*,2*R*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclopropyl)-1-phenylprop-2-en-1-one (17l). Following the *general procedure J*, **17l** (0.31 g, 0.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 76% yield as a yellow oil starting from **16** (0.28 g, 1.2 mmol), 1-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one (0.90 g, 2.4 mmol) and toluene (19 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.97-7.90 (m, 2H, C$_{arom}$-H), 7.60-7.38 (m, 3H, C$_{arom}$-H), 7.05 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.84 (dd, *J* = 15.0, 10.4 Hz, 1H, C*H*=CH), 3.68 (td, *J* = 6.4, 1.5 Hz, 2H, SiOCH_2CH$_2$), 1.85-1.74 (m, 1H, CHCH$_2$C*H*), 1.72-1.63 (m, 2H, SiOCH$_2$CH_2), 1.48-1.35 (m, 1H, CHCH_aH$_b$CH), 1.26-1.17 (m, 1H, C*H*CH$_2$CH), 0.89 (s, 9H, 3 x CH_3), 0.65 (dt, *J* = 6.4, 4.8 Hz, 1H, CHCH$_a$$H_b$CH), 0.001 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 189.7 (C=O), 152.1 (*C*H=CH), 138.3 (C$_{arom}$-C), 132.5 (CH=*C*H), 128.7 (C$_{arom}$-H), 128.6 (C$_{arom}$-H), 125.0 (C$_{arom}$-H), 63.0 (SiO*C*H$_2$CH$_2$), 32.9 (SiOCH$_2$*C*H$_2$), 26.1 (3 x CH_3), 20.3 (CHCH$_2$*C*H), 19.4 (Si*C*(CH$_3$)$_3$), 18.5 (*C*HCH$_2$CH), 16.1 (CH*C*H$_2$CH), -5.2 (2 x CH_3).



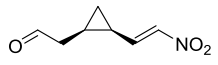
2-((1*R*,2*R*)-2-((*E*)-2-nitrovinyl)cyclopropyl)ethan-1-ol (SI8a). Following the *general procedure K*, **SI8a** (0.18 g, 1.1 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 62% yield as a yellow oil starting from **17a** (0.50 g, 1.8 mmol), HCl in dioxane (1.15 mL g, 4.6 mmol) and MeOH (4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.11 (d, *J* = 13.1 Hz, 1H, CH=C*H*), 6.99 (dd, *J* = 13.1, 11.0 Hz, 1H, C*H*=CH), 3.64 (t, *J* = 6.5 Hz, 2H, OHCH_2CH$_2$), 2.57-2.41 (br s, 1H, OH), 1.73-1.59 (m, 3H, OHCH$_2$CH_2, CHCH$_2$C*H*), 1.47 (dp, *J* = 15.2, 7.3 Hz, 1H, C*H*CH$_2$CH), 1.29 (td, *J* = 8.1, 5.0 Hz, 1H, CHCH_aH$_b$CH), 0.69 (dt, *J* = 6.6, 5.0 Hz, CHCH$_a$$H_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 146.1 (*C*H=CH), 138.3 (CH=*C*H),

[16] Apel, C.; Hatmann, S. S.; Letz, D.; Christtmann, M. *Angew. Chem. Int. Ed*. **2019**, *58*, 5075.

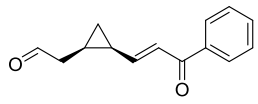
62.1 (OH*C*$H_2$$CH_2$), 32.4 (OH$CH_2$*C*$H_2$), 19.7 ($CHCH_2$*C*H), 16.4 (CH*C*$H_2$CH), 16.2 (*C*H$CH_2$CH). **IR** (ATR): 3447 (O-H st), 2972 (C-H st), 1734 (C=O st), 1634 (C=C st), 1511 (NO_2 st as), 1347 (NO_2 st sim) cm^{-1}.



(*E*)-3-((1*R*,2*R*)-2-(2-hydroxyethyl)cyclopropyl)-1-phenylprop-2-en-1-one (SI8l). Following the *general procedure L*, **SI8l** (0.07 g, 0.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 1:1 to 3:7) in 47% yield as a yellow oil starting from **17l** (0.22 g, 0.7 mmol), TBAF (0.75 mL, 0.7 mmol) and THF (7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.94-7.89 (m, 2H, C_{arom}-H), 7.55-7.48 (m, 1H, C_{arom}-H), 7.48-7.39 (m, 2H, C_{arom}-H), 7.05 (d, *J* = 15.0 Hz, 1H, CH=C*H*), 6.81 (dd, *J* = 15.0, 10.5 Hz, 1H, C*H*=CH), 3.67 (t, *J* = 6.5 Hz, 2H, SiOC*H*$_2$$CH_2$), 2.57-2.36 (br s, 1H, OH), 1.84-1.63 (m, 3H, SiOCH$_2$C*H*$_2$, $CHCH_2$C*H*), 1.43-1.32 (m, 1H, CHC*H*$_a$H$_b$CH), 1.26-1.15 (m, 1H, C*H*CH_2CH), 0.64 (dt, *J* = 6.4, 4.9 Hz, 1H, CHCH$_a$*H*$_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 18.5 (C=O), 152.3 (*C*H=CH), 138.0 (C_{arom}-C), 132.6 (CH=*C*H), 128.6 (C_{arom}-H), 128.5 (C_{arom}-H), 124.8 (C_{arom}-H), 62.6 (OH*C*$H_2$$CH_2$), 32.6 (OH$CH_2$*C*$H_2$), 20.2 ($CHCH_2$*C*H), 19.2 (*C*H$CH_2$CH), 15.9 (CH*C*$H_2$CH). **IR** (ATR): 3440 (O-H st), 3012 (C-H st), 1738 (C=O st), 1659 (C=C st) cm^{-1}.

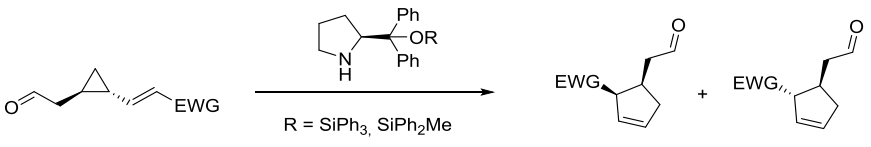


2-((1*R*,2*R*)-2-((*E*)-2-nitrovinyl)cyclopropyl)acetaldehyde (18a). Following the *general procedure N*, **18a** (0.17 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 96% yield as a yellow oil starting from **SI8a** (0.18 g, 1.1 mmol), Dess-Martin periodinane (0.72 g, 1.7 mmol) and CH_2Cl_2 (5 mL).**^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.2 Hz, 1H, CHO), 7.18-7.08 (m, 1H, CH=C*H*), 6.93 (m, 1H, C*H*=CH), 2.61 (ddd, *J* = 7.0, 3.1, 1.3 Hz, 2H, CHOC*H*$_2$), 1.42 (td, *J* = 8.1, 5.3 Hz, 2H, C*H*CH_2CH, $CHCH_2$C*H*), 0.80-0.68 (m, 2H, CHC*H*$_2$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.2 (CHO), 144.0 (*C*H=CH), 139.3 (CH=*C*H), 43.5 (CHO*C*H_2), 15.7 ($CHCH_2$*C*H), 15.6 (CH*C*H_2CH), 15.4 (*C*HCH_2CH). **IR** (ATR): 3020 (C-H st), 1741 (C=O st), 1516 (NO_2 st as), 1372 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for $[C_7H_{10}NO_3]^+$: 156.0661 [$(M+H)^+$]; found: 156.0655.



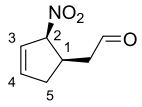
2-((1*R*,2*R*)-2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)cyclopropyl)acetaldehyde (18l). Following the *general procedure N*, **18l** (0.07 g, 0.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 98% yield as a yellow oil starting from **SI8l** (0.07 g, 0.3 mmol), Dess-Martin periodinane (0.20 g, 0.5 mmol) and CH_2Cl_2 (1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.4 Hz, 1H, CHO), 7.95-7.88 (m, 2H, C_{arom}-H), 7.58-7.49 (m, 1H, C_{arom}-H), 7.48-7.42 (m, 2H, C_{arom}-H), 7.08 (d, *J* = 15.1 Hz, 1H, CH=C*H*), 6.73 (dd, *J* = 15.0, 10.2 Hz, 1H, C*H*=CH), 2.59 (dt, *J* = 7.2, 1.0 Hz, 2H, CHOC*H*$_2$), 1.95-1.86 (m, 1H, $CHCH_2$C*H*), 1.66-1.53 (m, 1H, C*H*CH_2CH), 1.32 (td, *J* = 8.2, 5.1 Hz, 1H, CHC*H*$_a$H$_b$CH), 0.68 (dt, *J* = 6.4, 5.2 Hz, 1H, CHCH$_a$*H*$_b$CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.1 (CHO), 184.4 (C=O), 149.7 (*C*H=CH), 137.9 (C_{arom}-C), 132.8 (CH=*C*H), 128.6 (C_{arom}-H), 128.5 (C_{arom}-H), 125.9 (C_{arom}-H), 43.7 (CHO*C*H_2), 19.4 ($CHCH_2$*C*H), 15.2 (CH*C*H_2CH), 14.9 (*C*HCH_2CH). **IR** (ATR): 3016 (C-H st), 1741 (C=O st), 1659 (C=C st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{14}O_2Na]^+$: 237.0892 [$(M+Na)^+$]; found: 237.0886.

2.2. Organocatalytic enantioselective VCP-CP rearrangement

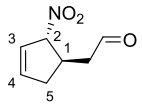


4a-z **cis-6a-z** ***trans*-6a-z**

General procedure O: An oven-dried 5 mL screw-capped test tube containing a stirring bar was charged with the corresponding cyclopropane **4a-z** (0.1 mmol, 1.0 eq) and dissolved in the appropriate solvent (0.5 mL, 0.2 *M*). The mixture was cooled to the desired temperature, and a solution of the catalyst (0.01 mmol, 10-20 mol%) in the appropiate solvent (0.5 mL, 0.2 *M*) was quickly added to the mixture. When the reaction was judged complete (monitored by TLC), solvent was evaporated and the crude was directly subjected to flash column chromatography to afford pure ***cis*-6a-z** and ***trans*-6a-z**.

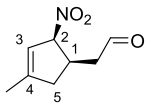


2-((1*R*,2*S*)-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*cis*-6a). Following the *general procedure O*, ***cis*-6a** (10.10 mg, 0.065 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 84% yield starting from aldehyde **4a** (12.00 mg, 0.077 mmol), catalyst **5l** (4.00 mg, 0.008 mmol) and 1,2-dichloroethane (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (s, 1H, CHO), 6.45 (dt, *J* = 5.3, 2.4 Hz, 1H, H4), 5.88 (dtd, *J* = 5.6, 2.6, 1.6 Hz, 1H, H3), 5.52 (dtd, *J* = 7.6, 2.4, 0.7 Hz, 1H, H2), 3.07 (h, *J* = 7.6, 1H, H1), 2.88-2.57 (m, 3H, CHOCH_2, H5a), 2.35 (ddq, *J* = 16.9, 8.2, 2.3 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.5 (CHO), 143.0 (C4), 126.0 (C3), 93.7 (C2), 44.0 (CHO*C*H_2), 37.4 (C5), 36.7 (C1). **IR** (ATR): 2915 (C-H st), 1720 (C=O st), 1544 (NO_2 st as), 1378 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 109 (M^+-NO_2, 25), 108 (20), 79 (100), 78 (26), 77 (65), 66 (33), 65 (20), 53 (30), 51 (22). **HRMS**: Calculated for $[C_7H_{10}NO_3]^+$: 156.0661 [(M+H)$^+$]; found: 156.0657 and for $[C_7H_8NO_3]^-$: 154.0504 [(M-H)$^-$]; found: 154.0506. **[α]$_D^{rt}$**: -143.8 (*c* = 0.5, CH_2Cl_2).

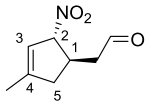


2-((1*R*,2*R*)-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*trans*-6a). Following the *general procedure O,* ***trans*-6a** (1.30 mg, 0.011 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 11% yield starting from aldehyde **4a** (12.00 mg, 0.077 mmol), catalyst **5l** (4.00 mg, 0.008 mmol) and 1,2-dichloroethane (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.81 (t, *J* = 1.1 Hz, 1H, CHO), 6.26-6.19 (m, 1H, H4), 5.88 (dq, *J* = 5.8, 2.2 Hz, 1H, H3), 5.21 (dq, *J* = 4.0, 2.0 Hz, 1H, H2), 3.26 (tdd, *J* = 8.2, 6.0, 4.1 Hz, 1H, H1), 2.99 (ddq, *J* = 17.4, 8.2, 2.4 Hz, 1H, H5a), 2.93-2.66 (m, 2H, CHOCH_2), 2.13 (ddq, *J* = 17.3, 4.3, 2.1 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.8 (CHO), 139.6 (C4), 125.6 (C3), 96.2 (C2), 48.0 (CHO*C*H_2), 38.6 (C5), 37.4 (C1). **IR** (ATR): 2922 (C-H st), 2851 (C-H st), 1720 (C=O st), 1548 (NO_2 st as), 1379 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 109 (M^+-NO_2, 23), 108 (19), 84 (54), 83 (100), 81 (63), 79 (52), 78 (23), 77 (38), 66 (26), 65 (22), 53 (28), 51 (20), 53 (28), 51 (20). **HRMS**:

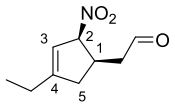
Calculated for $[C_7H_{10}NO_3]^+$: 156.0661 $[(M+H)^+]$; found: 156.0656 and for $[C_7H_8NO_3]^-$: 154.0504 $[(M-H)^-]$; found: 154.0503. $[\alpha]_D^{rt}$: +81.0 (*c* = 0.25, CH_2Cl_2).



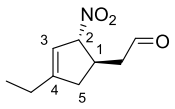
2-((1*R*,2*S*)-4-methyl-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*cis*-6b). Following the *general procedure O,* ***cis*-6b** (6.08 mg, 0.040 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 44% yield starting from aldehyde **4b** (15.00 mg, 0.090 mmol), catalyst **5l** (4.60 mg, 0.009 mmol) and 1,2-dichloroethane (0.9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (s, 1H, CHO), 5.56-5.42 (m, 2H, H2, H3), 3.12 (h, *J* = 7.6 Hz, 1H, H1), 2.67 (dd, *J* = 9.8, 7.3 Hz, 2H, CHOCH_2), 2.62-2.44 (m, 2H, H5), 1.90 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.6 (CHO), 154.6 (C4), 120.3 (C3), 95.0 (C2), 44.3 (CHO*C*H_2), 41.5 (C5), 37.1 (C1), 17.1 (CH_3). **IR** (ATR): 2972 (C-H st), 1738 (C=O st), 1544 (NO_2 st as), 1364 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for $[C_8H_{10}NO_3]^-$: 168.0661 $[(M-H)^-]$; found: 168.0647. $[\alpha]_D^{rt}$: -216.2 (*c* = 0.3, CH_2Cl_2).



2-((1*R*,2*R*)-4-methyl-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*trans*-6b). Following the *general procedure o,* ***trans*-6b** (5.20 mg, 0.031 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 34% yield starting from aldehyde **4b** (15.00 mg, 0.090 mmol), catalyst **5l** (4.60 mg, 0.009 mmol) and 1,2-dichloroethane (0.9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.80 (appd, *J* = 1.2 Hz, 1H, CHO), 5.51 (s, 1H, H3), 5.14 (s, 1H, H2), 3.33-3.20 (m, 1H, H1), 2.99-2.61 (m, 4H, H5, CHOCH_2), 1.85 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 150.7 (C4), 119.6 (C3), 96.8 (C2), 48.3 (CHO*C*H_2), 42.5 (C5), 37.9 (C1), 16.8 (CH_3). **IR** (ATR): 2965 (C-H st), 1738 (C=O st), 1547 (NO_2 st as), 1368 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for $[C_8H_{10}NO_3]^-$: 168.0661 $[(M-H)^-]$; found: 168.0644. $[\alpha]_D^{rt}$: +89.0 (*c* = 0.2, CH_2Cl_2).

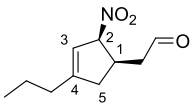


2-((1*R*,2*S*)-4-ethyl-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*cis*-6c). Following the *general procedure o,* ***cis*-6c** (11.50 mg, 0.063 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 61% yield starting from aldehyde **4c** (20.00 mg, 0.100 mmol), catalyst **5l** (6.00 mg, 0.010 mmol) and 1,2-dichloroethane (1.0 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (s, 1H, CHO), 5.53-5.42 (m, 2H, H2, H3), 3.09 (h, *J* = 7.9 Hz, 1H, H1), 2.72-2.16 (m, 6H, CH_2CHO, H5, CH_2CH$_3$), 1.11 (t, *J* = 7.5 Hz, 3H, CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.7 (CHO), 160.4 (C4), 118.2 (C3), 94.7 (C2), 44.3 (*C*H$_2$CHO), 39.9 (C5), 36.8 (C1), 24.6 (*C*H$_2$CH$_3$), 11.8 (CH$_2$*C*H$_3$). **IR** (ATR): 3012 (C-H st), 1741 (C=O st), 1443 (NO_2 st as), 1372 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 199 (76), 183 (M^+, 43), 154 (M^+-CHO, 6), 135 (20), 105 (16), 91 (25), 78 (67), 77 (32), 57 (100), 55 (19), 53 (25), 51 (26). **HRMS**: Calculated for $[C_9H_{12}NO_3]^-$: 182.0817 $[(M-H)^-]$; found: 182.0814. $[\alpha]_D^{rt}$: -129.2 (*c* = 0.56, CH_2Cl_2).

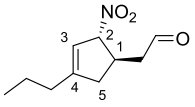


2-((1*R*,2*R*)-4-ethyl-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*trans*-6c). Following the *general procedure O,* ***trans*-6c** (5.00 mg, 0.027 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 22% yield starting from aldehyde **4c** (20.00 mg, 0.100 mmol), catalyst **5l** (6.00 mg, 0.010 mmol) and 1,2-dichloroethane (1.0 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (s, 1H, CHO), 5.52-5.48 (m, 1H, H3), 5.14 (s, 1H, H2), 3.26 (s, 1H, H1), 2.99-2.61 (m, 3H, CH_2CHO, H5a), 2.24-1.96 (m, 3H,

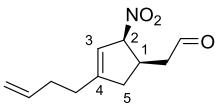
H5b, CH_2CH$_3$), 1.09 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 156.6 (C4), 117.7 (C3), 96.6 (C2), 48.3 (*C*H$_2$CHO), 40.9 (C5), 37.5 (C1), 24.3 (*C*H$_2$CH$_3$), 11.8 (CH$_2$*C*H$_3$). **IR** (ATR): 3020 (C-H st), 1734 (C=O st), 1440 (NO_2 st as), 1364 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for [$C_9H_{12}NO_3$]$^-$: 182.0817 [(M-H)$^-$]; found: 182.0816. **[α]$_D^{rt}$**: +66.3 (*c* = 0.39, CH_2Cl_2).



2-((1*R*,2*S*)-2-nitro-4-propylcyclopent-3-en-1-yl)acetaldehyde (*cis*-6d). Following the *general procedure O,* ***cis*-6d** (12.50 mg, 0.063 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 42% yield starting from aldehyde **4d** (30.00 mg, 0.150 mmol), catalyst **5l** (7.70 mg, 0.015 mmol) and 1,2-dichloroethane (1.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (s, 1H, CHO), 5.56-5.40 (m, 2H, H2, H3), 3.12-3.04 (m, 1H, H1), 2.78-2.62 (m, 2H, CH_2CHO), 2.62-2.48 (m, 1H, H5a), 2.38-2.15 (m, 3H, H5b, CH_2CH$_2$CH$_3$), 1.59-1.49 (m, 2H, CH$_2$CH_2CH$_3$), 0.93 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.7 (CHO), 158.8 (C4), 119.3 (C3), 94.8 (C2), 44.3 (*C*H$_2$CHO), 39.7 (*C*H$_2$CH$_2$CH$_3$), 36.8 (C1), 33.4 (C5), 20.6 (CH$_2$*C*H$_2$CH$_3$), 13.9 (CH$_2$CH$_2$*C*H$_3$). **IR** (ATR): 2937 (C-H st), 2859 (C-H st), 1724 (C=O st), 1547 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 154 (M$^+$-C_3H_7, 1), 151 (M$^+$-NO_2, 26), 121 (19), 109 (20), 108 (16), 107 (100), 93 (20), 91 (46), 81 (50), 79 (82), 77 (44), 67 (34). **HRMS:** Calculated for [$C_{10}H_{14}NO_3$]$^+$: 196.0974 [(M+H)$^+$]; found: 196.0974. [α]$_D^{rt}$: -168.2 (*c* = 0.1, CH_2Cl_2).

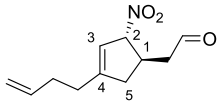


2-((1*R*,2*R*)-2-nitro-4-propylcyclopent-3-en-1-yl)acetaldehyde (*trans*-6d). Following the *general procedure O,* ***trans*-6d** (6.60 mg, 0.033 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 22% yield starting from aldehyde **4d** (30.00 mg, 0.150 mmol), catalyst **5l** (7.70 mg, 0.015 mmol) and 1,2-dichloroethane (1.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (s, 1H, CHO), 5.43-5.42 (m, 1H, H3), 5.14 (s, 1H, H2), 3.31-3.18 (m, 1H, H1), 2.96-2.59 (m, 2H, CH_2CHO), 2.16-1.97 (m, 3H, H5a, CH_2CH$_2$CH$_3$), 1.57-1.41 (H5b, CH$_2$CH_2CH$_3$), 0.97-0.84 (m, 3H, CH$_2$CH$_2$CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 155.1 (C4), 118.7 (C3), 96.6 (C2), 48.3 (*C*H$_2$CHO), 40.9 (*C*H$_2$CH$_2$CH$_3$), 37.5 (C1), 33.2 (C5), 20.6 (CH$_2$*C*H$_2$CH$_3$), 13.9 (CH$_2$CH$_2$*C*H$_3$). **IR** (ATR): 2937 (C-H st), 2859 (C-H st), 1724 (C=O st), 1547 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 151 (M$^+$-NO_2, 32), 121 (21), 109 (21), 108 (18), 107 (100), 93 (23), 91 (48), 81 (48), 79 (83), 77 (44), 67 (31). **HRMS**: Calculated for [$C_{10}H_{14}NO_3$]$^+$: 196.0974 [(M+H)$^+$]; found: 196.0981. **[α]$_D^{rt}$**: -16.8 (*c* = 0.5, CH_2Cl_2).

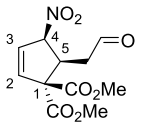


2-((1*R*,2*S*)-4-(but-3-en-1-yl)-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*cis*-6e). Following the *general procedure O,* ***cis*-6e** (5.60 mg, 0.027 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 34% yield starting from aldehyde **4e** (17.60 mg, 0.080 mmol), catalyst **5l** (4.30 mg, 0.008 mmol) and 1,2-dichloroethane (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (s, 1H, CHO), 5.81 (dd, *J* = 17.1, 10.2 Hz, 1H, CH$_2$CH$_2$C*H*=CH$_2$), 5.54 (s, 1H, H3), 5.46 (d, *J* = 7.6 Hz, 1H, H2), 5.10-4.96 (m, 2H, CH$_2$CH$_2$CH=CH_2), 3.09 (h, *J* = 7.6 Hz, 1H, H1), 2.72-2.51 (m, 3H, CH_2CHO, H5a), 2.41-2.21 (m, 5H, H5b, CH_2CH_2CH=CH$_2$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.6 (CHO), 158.1 (CH$_2$CH$_2$*C*H=CH$_2$), 137.4 (C4), 119.6 (C3), 115.5 (CH$_2$CH$_2$CH=*C*H$_2$), 94.6 (C2), 44.3 (*C*H$_2$CHO), 39.9 (C5), 36.8 (CH$_2$*C*H$_2$CH=CH$_2$), 31.4 (*C*H$_2$CH$_2$CH=CH$_2$), 30.7 (C1). **IR** (ATR): 2937 (C-H st), 2859 (C-H st), 1724 (C=O st), 1547 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 166 (M$^+$, 3), 148 (53), 132 (40), 128 (65), 115 (38),

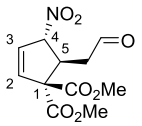
104 (71), 91 (100), 79 (53), 68 (35), 55 (65). **HRMS**: Calculated for $[C_{11}H_{14}NO_3]^+$: 208.0974 $[(M+H)^+]$; found: 208.0990. **[α]**$_D^{rt}$: +60.2 (*c* = 0.5, CH_2Cl_2).



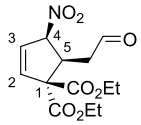
2-((1*R*,2*R*)-4-(but-3-en-1-yl)-2-nitrocyclopent-3-en-1-yl)acetaldehyde (*trans*-6e). Following the *general procedure 0*, ***trans*-6e** (3.20 mg, 0.015 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 19% yield starting from aldehyde **4e** (17.60 mg, 0.080 mmol), catalyst **5l** (4.30 mg, 0.008 mmol) and 1,2-dichloroethane (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (s, 1H, CHO), 5.79 (dd, *J* = 15.9, 9.1 Hz, 2H, $CH_2CH_2CH=CH_2$), 5.7-4.96 (m, 3H, $CH_2CH_2CH=CH_2$, H2, H3), 3.29-3.22 (m, 1H, H1), 2.99-2.63 (m, 4H, CH_2CHO, H5), 1.28-1.16 (m, 4H, $CH_2CH_2CH=CH_2$). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.9 (CHO), 154.3 ($CH_2CH_2CH=CH_2$), 137.4 (C4), 119.1 (C3), 115.6 ($CHCH_2CH=CH_2$), 96.5 (C2), 48.3 (CH_2CHO), 40.9 (C5), 37.5 ($CH_2CH_2CH=CH_2$), 31.4 ($CH_2CH_2CH=CH_2$), 30.4 (C1). **IR** (ATR): 2937 (C-H st), 2859 (C-H st), 1724 (C=O st), 1547 (NO_2 st as) cm^{-1}. **MS** (EI) m/z (%): 166 (M^+, 3), 148 (53), 132 (40), 128 (65), 115 (38), 104 (71), 91 (100), 79 (53), 68 (35), 55 (65). **HRMS**: Calculated for $[C_{11}H_{14}NO_3]^+$: 208.0974 $[(M+H)^+]$; found: 208.0987. **[α]**$_D^{rt}$: +34.7 (*c* = 0.3, CH_2Cl_2).



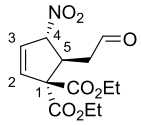
Dimethyl (4*R*,5*S*)-4-nitro-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarboxylate (*cis*-6f). Following the *general procedure O*, ***cis*-6f** (5.50 mg, 0.021 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 37% yield starting from aldehyde **4f** (15.00 mg, 0.060 mmol), catalyst **5l** (2.80 mg, 0.006 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.81 (s, 1H, CHO), 6.52 (d, *J* = 5.9 Hz 1H, H2), 6.20-6.14 (m, 1H, H3), 5.68-5.61 (m, 1H, H4), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.66-3.57 (m, 1H, H5), 3.21 (dd, *J* = 19.3, 4.9 Hz, 1H, CH_aH_bCHO), 2.86 (dd, *J* = 19.4, 10.3 Hz, 1H, CH_aH_bCHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.2 (CHO), 168.0 (C=O), 135.1 (C3), 128.1 (C2), 91.2 (C4), 66.8 (C1), 53.7 (OCH_3), 53.1 (OCH_3), 42.4 (CH_2CHO), 29.6 (C5). **IR** (ATR): 2969 (C-H st), 1738 (C=O st), 1436 (NO_2 st as), 1368 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for $[C_{11}H_{12}NO_7]^-$: 270.0614 $[(M-H)^-]$; found: 270.0606. **[α]**$_D^{rt}$: -178.6 (*c* = 0.5, CH_2Cl_2).



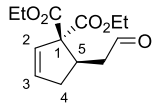
Dimethyl (4*S*,5*S*)-4-nitro-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarboxylate (*trans*-6f). Following the *general procedure O*, ***trans*-6f** (3.80 mg, 0.014 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 25% yield starting from aldehyde **4f** (15.00 mg, 0.060 mmol), catalyst **5l** (2.80 mg, 0.006 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (t, *J* = 1.3 Hz, 1H, CHO), 6.30 (dd, *J* = 5.8 Hz, 2.0 Hz, 1H, H2), 6.18 (dd, *J* = 5.8, 2.0 Hz, 1H, H3), 5.41 (dt, *J* = 7.2, 1.9 Hz, 1H, H4), 3.93-3.86 (m, 1H, H5), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.09-2.82 (m, 2H, CH_2CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.0 (CHO), 168.9 (C=O), 136.1 (C2), 130.9 (C3), 94.0 (C4), 68.8 (C1), 53.5 (CH_3), 53.5 (CH_3), 43.7 (C5), 43.6 (CH_2CHO). **IR** (ATR): 2972 (C-H st), 1738 (C=O st), 1440 (NO_2 st as), 1214 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 165 (15), 161 (15), 137 (15), 133 (19), 105 (50), 91 (22), 79 (25), 78 (21), 77 (71), 59 (100), 51 (35). **HRMS**: Calculated for $[C_{11}H_{12}NO_7]^-$: 270.0614 $[(M-H)^-]$; found: 270.0610. **[α]**$_D^{rt}$: +131.4 (*c* = 0.008, CH_2Cl_2).



Diethyl (4*R*,5*S*)-4-nitro-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarboxylate (*cis*-6g). Following the *general procedure O,* ***cis*-6g** (6.30 mg, 0.021 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 42% yield starting from aldehyde **4g** (15.00 mg, 0.050 mmol), catalyst **5l** (2.20 mg, 0.005 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.82 (s, 1H, CHO), 6.51 (d, *J* = 5.8 Hz, 1H, H3), 6.17 (dd, *J* = 5.8, 2.8 Hz, 1H, H3), 5.63 (dd, *J* = 7.3, 2.8 Hz, 1H, H4), 4.30-4.16 (m, 4H, OCH_2CH_3), 3.64 (ddd, *J* = 10.3, 7.4, 4.7 Hz, 1H, H5), 3.19 (dd, *J* = 19.4, 4.7 Hz, 1H, CH_aH_bCHO), 2.87 (dd, *J* = 19.3, 10.3 Hz, 1H, CH_aH_bCHO), 1.28 (td, *J* = 7.1, 2.7 Hz, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.2 (CHO), 168.9 (C=O), 167.6 (C=O), 140.6 (C2), 128.5 (C3), 91.1 (C4), 67.1 (C1), 62.7 (OCH_2CH_3), 62.4 (OCH_2CH_3), 42.1 (C5), 41.2 (CH_2CHO), 14.1 (OCH_2CH_3), 14.1 (OCH_2CH_3). **IR** (ATR): 2969 (C-H st), 1738 (C=O st), 1558 (NO_2 st as), 1368 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 270 (M^+-CHO, 1), 254 (M^+-NO_2, 1), 207 (21), 226 (M^+-CO_2Et, 1), 161 (43), 153 (M^+-2 x CO_2Et, 3), 151 (19), 135 (57), 134 (26), 133 (32), 123 (26), 107 (27), 106 (18), 105 (68), 93 (16), 92 (17), 79 (100), 78 (41), 77 (80), 65 (20), 51 (32). **HRMS**: Calculated for $[C_9H_{16}NO_7]^-$: 298.0927 [(M-H)$^-$]; found: 298.0915. **[α]$_D^{rt}$**: -97.9 (*c* = 0.5, CH_2Cl_2).

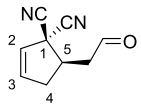


Diethyl (4*R*,5*S*)-4-nitro-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarboxylate (*trans*-6g). Following the *general procedure O,* ***trans*-6g** (3.90 mg, 0.013 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 26% yield starting from aldehyde **4g** (15.00 mg, 0.050 mmol), catalyst **5l** (2.20 mg, 0.005 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (s, 1H, CHO), 6.31 (dd, *J* = 5.8, 1.9 Hz, 1H, H2), 6.17 (dd, *J* = 5.8, 1.9 Hz, 1H, H3), 5.39 (dt, *J* = 7.3, 1.9 Hz, 1H, H4), 4.32-4.15 (m, 4H, OCH_2CH_3), 3.89 (td, *J* = 7.5, 5.6 Hz, 1H, H5), 3.09-2.84 (m, 2H, CH_2CHO), 1.34-1.22 (m, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.0 (CHO), 168.4 (C=O), 136.3 (C2), 130.7 (C3), 94.2 (C4), 68.9 (C1), 62.8 (OCH_2CH_3), 62.6 (OCH_2CH_3), 43.7 (CH_2CHO), 43.6 (C5), 14.1 (OCH_2CH_3), 14.1 (OCH_2CH_3). **IR** (ATR): 2972 (C-H st), 1738 (C=O st), 1432 (NO_2 st as), 1364 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 299 (M^+, 1), 270 (M^+-CHO, 2), 254 (M^+-NO_2, 3), 226 (M^+-CO_2Et, 1), 207 (36), 155 (M^+-2 x CO_2Et, 2), 105 (26), 85 (51), 83 (100), 81 (16), 77 (24), 52 (16), 51 (17). **HRMS**: Calculated for $[C_9H_{16}NO_7]^-$: 298.0927 [(M-H)$^-$]; found: 298.0927. **[α]$_D^{rt}$**: +5.3 (*c* = 0.3, CH_2Cl_2).

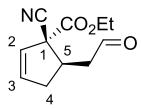


Diethyl (*R*)-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarboxylate (6h). Following the *general procedure O*, **6h** (6.70 mg, 0.030 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 34% yield starting from aldehyde **4h** (20.00 mg, 0.800 mmol), catalyst **5l** (4.00 mg, 0.008 mmol) and 1,2-dichloroethane (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.6 Hz, CHO), 6.02 (dt, *J* = 5.4, 2.5 Hz, 1H, H2), 5.84 (dd, *J* = 5.0, 2.8 Hz, 1H, H3), 4.27-4.11 (m, 4H, OCH_2CH_3), 3.35 (ddd, *J* = 11.8, 9.7, 5.9 Hz, 1H, H5), 2.88-2.72 (m, 2H, H4), 2.56 (ddd, *J* = 17.3, 10.1, 1.9 Hz, 1H, CH_aH_bCHO), 2.16 (ddt, *J* = 16.3, 7.2, 2.2 Hz, 1H, CH_aH_bCHO), 1.26 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.1 (CHO), 170.5 (C=O), 169.9 (C=O), 135.3 (C2), 129.5 (C3), 69.0 (C1), 61.7 (OCH_2CH_3), 61.7 (OCH_2CH_3), 45.8 (CH_2CHO), 39.0 (C5), 38.5 (C5), 38.5 (C4), 14.2 (OCH_2CH_3), 14.1 (OCH_2CH_3). **IR** (ATR): 3016 (=CH st), 1741 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 254 (M^+, 2), 225 (M^+-CHO, 2), 208 (46), 182 (M^+-CO_2Et, 2), 162 (20), 135 (89), 134 (43), 110 (M^+-2 x CO_2Et, 2), 107 (38), 93 (20),

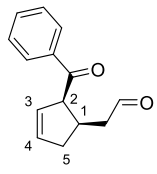
85 (28), 83 (38), 79 (100), 77 (46). **HRMS**: Calculated for $[C_{13}H_{18}O_5Na]^+$: 277.1052 [$(M+Na)^+$]; found: 277.1062. $[\alpha]_D^{rt}$: +14.5 (*c* = 0.5, CH_2Cl_2).



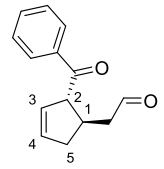
(*R*)-5-(2-oxoethyl)cyclopent-2-ene-1,1-dicarbonitrile (6i). Following the *general procedure O*, **6i** (6.50 mg, 0.041 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) in 56% yield starting from aldehyde **4i** (11.60 mg, 0.070 mmol), catalyst **5l** (3.70 mg, 0.007 mmol) and 1,2-dichloroethane (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.85 (s, 1H, CHO), 6.29 (dt, *J* = 5.4, 2.5 Hz, 1H, H2), 5.80 (dt, *J* = 5.6, 2.2 Hz, 1H, H3), 3.34 (qd, *J* = 8.3, 5.6 Hz, 1H, H5), 3.14 (dd, *J* = 18.8, 5.6 Hz, 1H, C$H_a$$H_b$CHO), 2.99 (dtt, *J* = 11.0, 8.8, 4.0 Hz, 2H, H4), 2.27 (ddt, *J* = 17.3, 8.3, 2.4 Hz, 1H, $CH_a$$H_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 197.9 (CHO), 139.7 (C2), 124.6 (C3), 115.1 (CN), 112.8 (CN), 45.6 (C4), 43.8 (*C*H_2CHO), 37.6 (C5). **IR** (ATR): 2855 (C-H st), 2244 (C-N st), 1724 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 133 (40), 131 (M^+-CHO, 29), 117 (21), 105 (34), 104 (100), 91 (40), 78 (26), 77 (33), 51 (17). **HRMS**: Calculated for $[C_9H_7N_2O]^-$: 159.0558 [$(M-H)^-$]; found: 159.0556. $[\alpha]_D^{rt}$: +3.5 (*c* = 0.25, CH_2Cl_2).



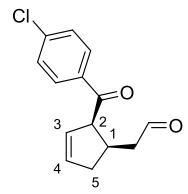
Ethyl (5*R*)-1-cyano-5-(2-oxoethyl)cyclopent-2-ene-1-carboxylate (6j). Following the *general procedure O*, **6j** (16.20 mg, 0.078 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 54% yield starting from aldehyde **4j** (30.00 mg, 0.150 mmol), catalyst **5l** (7.40 mg, 0.015 mmol) and 1,2-dichloroethane (1.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.82 (s, 1H, CHO), 6.13 (dt, *J* = 5.4, 2.5 Hz, 1H, H2), 5.73 (ddd, *J* = 5.7, 2.7, 1.7 Hz, 1H, H3), 4.37-4.25 (m, 2H, OC$H_2$$CH_3$), 3.30 (qd, *J* = 8.1, 6.6 Hz, 1H, H5), 3.08 (dd, *J* = 18.7, 6.6 Hz, 1H, H4a), 3.00-2.80 (m, 2H, CH_2CHO), 2.23 (ddt, *J* = 16.9, 8.4, 2.4 Hz, 1H, H4b), 1.34 (td, *J* = 7.2, 2.4 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 199.4 (CHO), 168.1 (C=O), 137.4 (C4), 127.2 (C3), 116.6 (CN), 63.4 (O*C*$H_2$$CH_3$), 57.8 (C1), 46.5 (*C*$H_2$CHO), 40.6 (C5), 38.3 (C4), 14.1 (OCH_2*C*H_3). **IR** (ATR): 2969 (C-H st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 135 (M^+-CO_2Et, 8), 134 (20), 106 (25), 105 (16), 104 (26), 92 (100), 79 (47), 78 (18), 77 (42), 51 (15). **HRMS**: Calculated for $[C_{11}H_{14}NO_3]^+$: 208.0974 [$(M+H)^+$]; found: 208.0978. $[\alpha]_D^{rt}$: -68.9 (*c* = 0.02, CH_2Cl_2).



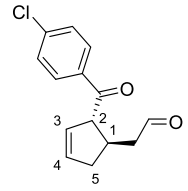
2-((1*R*,2*S*)-2-benzoylcyclopent-3-en-1-yl)acetaldehyde (*cis*-6l). Following the *general procedure O*, ***cis*-6l** (7.20 mg, 0.030 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 48% yield starting from aldehyde **4l** (15.00 mg, 0.070 mmol), catalyst **5m** (6.30 mg, 0.014 mmol) and 1,2-dichloroethane (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.64 (s, 1H, CHO), 8.04-7.94 (m, 2H, C_{arom}-H), 7.65-7.42 (m, 3H, C_{arom}-H), 5.98 (dq, *J* = 4.7, 2.3 Hz, 1H, H3), 5.79 (dq, *J* = 6.2, 2.2 Hz, 1H, H4), 474 (dt, *J* = 8.2, 2.1 Hz, 1H, H2), 3.17 (dtd, *J* = 14.5, 8.0, 6.5 Hz, 1H, H1), 2.76-2.67 (m, 1H, C$H_a$$H_b$CHO), 2.63 (t, *J* = 7.0 Hz, 2H, H5), 2.36-2.25 (m, 1H, $CH_a$$H_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.8 (CHO), 201.0 (C=O), 137.3 (C_{arom}-C), 133.5 (C3), 133.4 (C4), 129.8 (C_{arom}-H), 128.9 (C_{arom}-H), 128.5 (C_{arom}-H), 55.0 (C2), 45.7 (*C*H_2CHO), 39.1 (C5), 36.1 (C1). **IR** (ATR): 3019 (=CH st), 2972 (C-H st), 1734 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 214 (M^+, 2), 194 (15), 185 (M^+-CHO, 8), 172 (M^+-CH_2-CHO, 1), 165 (24), 105 (100), 77 (61), 51 (22). **HRMS**: Calculated for $[C_{14}H_{15}O_2]^-$: 215.1072 [$(M+H)^+$]; found: 215.1078. $[\alpha]_D^{rt}$: -82.7 (*c* = 0.5, CH_2Cl_2).



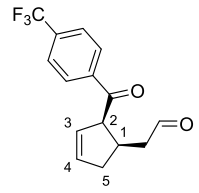
2-((1*R*,2*R*)-2-benzoylcyclopent-3-en-1-yl)acetaldehyde (*trans*-6l). Following the *general procedure O*, ***trans*-6l** (2.80 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 20% yield starting from aldehyde **4l** (15.00 mg, 0.070 mmol), catalyst **5m** (6.30 mg, 0.014 mmol) and 1,2-dichloroethane (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (t, *J* = 2.0 Hz, CHO), 8.02-7.95 (m, 2H, C_{arom}-H), 7.62-7.54 (m, 1H, C_{arom}-H), 7.51-7.46 (m, 2H, C_{arom}-H), 5.86 (dq, *J* = 5.0, 2.4 Hz, 1H, H3), 5.70 (dq, *J* = 4.8, 2.2 Hz, 1H, H4), 4.20 (dt, *J* = 5.2, 2.6 Hz, 1H, H2), 3.37 (h, *J* = 6.9 Hz, 1H, H1), 2.93-2.80 (m, 1H, C$H_a$$H_b$CHO), 2.66-2.60 (m, 2H, H5), 2.14 (ddd, *J* = 16.8, 5.3, 2.5 Hz, C$H_a$$H_b$CHO, 1H). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.9 (CHO), 199.3 (C=O), 136.6 (C_{arom}-C), 133.3 (C3), 133.0 (C4), 128.8 (C_{arom}-H), 128.7 (C_{arom}-H), 60.0 (C2), 49.6 (*C*H_2CHO), 38.8 (C5), 33.9 (C1). **IR** (ATR): 3030 (=CH st), 2972 (C-H st), 1741 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 214 (M^+, 1), 105 (100), 77 (43), 51 (16). **HRMS**: Calculated for $[C_{14}H_{15}O_2]^-$: 215.1072 $[(M+H)^+]$; found: 215.1078. **[α]**$_D^{rt}$: +132.1 (*c* = 0.2, CH_2Cl_2).



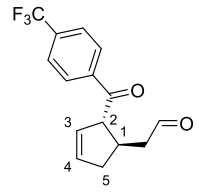
2-((1*R*,2*S*)-2-(4-chlorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6m). Following the *general procedure O*, ***cis*-6m** (7.10 mg, 0.030 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 48% yield starting from aldehyde **4m** (15.00 mg, 0.060 mmol), catalyst **5m** (5.40 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.64 (s, 1H, CHO), 7.97-7.89 (m, 2H, C_{arom}-H), 7.50-7.41 (m, 2H, C_{arom}-H), 6.00-5.96 (m, 1H, H3), 5.77-5.73 (m, 1H, H4), 4.71-4.66 (m, 1H, H2), 3.13 (h, *J* = 7.6 Hz, 1H, H1), 2.73-2.63 (m, 3H, C*H*$_2$CHO, H5a), 2.35-2.25 (m, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 199.9 (C=O), 140.0 (C_{arom}-C), 135.5 (C_{arom}-C), 133.7 (C3), 129.9 (C_{arom}-H), 129.6 (C4), 129.3 (C_{arom}-H), 54.8 (C2), 45.6 (*C*H_2CHO), 39.0 (C5), 36.1 (C1). **IR** (ATR): 3023 (=CH st), 1741 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 248 (M^+, 2), 228 (23), 219 (M^+-CHO, 5), 165 (40), 141 (36), 139 (100), 137 (M^+-C_6H_4Cl, 2), 111 (32), 109 (M^+-C_7H_4OCl, 2), 75 (16). **HRMS**: Calculated for $[C_{14}H_{13}O_2ClNa]^+$: 271.0502 $[(M+Na)^+]$; found: 271.0504. **[α]**$_D^{rt}$: -36.8 (*c* = 0.2, CH_2Cl_2).



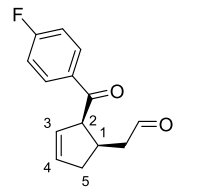
2-((1*R*,2*R*)-2-(4-chlorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6m). Following the *general procedure O*, ***trans*-6m** (3.20 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 22% yield starting from aldehyde **4m** (15.00 mg, 0.060 mmol), catalyst **5m** (5.40 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (t, *J* = 1.9 Hz, CHO), 7.94-7.90 (m, 2H, C_{arom}-H), 7.48-7.42 (m, 2H, C_{arom}-H), 5.89-5.85 (m, 1H, H3), 5.68-5.64 (m, 1H, H4), 4.16-4.11 (m, 1H, H2), 3.38-3.29 (m, 1H, H1), 2.91-2.80 (m, 1H, H5a), 2.62 (dd, *J* = 7.2, 1.9 Hz, 2H, C*H*$_2$CHO), 2.19-2.09 (m, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 198.1 (C=O), 139.8 (C_{arom}-C), 134.9 (C_{arom}-C), 133.4 (C3), 130.1 (C_{arom}-H), 129.2 (C_{arom}-H), 128.3 (C4), 68.0 (C2), 49.5 (*C*H_2CHO), 38.8 (C5), 33.8 (C1). **IR** (ATR): 2851 (C-H st), 1726 (C=O st), 1676 (C=C st), 1091 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 248 (M^+, 1), 219 (M^+-CHO, 1), 141 (32), 139 (100), 111 (26), 109 (M^+-C_7H_4OCl, 1). **HRMS**: Calculated for $[C_{14}H_{13}O_2ClNa]^+$: 271.0502 $[(M+Na)^+]$; found: 271.0508. **[α]**$_D^{rt}$: +1502.0 (*c* = 0.03, CH_2Cl_2).



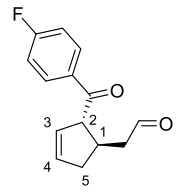
2-((1*R*,2*S*)-2-(4-(trifluoromethyl)benzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6n). Following the *general procedure O*, ***cis*-6n** (3.90 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 28% yield starting from aldehyde **4n** (15.00 mg, 0.050 mmol), catalyst **5m** (4.80 mg, 0.011 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.65 (s, 1H, CHO), 8.09 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.75 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.01 (dq, *J* = 5.9, 2.3 Hz, 1H, H3), 5.76 (dq, *J* = 6.1, 2.2 Hz, 1H, H4), 4.75 (dp, *J* = 8.1, 2.1 Hz, 1H, H2), 3.14 (h, *J* = 7.5 Hz, 1H, H1), 2.75-2.63 (m, 3H, CH_2CHO, H5a), 2.33 (ddq, *J* = 16.4, 6.8, 2.3 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 200.2 (C=O), 135.1 (C_{arom}-C), 134.0 (C3), 130.3 (C_{arom}-C), 129.3 (C4), 128.8 (C_{arom}-H), 128.1 (CF_3), 126.0 (q, $^3J_{CF}$ = 3.7 Hz, *C*H$_{arom}$C$_{arom}$CF$_3$), 55.1 (C2), 45.6 (*C*H$_2$CHO), 39.0 (C5), 36.1 (C1). **IR** (ATR): 2966 (C-H st), 1738 (C=O st), 1368 (C-F st), 768 (CF_3) cm^{-1}. **HRMS**: Calculated for $[C_{15}H_{13}O_2F_3Na]^+$: 305.0765 [(M+Na)$^+$]; found: 305.0775. **[α]**$_D^{rt}$: -105.5 (*c* = 0.3, CH_2Cl_2).



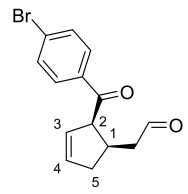
2-((1*R*,2*R*)-2-(4-(trifluoromethyl)benzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6n). Following the *general procedure O*, ***trans*-6n** (0.70 mg, 0.002 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 4% yield starting from aldehyde **4n** (15.00 mg, 0.050 mmol), catalyst **5m** (4.80 mg, 0.011 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.78 (t, *J* = 1.7 Hz, 1H, CHO), 8.08 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.75 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 5.89 (dq, *J* = 4.9, 2.4 Hz, 1H, H3), 5.66 (dt, *J* = 5.9, 2.3 Hz, 1H, H4), 4.18 (dt, *J* = 5.2, 2.6 Hz, 1H, H2), 3.43-3.29 (m, 1H, H2), 2.87 (ddq, *J* = 16.3, 8.2, 2.5 Hz, H5a), 2.65 (dd, *J* = 7.4, 1.7 Hz, 2H, C*H*$_2$CHO), 2.16 (ddd, *J* = 16.6, 5.2, 2.4 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 201.6 (CHO), 201.1 (C=O), 135.6 (C_{arom}-C), 135.0 (C_{arom}-C), 133.6 (C3), 129.0 (C_{arom}-H), 127.9 (C4), 127.2 (CF_3), 125.9 (q, $^3J_{CF}$ = 3.5 Hz, *C*H$_{arom}$C$_{arom}$CF$_3$), 60.3 (C2), 49.5 (*C*H$_2$CHO), 38.9 (C5), 33.7 (C1). **IR** (ATR): 2972 (C-H st), 1735 (C=O st), 1368 (C-F st), 772 (CF_3) cm^{-1}. **MS** (EI) m/z (%): 282 (M$^+$, 1), 238 (17), 173 (100), 145 (50), 81 (16). **HRMS**: Calculated for $[C_{15}H_{13}O_2F_3Na]^+$: 305.0765 [(M+Na)$^+$]; found: 305.0775. **[α]**$_D^{rt}$: +71.6 (*c* = 0.2, CH_2Cl_2).



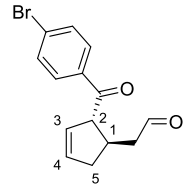
2-((1*R*,2*S*)-2-(4-fluorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6o). Following the *general procedure O*, ***cis*-6o** (10.60 mg, 0.050 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 52% yield starting from aldehyde **4o** (20.00 mg, 0.090 mmol), catalyst **5m** (7.70 mg, 0.018 mmol) and 1,2-dichloroethane (0.9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.65 (s, 1H, CHO), 8.08-7.87 (m, 2H, C_{arom}-H), 7.21-7.08 (m, 2H, C_{arom}-H), 5.99 (dq, *J* = 5.8, 2.3 Hz, 1H, H3), 5.76 (d, *J* = 6.1, 2.2 Hz, 1H, H4), 4.70 (dp, *J* = 8.2, 2.1 Hz, 1H, H2), 3.13 (p, *J* = 7.4 Hz, 1H, H1), 2.76-2.59 (m, 3H, C*H*$_2$CHO, H5a), 2.31 (dd, *J* = 16.3, 6.6, 2.2 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 201.7 (CHO), 199.5 (C=O), 166.1 (d, $^1J_{C\text{-}F}$ = 255.0 Hz, CCHCH*C*F), 135.2 (d, $^3J_{C\text{-}F}$ = 15.5 Hz, C*C*HCHCF), 133.6 (C3), 131.2 (d, $^4J_{C\text{-}F}$ = 9.4 Hz, *C*CHCHCF), 129.7 (C4), 116.1 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CCH*C*HCF), 54.8 (C2), 45.7 (*C*H$_2$CHO), 39.1 (C5), 36.1 (C1). **IR** (ATR): 3020 (=CH st), 1734 (C=O st), 1368 (C-F st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{13}O_2FNa]^+$: 255.0797 [(M+Na)$^+$]; found: 255.0804. **[α]**$_D^{rt}$: -85.3 (*c* = 0.7, CH_2Cl_2).



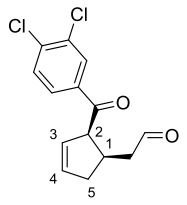
2-((1*R*,2*R*)-2-(4-fluorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6o). Following the *general procedure O*, ***trans*-6o** (3.80 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 19% yield starting from aldehyde **4o** (20.00 mg, 0.090 mmol), catalyst **5m** (7.70 mg, 0.018 mmol) and 1,2-dichloroethane (0.9 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (t, *J* = 1.9 Hz, 1H, CHO), 8.09-9.97 (m, 2H, C_{arom}-H), 7.22-7.12 (m, 2H, C_{arom}-H), 5.93-5.82 (m, 1H, H3), 5.68 (dt, *J* = 5.7, 2.2 Hz, 1H, H4), 4.18-4.09 (m, 1H, H2), 3.41-3.30 (m, 1H, H1), 2.86 (ddq, *J* = 16.9, 8.4, 2.4 Hz, 1H, C$H_a$$H_b$CHO), 2.63 (dd, *J* = 7.2, 1.9 Hz, H5), 2.15 (ddt, *J* = 16.9, 5.4, 2.4 Hz, 1H, CH_aH_bCHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 197.7 (C=O), 165.9 (d, $^1J_{C\text{-}F}$ = 254.0 Hz, CCHCH*C*F), 133.3 (C3), 133.0 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, *C*CHCHCF), 131.3 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, C*C*HCHCF), 128.5 (C4), 116.0 (d, $^2J_{C\text{-}F}$ = 22 Hz, CCH*C*HCF), 59.9 (C2), 49.5 (*C*H_2CHO), 38.8 (C5), 33.9 (C1). **IR** (ATR): 3016 (=CH st), 2969 (C-H st), 1368 (C-F st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{13}O_2FNa]^+$: 255.0797 [(M+Na)$^+$]; found: 255.0803. **[α]**$_D^{rt}$: +129.4 (*c* = 0.3, CH_2Cl_2).



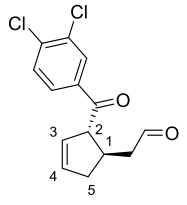
2-((1*R*,2*S*)-2-(4-bromobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6p). Following the *general procedure O*, ***cis*-6p** (4.70 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 37% yield starting from aldehyde **4o** (15.00 mg, 0.040 mmol), catalyst **5m** (3.90 mg, 0.009 mmol) and 1,2-dichloroethane (0.4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.64 (s, 1H, CHO), 7.88-7.82 (m, 2H, C_{arom}-H), 7.65-7.56 (m, 2H, C_{arom}-H), 6.01-5.96 (m, 1H, H3), 5.77-5.73 (m, 1H, H4), 4.73-4.62 (m, 1H, H2), 3.13 (h, *J* = 7.4 Hz, 1H, H1), 2.74-2.59 (m, 3H, CH_2CHO, H5a), 2.35-2.25 (m, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 200.1 (C=O), 153.9 (C_{arom}-C), 133.7 (C3), 132.3 (C_{arom}-H), 130.0 (C_{arom}-H), 129.5 (C4), 128.8 (C_{arom}-C), 54.8 (C2), 45.6 (*C*H_2CHO), 39.0 (C5), 36.1 (C1). **IR** (ATR): 3020 (=CH st), 1720 (CO st), 1674 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 274 (23), 272 (21), 263 (M^+-CHO, 3), 185 (100), 183 (68), 165 (47), 163 (16), 157 (26), 155 (25), 109 (M^+-C_7H_4BrO, 3), 76 (15). **HRMS**: Calculated for $[C_{14}H_{13}O_2BrNa]^+$: 314.9997 [(M+Na)$^+$]; found: 315.0001. **[α]**$_D^{rt}$: -140.75 (*c* = 0.4, CH_2Cl_2).



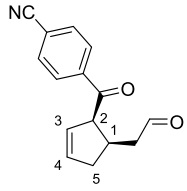
2-((1*R*,2*R*)-2-(4-bromobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6p). Following the *general procedure O*, ***trans*-6p** (2.90 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 23% yield starting from aldehyde **4p** (15.00 mg, 0.400 mmol), catalyst **5m** (3.90 mg, 0.009 mmol) and 1,2-dichloroethane (0.4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (s, 1H, CHO), 7.86-7.81 (m, 2H, C_{arom}-H), 7.64-7.59 (m, 2H, C_{arom}-H), 5.88-5.84 (m, 1H, H3), 5.68-5.63 (m, 1H, H4), 4.15-4.11 (m, 1H, H2), 3.40-3.27 (m, 1H, H1), 2.92-2.78 (m, 1H, H5a), 2.64-2.60 (m, 2H, CH_2CHO), 2.18-2.09 (m, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.7 (CHO), 198.3 (C=O), 135.3 (C_{arom}-C), 133.4 (C3), 132.2 (C_{arom}-H), 130.2 (C_{arom}-H), 128.5 (C_{arom}-C), 128.3 (C4), 60.0 (C2), 49.5 (*C*H_2CHO), 38.8 (C5), 33.8 (C1). **IR** (ATR): 3026 (=CH st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 263 (M^+-CHO, 3), 207 (15), 185 (100), 183 (96), 157 (18), 155 (24), 109 (M^+-C_7H_4BrO, 2), 79 (16), 66 (17). **HRMS**: Calculated for $[C_{14}H_{13}O_2BrNa]^+$: 314.9997 [(M+Na)$^+$]; found: 315.0001. **[α]**$_D^{rt}$: +79.8 (*c* = 0.2, CH_2Cl_2).



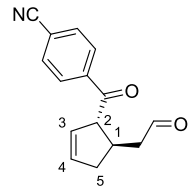
2-((1*R*,2*S*)-2-(3,4-dichlorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6q). Following the *general procedure O*, ***cis*-6q** (7.90 mg, 0.030 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 56% yield starting from aldehyde **4q** (14.00 mg, 0.050 mmol), catalyst **5m** (4.70 mg, 0.010 mmol) and CH_2Cl_2 (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.65 (s, 1H, CHO), 8.06 (d, *J* = 2.1 Hz, 1H, C_{arom}-H), 7.81 (dd, *J* = 8.4, 2.1 Hz, 1H, C_{arom}-H), 7.56 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.00 (d, *J* = 6.5, 2.3 Hz, 1H, H3), 5.73 (dq, *J* = 6.1, 2.2 Hz, 1H, H4), 4.66 (dp, *J* = 8.1, 2.1 Hz, 1H, H2), 3.11 (h, *J* = 7.5 Hz, 1H, H1), 2.75-2.60 (m, 3H, C*H*$_2$CHO, H5a), 2.31 (ddq, *J* = 16.3, 6.8, 2.2, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.6 (CHO), 198.9 (C=O), 138.1 (C_{arom}-C), 136.7 (C_{arom}-C), 135.1 (C_{arom}-C), 134.1 (C_{arom}-H), 131.0 (C3), 130.4 (C4), 129.3 (C_{arom}-H), 127.5 (C_{arom}-H), 54.8 (C2), 45.6 (*C*H$_2$CHO), 39.0 (C5), 36.1 (C1). **IR** (ATR): 3005 (=CH st), 1741 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{12}O_2Cl_2Na]^+$: 305.0112 [(M+Na)$^+$]; found: 305.0114. **[α]$_D^{rt}$**: -125.2 (*c* = 0.2, CH_2Cl_2).



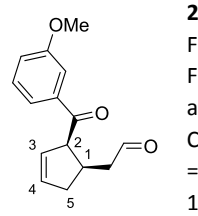
2-((1*R*,2*R*)-2-(3,4-dichlorobenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6q). Following the *general procedure O*, ***trans*-6q** (2.20 mg, 0.008 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 16% yield starting from aldehyde **4q** (14.00 mg, 0.050 mmol), catalyst **5m** (4.70 mg, 0.010 mmol) and CH_2Cl_2 (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (t, *J* = 1.7 Hz, 1H, CHO), 8.05 (d, *J* = 2.0 Hz, 1H, C_{arom}-H), 7.80 (dd, *J* = 8.4, 2.1 Hz, 1H, C_{arom}-H), 7.57 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 5.89 (dq, *J* = 4.9, 2.4 Hz, 1H, H3), 5.64 (dq, *J* = 6.0, 2.3 Hz, 1H, H4), 4.10 (dp, *J* = 5.0, 2.4 Hz, 1H, H1), 3.41-3.27 (m, 1H, H1), 2.86 (ddq, *J* = 16.4, 8.1, 2.5 Hz, 1H, C*H*$_a$H$_b$CHO), 2.64 (dt, *J* = 7.4, 1.3 Hz, 2H, H5), 2.21-2.08 (m, 1H, CH$_a$*H*$_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.6 (CHO), 197.1 (C=O), 137.9 (C_{arom}-C), 136.2 (C_{arom}-C), 133.7 (C_{arom}-H), 133.6 (C_{arom}-C), 131.0 (C3), 130.7 (C4), 127.9 (C_{arom}-H), 127.7 (C_{arom}-H), 60.0 (C2), 49.5 (*C*H$_2$CHO), 38.8 (C5), 33.8 (C1). **IR** (ATR): 3026 (=CH st), 1741 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{12}O_2Cl_2Na]^+$: 305.0112 [(M+Na)$^+$]; found: 305.0119. **[α]$_D^{rt}$**: +94.1 (*c* = 0.08, CH_2Cl_2).



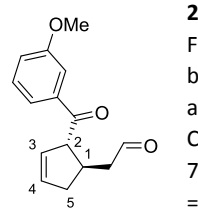
4-((1*S*,5*R*)-5-(2-oxoethyl)cyclopent-2-ene-1-carbonyl)benzonitrile (*cis*-6r). Following the *general procedure O*, ***cis*-6r** (2.80 mg, 0.012 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) after 10 min in 19% yield starting from aldehyde **4r** (15.00 mg, 0.060 mmol), catalyst **5m** (5.60 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.65 (s, 1H, CHO), 8.13-8.02 (m, 2H, C_{arom}-H), 7.82-7.75 (m, 2H, C_{arom}-H), 6.01 (dq, *J* = 6.6, 2.3 Hz, 1H, H3), 5.73 (d, *J* = 6.3, 2.2 Hz, 1H, H4), 4.73 (dt, *J* = 7.8, 1.6 Hz, 1H, H2), 3.11 (p, *J* = 7.5 Hz, 1H, H1), 2.74-2.72 (m, 3H, CH_2CHO, H5a), 2.33 (ddq, *J* = 16.2, 6.9, 2.2 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.6 (CHO), 200.0 (C=O), 140.2 (C_{arom}-C), 134.3 (C3), 132.8 (C_{arom}-H), 132.4 (C_{arom}-C), 129.1 (C4), 128.9 (C_{arom}-H), 118.0 (CN), 55.0 (C2), 45.6 (*C*H$_2$CHO), 39.0 (C5), 36.2 (C1). **IR** (ATR): 3016 (=CH st), 1734 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{17}H_{16}NO_4]^-$: 298.1079 [(M+CH_3CO)$^-$]; found: 298.1069. **[α]$_D^{rt}$**: +32.7 (*c* = 0.04, CH_2Cl_2).



4-((1*R*,5*R*)-5-(2-oxoethyl)cyclopent-2-ene-1-carbonyl)benzonitrile (*trans*-6r). Following the *general procedure O*, ***trans*-6r** (0.80 mg, 0.003 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 5% yield starting from aldehyde **4r** (15.00 mg, 0.060 mmol), catalyst **5m** (5.60 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (s, 1H, CHO), 8.09-8.02 (m, 2H, C_{arom}-H), 7.83-7.75 (m, 2H, C_{arom}-H), 5.90 (dq, *J* = 4.9, 2.4 Hz, 1H, H3), 5.68-5.59 (m, 2H, H4), 4.15 (dt, *J* = 5.2, 2.6 Hz, 1H, H2), 3.42-3.28 (m, 1H, H1), 2.93-2.80 (m, 1H, C*H*$_a$H$_b$CHO), 2.66 (ddd, *J* = 7.4, 2.9, 1.7 Hz, 2H, H5), 2.16 (ddd, *J* = 16.7, 5.2, 2.4 Hz, 1H, CH$_a$*H*$_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.5 (CHO), 198.1 (C=O), 144.6 (C_{arom}-C), 133.9 (C3), 132.7 (C_{arom}-H), 129.1 (C_{arom}-H), 127.6 (C2), 100.1 (CN), 99.1 (C_{arom}-C), 60.3 (C2), 49.5 (*C*H$_2$CHO), 38.9 (C5), 33.8 (C1). **IR** (ATR): 3020 (=CH st), 1741 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{15}H_{12}NO_2]^-$: 238.0868 [(M-H)$^-$]; found: 238.0868. **[α]**$_D^{rt}$: +85.3 (*c* = 0.2, CH_2Cl_2).

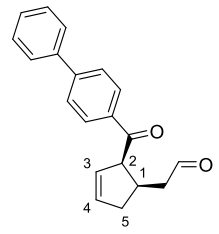


2-((1*R*,2*S*)-2-(3-methoxybenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6t). Following the *general procedure O*, ***cis*-6t** (3.60 mg, 0.015 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 40% yield starting from aldehyde **4t** (40.00 mg, 0.160 mmol), catalyst **5m** (14.70 mg, 0.030 mmol) and CH_2Cl_2 (1.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.65 (s, 1H, CHO), 7.58 (dt, *J* = 7.7, 1.3 Hz, 1H, C_{arom}-H), 7.50 (dd, *J* = 2.7, 1.6 Hz, 1H, C_{arom}-H), 7.39 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.12 (dd, *J* = 8.2, 2.7, 1.0 Hz, 1H, C_{arom}-H), 5.97 (dq, *J* = 6.5, 2.3 Hz, 1H, H3), 5.78 (dq, *J* = 6.1, 2.1 Hz, 1H, H4), 4.70 (dt, *J* = 8.1, 2.1 Hz, 1H, H2), 3.86 (s, 3H, OCH_3), 3.16 (qt, *J* = 8.1, 6.4 Hz, 1H, H1), 2.75-2.58 (m, 3H, C*H*$_2$CHO, H5a), 2.30 (ddq, *J* = 16.3, 6.5, 2.2 Hz, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.8 (CHO), 200.8 (C=O), 160.1 (C_{arom}-C), 138.6 (C_{arom}-C), 133.4 (C3), 129.9 (C4), 129.8 (C_{arom}-H), 121.1 (C_{arom}-H), 120.0 (C_{arom}-H), 112.6 (C_{arom}-H), 55.6 (OCH_3), 55.1 (C2), 45.7 (*C*H$_2$CHO), 39.1 (C5), 36.2 (C1). **IR** (ATR): 3016 (=CH st), 1738 (C=O st), 1429 cm^{-1}. **MS** (EI) m/z (%): 224 (24), 213 (M$^+$-OCH_3, 1), 185 (16), 175 (22), 170 (23), 153 (23), 152 (20), 144 (20), 135 (24), 128 (20), 113 (20), 110 (16), 101 (20), 89 (19), 77 (56), 67 (22), 51 (100). **HRMS**: Calculated for $[C_{15}H_{16}O_3Na]^+$: 267.0997 [(M+Na)$^+$]; found: 267.1001. **[α]**$_D^{rt}$: -125.3 (*c* = 0.6, CH_2Cl_2).

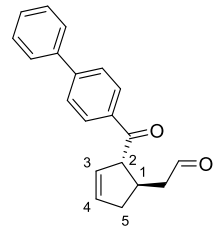


2-((1*R*,2*R*)-2-(3-methoxybenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6t). Following the *general procedure O,* ***trans*-6t** (2.60 mg, 0.011 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 17% yield starting from aldehyde **4t** (40.00 mg, 0.160 mmol), catalyst **5m** (14.70 mg, 0.030 mmol) and CH_2Cl_2 (1.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.77 (t, *J* = 1.9 Hz, 1H, CHO), 7.56 (dt, *J* = 7.7, 1.3 Hz, 1H, C_{arom}-H), 7.50 (dd, *J* = 2.7, 1.6 z, 1H, C_{arom}-H), 7.39 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.12 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, C_{arom}-H), 5.85 (dq, *J* = 5.8, 2.4 Hz, 1H, H3), 5.75-5.66 (m, 1H, H4), 4.17 (dp, *J* = 5.1, 2.5 Hz, 1H, H2), 3.86 (s, 3H, OCH_3), 3.35 (ddt, *J* = 13.4, 7.3, 5.3 Hz, 1H, H1), 2.94-2.79 (m, 1H, C*H*$_a$H$_b$CHO), 2.67-2.57 (m, 2H, H5), 2.22-2.07 (m, 1H, CH$_a$*H*$_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.8 (CHO), 199.1 (C=O), 160.1 (C_{arom}-C), 138.0 (C_{arom}-C), 133.0 (C3), 129.8 (C4), 128.8 (C_{arom}-H), 121.2 (C_{arom}-H), 119.8 (C_{arom}-H), 113.0 (C_{arom}-H), 60.1 (OCH_3), 55.6 (C2), 49.6 (*C*H$_2$CHO), 38.8 (C5), 34.0 (C1). **IR** (ATR): 3026 (=CH st), 1741 (C=O st), 1720

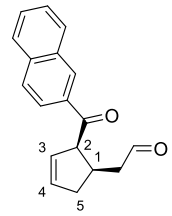
(C=C st) cm^{-1} **HRMS**: Calculated for $[C_{15}H_{17}O_3]^+$: 245.1178 $[(M+H)^+]$; found: 245.1179. $[\alpha]_D^{rt}$: +153.6 (*c* = 0.2, CH_2Cl_2).



2-((1*R*,2*S*)-2-([1,1'-biphenyl]-4-carbonyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6u). Following the *general procedure O*, ***cis*-6u** (7.05 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 47% yield starting from aldehyde **4u** (15.00 mg, 0.050 mmol), catalyst **5m** (4.70 mg, 0.010 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) 9.67 (t, *J* = 1.0 Hz, 1H, CHO), 8.09-8.05 (m, 2H, C_{arom}-H), 7.72-7.67 (m, 2H, C_{arom}-H), 7.66-7.61 (m, 2H, C_{arom}-H), 7.52-7.44 (m, 2H, C_{arom}-H), 7.44-7.38 (m, 1H, C_{arom}-H), 6.00 (dq, *J* = 4.7, 2.3 Hz, 1H, H3), 5.84-5.79 (m, 1H, H4), 4.77 (dp, *J* = 8.3, 2.1 Hz, 1H, H2), 3.23-3.15 (m, 1H, H1), 2.76-2.63 (m, 3H, H5a, C*H*$_2$CHO), 2.33 (ddq, *J* = 16.3, 6.5, 2.2 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.9 (CHO), 200.6 (C=O), 146.2 (C_{arom}-C), 139.9 (C_{arom}-C), 135.9 (C_{arom}-C), 133.4 (C3), 129.9 (C4), 129.1 (C_{arom}-H), 129.0 (C_{arom}-H), 128.4 (C_{arom}-H), 127.6 (C_{arom}-H), 127.4 (C_{arom}-H), 55.0 (C2), 45.8 (*C*H_2CHO), 39.1 (C5), 36.2 (C1). **IR** (ATR): 3016 (=CH st), 2969 (C-H st), 1734 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{20}H_{19}O]^+$: 291.1385 $[(M+H)^+]$; found: 291.1380. $[\alpha]_D^{rt}$: -206.6 (*c* = 0.1, CH_2Cl_2).

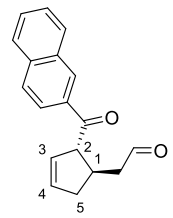


2-((1*R*,2*R*)-2-([1,1'-biphenyl]-4-carbonyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6u). Following the *general procedure O*, ***trans*-6u** (2.35 mg, 0.008 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 16% yield starting from aldehyde **4u** (15.00 mg, 0.050 mmol), catalyst **5m** (4.70 mg, 0.010 mmol) and 1,2-dichloroethane (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (t, *J* = 1.9 Hz, 1H, CHO), 8.08-8.04 (m, 2H, C_{arom}-H), 7.72-7.70 (m, 2H, C_{arom}-H), 7.68-7.59 (m, 2H, C_{arom}-H), 7.49-7.47 (m, 2H, C_{arom}-H), 7.41 (t, *J* = 7.4 Hz, 2H, C_{arom}-H), 5.88 (dq, *J* = 4.8, 2.1 Hz, 1H, H3), 5.74 (dq, *J* = 4.5, 2.1 Hz, 1H, H4), 4.23 (dq, *J* = 4.8, 2.4 Hz, 1H, H2), 3.43-3.34 (m, 1H, H1), 2.93-2.82 (m, 1H, C*H*$_a$H$_b$CHO), 2.69-2.60 (m, 2H, H5), 2.16 (ddd, *J* = 17.0, 5.6, 2.7 Hz, 1H, CH$_a$*H*$_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 201.9 (CHO), 198.9 (C=O), 146.0 (C_{arom}-C), 139.9 (C_{arom}-C), 135.3 (C_{arom}-C), 133.0 (C3), 129.3 (C_{arom}-H), 129.1 (C_{arom}-H), 128.8 (C_{arom}-H), 128.4 (C_{arom}-H), 127.5 (C_{arom}-H), 127.4 (C_{arom}-H), 60.0 (C2), 49.6 (*C*H_2CHO), 38.9 (C5), 33.9 (C1). **IR** (ATR): 3012 (=CH st), 1734 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{20}H_{19}O_2]^+$: 291.1385 $[(M+H)^+]$; found: 291.1377. $[\alpha]_D^{rt}$: +323.3 (*c* = 0.02, CH_2Cl_2).

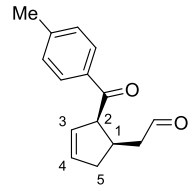


2-((1*R*,2*S*)-2-(2-naphthoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6v). Following the *general procedure O*, ***cis*-6v** (6.10 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 40% yield starting from aldehyde **4v** (15.00 mg, 0.060 mmol), catalyst **5m** (5.10 mg, 0.011 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.63 (s, 1H, CHO), 8.53 (d, *J* = 1.8 Hz, 1H, C_{arom}-H), 8.08-7.96 (m, 2H, C_{arom}-H), 7.96-7.84 (m, 2H, C_{arom}-H), 7.59 (dddd, *J* = 14.8, 8.4, 7.0, 1.5 Hz, 2H, C_{arom}-H), 6.01 (dt, *J* = 6.4, 2.3 Hz, 1H, H3), 5.84 (dq, *J* = 6.1, 2.1 Hz, 1H, H4), 4.91 (dp, *J* = 8.2, 2.1 Hz, 1H, H2), 3.24 (qt, *J* = 8.0, 6.4 Hz, 1H, H1), 2.80-2.58 (m, 3H, C*H*$_2$CHO, H5a), 2.34 (ddq, *J* = 16.3, 6.4, 2.2 Hz,

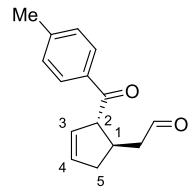
1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.8 (CHO), 200.9 (C=O), 135.8 (C_{arom}-C), 134.6 (C_{arom}-C), 133.4 (C_{arom}-H), 132.7 (C_{arom}-C), 130.3 (C3), 128.9 (C4), 128.8 (C_{arom}-H), 127.9 (C_{arom}-H), 127.0 (C_{arom}-H), 124.1 (C_{arom}-H), 54.9 (C2), 45.8 (*C*H_2CHO), 39.1 (C5), 36.2 (C1). **IR** (ATR): 3016 (=CH st), 1734 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{18}H_{16}O_2Na]^+$: 287.1048 [$(M+Na)^+$]; found: 287.1051. **[α]**$_D^{rt}$: -111.8 (*c* = 0.5, CH_2Cl_2).



2-((1*R*,2*R*)-2-(2-naphthoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6v). Following the *general procedure O*, ***trans*-6v** (2.30 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 16% yield starting from aldehyde **4v** (15.00 mg, 0.060 mmol), catalyst **5m** (5.10 mg, 0.011 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.79 (t, *J* = 2.0 Hz, 1H, CHO), 8.50 (s, 1H, C_{arom}-H), 8.08-7.79 (m, 2H, C_{arom}-H), 7.68-7.53 (m, 2H, C_{arom}-H), 7.48-7.31 (m, 2H, C_{arom}-H), 5.93-5.85 (m, 1H, H3), 5.82-5.73 (m, 1H, H4), 4.40-4.36 (m, 1H, H2), 3.51-3.37 (m, 1H, H1), 2.90 (ddt, *J* = 16.3, 8.4, 2.5 Hz, 1H, C*H*$_a$H$_b$CHO), 2.67 (dt, *J* = 7.5, 2.0 Hz, 2H, H5), 2.26-2.11 (m, 1H, CH$_a$*H*$_b$CHO). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.9 (CHO), 201.7 (C=O), 135.1 (C_{arom}-C), 133.1 (C_{arom}-C), 130.3 (C_{arom}-H), 128.9 (C3), 128.7 (C4), 128.1 (C_{arom}-C), 127.9 (C_{arom}-H), 127.5 (C_{arom}-H), 127.0 (C_{arom}-H), 124.4 (C_{arom}-H), 60.0 (C2), 49.6 (*C*H_2CHO), 38.9 (C5), 34.0 (C1). **IR** (ATR): 3016 (=CH st), 1738 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{18}H_{17}O_2]^-$: 265.1229 [$(M+H)^+$]; found: 265.1233. **[α]**$_D^{rt}$: +199.9 (*c* = 0.2, CH_2Cl_2).

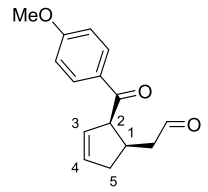


2-((1*R*,2*S*)-2-(4-methylbenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6w). Following the *general procedure O*, ***cis*-6w** (12.10 mg, 0.050 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 40% yield starting from aldehyde **4w** (30.00 mg, 0.130 mmol), catalyst **5m** (11.80 mg, 0.030 mmol) and CH_2Cl_2 (1.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.63 (s, 1H, CHO), 7.93-7.82 (m, 2H, C_{arom}-H), 7.28-7.22 (m, 2H, C_{arom}-H), 5.99-5.95 (m, 1H, H3), 5.80-5.76 (m, 1H, H4), 4.73-4.88 (m, 1H, H2), 3.22-3.10 (m, 1H, H1), 2.75-2.55 (m, 3H, C*H*$_2$CHO, H5a), 2.41 (s, 3H, CH_3), 2.29 (ddt, *J* = 16.3, 6.4, 2.1 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.9 (CHO), 200.6 (C=O), 144.4 (C_{arom}-C), 134.8 (C_{arom}-C), 133.2 (C3), 129.9 (C4), 129.6 (C_{arom}-H), 128.6 (C_{arom}-H), 54.8 (C2), 45.7 (C*H*$_2$CHO), 39.10 (C5), 36.1 (C1), 21.8 (CH_3). **IR** (ATR): 2926 (C-H st), 1724 (C=O st), 1674 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 228 (M^+, 2), 208 (35), 199 (M^+-CHO, 6), 185 (35), 165 (31), 119 (100), 109 (M^+-C_7H_7O, 1), 91 (42), 65 (16). **HRMS**: Calculated for $[C_{15}H_{16}O_2Na]^+$: 251.1048 [$(M+Na)^+$]; found: 251.1053. **[α]**$_D^{rt}$: -86.1 (*c* = 0.7, CH_2Cl_2).

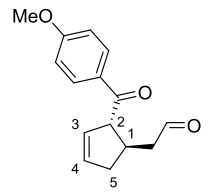


2-((1*R*,2*R*)-2-(4-methylbenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6w). Following the *general procedure O*, ***trans*-6w** (5.00 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 17% yield starting from aldehyde **4w** (30.00 mg, 0.130 mmol), catalyst **5m** (11.80 mg, 0.030 mmol) and CH_2Cl_2 (1.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (t, *J* = 2.0 Hz, 1H, CHO), 7.92-7.84 (m, 2H, C_{arom}-H), 7.29-7.26 (m, 2H, C_{arom}-H), 5.87-5.82 (m, 1H, H3), 5.71-5.67 (m, 1H, H4), 4.20-4.16 (m, 1H, H2), 3.41-3.30 (m, 1H, H1), 2.86 (ddd, *J* = 16.8, 8.4, 2.6 Hz, 1H, H5a), 2.63-2.59 (dt, *J* = 7.5, 1.8 Hz, 2H, C*H*$_2$CHO), 2.42 (s, 3H, CH_3), 2.13 (ddd, *J* = 16.8, 5.5 2.4 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.9 (CHO),

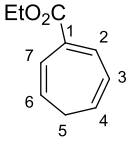
198.9 (C=O), 144.2 (C_{arom}-C), 134.1 (C_{arom}-C), 132.8 (C3), 129.5 (C_{arom}-H), 128.9 (C4), 128.8 (C_{arom}-H), 59.8 (C2), 49.6 (CH_2CHO), 38.8 (C5), 33.9 (C1), 21.8 (CH_3). **IR** (ATR): 2915 (C-H st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 648 (45), 647 (100), 316 (83), 281 (20), 208 (16), 207 (60), 199 (M^+-CHO, 1), 191 (28), 109 (M^+-C_8H_7O, 2), 57 (64). **HRMS**: Calculated for $[C_{15}H_{16}O_2Na]^+$: 251.1048 [(M+Na)$^+$]; found: 251.1055. **[α]**$_D^{rt}$: +57.0 (*c* = 0.3, CH_2Cl_2).



2-((1*R*,2*S*)-2-(4-methoxybenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*cis*-6x). Following the *general procedure O*, ***trans*-6x** (5.00 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 33% yield starting from aldehyde **4x** (15.00 mg, 0.060 mmol), catalyst **5m** (5.50 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.63 (s, 1H, CHO), 8.01-7.91 (m, 2H, C_{arom}-H), 7.00-6.86 (m, 2H, C_{arom}-H), 5.98-5.94 (m, 1H, H3), 5.79-5.75 (m, 1H, H4), 4.71-4.66 (m, 1H, H2), 3.87 (s, 3H, OCH_3), 3.21-3.09 (m, 1H, H1), 2.74-2.54 (m, 3H, CH_2CHO, H5a), 2.29 (ddq, *J* = 16.3, 6.5, 2.3 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm) 201.9 (CHO), 199.4 (C=O), 163.9 (C_{arom}-C), 133.1 (C3), 130.8 (C_{arom}-H), 130.3 (C_{arom}-C), 130.0 (C4), 114.1 (C_{arom}-H), 55.6 (OCH_3), 54.6 (C2), 45.8 (CH_2CHO), 39.1 (C5), 36.1 (C1). **IR** (ATR): 3012 (=CH st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 224 (23), 216 (27), 215 (M^+-CHO, 20), 207 (27), 185 (22), 153 (23), 152 (23), 135 (100), 109 (M^+-$C_8H_7O_2$, 3), 77 (21). **HRMS**: Calculated for $[C_{15}H_{16}O_3Na]^+$: 267.0097 [(M+Na)$^+$]; found: 267.1005. **[α]**$_D^{rt}$: -141.5 (*c* = 0.3, CH_2Cl_2).



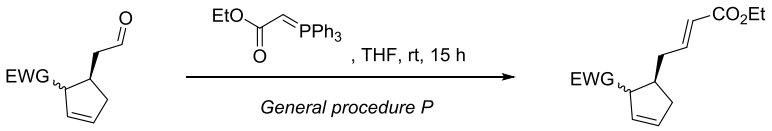
2-((1*R*,2*R*)-2-(4-methoxybenzoyl)cyclopent-3-en-1-yl)acetaldehyde (*trans*-6x). Following the *general procedure O*, ***trans*-6x** (2.20 mg, 0.009 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 15% yield starting from aldehyde **4x** (15.00 mg, 0.060 mmol), catalyst **5m** (5.50 mg, 0.012 mmol) and 1,2-dichloroethane (0.6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 9.76 (t, *J* = 2.0 Hz, 1H, CHO), 7.99-7.94 (m, 2H, C_{arom}-H), 6.98-6.92 (m, 2H, C_{arom}-H), 5.87-5.82 (m, 1H, H3), 5.71-5.67 (m, 1H, H4), 4.18-4.11 (m, 1H, H2), 3.88 (s, 3H, OCH_3), 3.44-3.27 (m, 1H, H1), 2.85 (ddt, *J* = 16.2, 8.0, 2.4 Hz, 1H, H5a), 2.62-2.57 (m, 2H, CH_2CHO), 2.13 (ddq, *J* = 16.7, 4.7, 2.3 Hz, 1H, H5b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.0 (CHO), 197.8 (C=O), 163.7 (C_{arom}-C), 132.8 (C3), 131.0 (C_{arom}-H), 129.6 (C_{arom}-C), 129.1 (C4), 114.0 (C_{arom}-H), 59.6 (OCH_3), 55.6 (C2), 49.5 (CH_2CHO), 38.8 (C5), 34.0 (C1). **IR** (ATR): 3012 (=CH st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 135 (100), 77 (13). **HRMS**: Calculated for $[C_{15}H_{16}O_3Na]^+$: 267.0097 [(M+Na)$^+$]; found: 267.1004. **[α]**$_D^{rt}$: +97.8 (*c* = 0.3, CH_2Cl_2).



ethyl cyclohepta-1,3,6-triene-1-carboxylate (11). Following the *general procedure O*, **11** (4.8 mg, 0.03 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 24% yield starting from aldehyde **4x** (21.5 mg, 0.12 mmol), catalyst **5m** (6.1 mg, 0.012 mmol) and 1,2-dichloroethane (1.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.69 (d, *J* = 6.0 Hz, 1H, H2), 6.73 (d, *J* = 9.6 Hz, 1H, H7), 6.34 (dd, *J* = 9.4, 6.0 Hz,

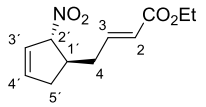
1H, H3), 5.74-5.60 (m, 1H, H4), 5.54-5.40 (m, 1H, H6), 4.29 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 2.30 (t, *J* = 6.8 Hz, 2H, H5), 1.35 (t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

2.3. Derivatization of the adducts

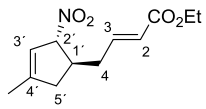


***cis*/*trans*-6a-z** ***cis*/*trans*-I-XXII**

General Procedure P: To a solution of ***cis*/*trans*-6a-z** (0.05 mmol, 1.0 eq) in THF (0.8 mL, 0.064 *M*), carbethoxymethylene)triphenylphosphorane (0.1 mmol, 2.0 eq) was added and the reaction mixture was stirred at room temperature for 15 hours. Once the reaction was finished, the solvent was removed and the crude was directly subjected to FC to afford pure **I-XXII**.

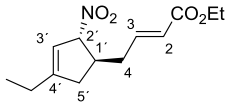


Ethyl (*E*)-4-((1*R*,2*R*)-2-nitrocyclopent-3-en-1-yl)but-2-enoate (*trans*-I). Following the *general procedure P*, ***trans*-I** (7.60 mg, 0.034 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 59% yield starting from aldehyde ***cis*-6a** (9.00 mg, 0.058 mmol), (carbethoxymethylene)triphenylphosphorane (40.00 mg, 0.120 mmol) and THF (0.9 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereoisomer (1.10 mg, 0.005 mmol) in 54% yield starting from aldehyde ***trans*-6a** (1.40 mg, 0.009 mmol), (carbethoxymethylene)triphenylphosphorane (6.00 mg, 0.018 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, CDCl$_3$) (δ, ppm): 6.88 (dt, *J* = 15.6, 7.1 Hz, 1H, H3), 6.23 (dtd, *J* = 5.9, 2.4, 1.5 Hz, 1H, H4´), 5.97-5.80 (m, 2H, H3´, H2), 5.15 (dtt, *J* = 3.9, 2.5, 1.4 Hz, 1H, H2´), 4.19 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.00 (tdt, *J* = 8.0, 6.1, 3.9 Hz, 1H, H1´), 2.86 (ddq, *J* = 17.3, 8.1, 2.4 Hz, 1H, H5´a), 2.53 (dddd, *J* = 14.8, 7.3, 6.2, 1.6 Hz, 1H, H4a), 2.38 (dtd, *J* = 14.9, 8.4, 7.9, 1.5 Hz, 1H, H4b), 2.24-2.08 (m, 1H, H5´b), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). The e.e. was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 13.22 min, τ_{minor} = 14.55 min (87% e.e. for the *cis* diastereomer) and τ_{major} = 13.26 min, τ_{minor} = 14.57 min (97% e.e. for the *trans* diastereomer).

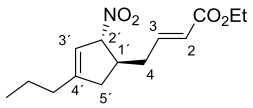


Ethyl (*E*)-4-((1*S*,2*R*)-4-methyl-2-nitrocyclopent-3-en-1-yl)but-2-enoate (*trans*-II). Following the *general procedure P,* ***trans*-II** (6.80 mg, 0.028 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 51% yield starting from aldehyde ***cis*-6b** (9.40 mg, 0.055 mmol), (carbethoxymethylene)triphenylphosphorane (38.00 mg, 1.100 mmol) and THF (0.8 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (6.60 mg, 0.027

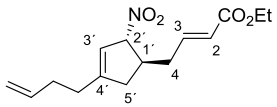
mmol) in 96% yield starting from aldehyde ***trans*-6b** (4.80 mg, 0.028 mmol), (carbethoxymethylene)triphenylphosphorane (20.00 mg, 0.056 mmol) and THF (0.4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) 6.87 (dt, *J* = 15.4, 7.1 Hz, 1H, H3), 5.89 (dt, *J* = 15.8, 1.5 Hz, 1H, H2), 5.49 (s, 1H, H3´), 5.10 (s, 1H, H2´), 4.10 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.99 (d, *J* = 6.1 Hz, 1H, H1´), 2.89-2.68 (m, 1H, H5´a), 2.44 (ddd, *J* = 37.2, 14.8, 7.4 Hz, 2H, H4), 2.05 (d, *J* = 16.7 Hz, 1H, H5´b), 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 29.27 min, τ_{minor} = 23.81 min (76% e.e. for the *cis* diastereomer) and τ_{major} = 20.83 min, τ_{minor} = 26.71 min (90% e.e. for the *trans* diastereomer).



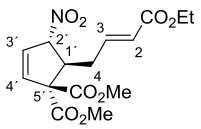
Ethyl (*E*)-4-((1*S*,2*R*)-4-ethyl-2-nitrocyclopent-3-en-1-yl)but-2-enoate (*trans*-III). Following the *general procedure P,* ***trans*-III** (7.20 mg, 0.028 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 66% yield starting from aldehyde ***cis*-6c** (7.90 mg, 0.043 mmol), (carbethoxymethylene)triphenylphosphorane (30.00 mg, 0.086 mmol) and THF (0.7 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (3.80 mg, 0.015 mmol) in 63% yield starting from aldehyde ***trans*-6c** (4.50 mg, 0.024 mmol), (carbethoxymethylene)triphenylphosphorane (17.00 mg, 0.048 mmol) and THF (0.4 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.87 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 5.89 (dt, *J* = 15.6, 1.6 Hz, 1H, H2), 5.51-5.44 (m, 1H, H3´), 5.11-5.09 (m, 1H, H2´), 4.19 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.01-2.96 (m, 1H, H1´), 2.79 (dd, *J* = 16.8, 8.1 Hz, 1H, H4a), 2.57-2.29 (m, 2H, H5´), 2.28-2.01 (m, 3H, H4b, CH_2CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.09 (t, *J* = 7.4 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 39.07 min, τ_{minor} = 49.93 min (76% e.e. for the *cis* diastereomer) and τ_{major} = 54.82 min, τ_{minor} = 70.84 min (86% e.e. for the *trans* diastereomer).



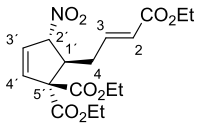
Ethyl (*E*)-4-((1*S*,2*R*)-2-nitro-4-propylcyclopent-3-en-1-yl)but-2-enoate (*trans*-IV). Following the *general procedure P,* ***trans*-IV** (12.10 mg, 0.045 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 72% yield starting from aldehyde ***cis*-6d** (12.50 mg, 0.060 mmol), (carbethoxymethylene)triphenylphosphorane (44.00 mg, 0.130 mmol) and THF (0.6 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (3.80 mg, 0.020 mmol) in 66% yield starting from aldehyde ***trans*-6d** (5.80 mg, 0.033 mmol), (carbethoxymethylene)triphenylphosphorane (23.00 mg, 0.066 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.87 (dt, *J* = 15.7, 7.1 Hz, H3), 5.89 (dt, *J* = 15.6, 1.5 Hz, H2), 5.50-5.48 (m, 1H, H3´), 5.16-5.07 (m, 1H, H2´), 4.20 (q, *J* = 7.1 Hz, 3H, OCH_2CH_3), 3.05-2.90 (m, 1H, H1´), 2.79 (dd, *J* = 16.7, 8.2 Hz, 1H, H5´a), 2.58-2.29 (m, 2H, H4), 2.14 (t, *J* = 7.7 Hz, 2H, $CH_2CH_2CH_3$), 2.09-2.02 (m, 1H, H5´b), 1.57-1.47 (m, 2H, $CH_2CH_2CH_3$), 1.35-1.21 (m, 3H, $CH_2CH_2CH_3$), 0.96-0.88 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 8.38 min, τ_{minor} = 9.53 min (44% e.e. for the *cis* diastereomer) and τ_{major} = 8.43 min, τ_{minor} = 13.21 min (79% e.e. for the *trans* diastereomer).



Ethyl (*E*)-4-((1*S*,2*R*)-4-(but-3-en-1-yl)-2-nitrocyclopent-3-en-1-yl)but-2-enoate (*trans*-V). Following the *general procedure P,* ***trans*-V** (3.80 mg, 0.014 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 53% yield starting from aldehyde ***cis*-6e** (5.60 mg, 0.030 mmol), (carbethoxymethylene)triphenylphosphorane (19.00 mg, 0.050 mmol) and THF (0.3 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (2.40 mg, 0.009 mmol) in 59% yield starting from aldehyde ***trans*-6e** (3.20 mg, 0.020 mmol), (carbethoxymethylene)triphenylphosphorane (10.00 mg, 0.030 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.95-6.79 (m, 1H, H3), 5.92-5.71 (m, 2H, CH_2CH_2CH=CH_2), 5.52 (s, 1H, H2), 5.30 (s, 1H, H3´), 5.09 (d, *J* = 9.9 Hz, 1H, CH_2CH_2CH=CH_2), 5.00 (d, *J* = 10.5 Hz, H2´), 4.24-4.10 (m, 2H, OCH_2CH_3), 3.02-2.84 (m, 1H, H1´), 2.83-2.66 (m, 1H, H4a), 2.07 (d, *J* = 15.3 Hz, 1H, H4b), 1.26-1.18 (m, 4H, CH_2CH_2CH=CH_2), 0.88-0.84 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak ID-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 15.12 min, τ_{minor} = 16.05 min (32% e.e. for the *cis* diastereomer) and τ_{major} = 15.39 min, τ_{minor} = 16.36 min (47% e.e. for the *trans* diastereomer).

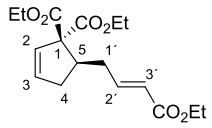


Dimethyl (4*S*,5*S*)-5-((*E*)-4-ethoxy-4-oxobut-2-en-1-yl)-4-nitrocyclopent-2-ene-1,1-dicarboxylate (*trans*-VI). Following the *general procedure P*, ***trans*-VI** (3.00 mg, 0.009 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 45% yield starting from aldehyde ***cis*-6f** (5.50 mg, 0.020 mmol), (carbethoxymethylene)triphenylphosphorane (14.00 mg, 0.040 mmol) and THF (0.3 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (2.40 mg, 0.007 mmol) in 51% yield starting from aldehyde ***trans*-6g** (3.80 mg, 0.014 mmol), (carbethoxymethylene)triphenylphosphorane (9.00 mg, 0.028 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.88 (ddd, *J* = 15.2, 8.4, 6.4 Hz, 1H, H3), 6.30 (dd, *J* = 5.8, 1.8 Hz, 1H, H3´), 6.12 (dd, *J* = 5.8, 2.1 Hz, 1H, H4´), 5.90 (d, *J* = 15.6 Hz, 1H, H2), 5.32-5.24 (m, 1H, H2´), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.81 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.73-3.62 (m, 1H, H1´), 2.75-2.63 (m, 1H, H4a), 2.43-2.37 (m, 1H, H4b), 1.26 (t, *J* = 7.1 Hz, 2H, O-CH_2-CH_3). The e.e. was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 22.02 min, τ_{minor} = 33.25 min (90% e.e. for the *cis* diastereomer) and τ_{major} = 22.78 min, τ_{minor} = 38.29 min (97% e.e. for the *trans* diastereomer).

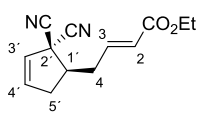


Diethyl (4*S*,5*S*)-5-((*E*)-4-ethoxy-4-oxobut-2-en-1-yl)-4-nitrocyclopent-2-ene-1,1-dicarboxylate (*trans*-VII). Following the *general procedure P*, ***trans*-VII** (4.30 mg, 0.012 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 36% yield starting from aldehyde ***cis*-6g** (9.50 mg, 0.032 mmol), (carbethoxymethylene)triphenylphosphorane (22.00 mg, 0.060 mmol) and THF (0.5 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereisomer (2.30 mg, 0.006 mmol) in 33% yield starting from aldehyde ***trans*-6g** (5.30 mg, 0.018 mmol), (carbethoxymethylene)triphenylphosphorane (12.00 mg, 0.040 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.90 (ddd, *J* = 14.9, 8.4, 6.3 Hz, 1H, H3), 6.31 (dd, *J* = 5.7, 1.8 Hz, 1H, H3´), 6.11 (dd, *J* = 5.7, 2.2 Hz, 1H, H2´), 5.89 (dt, *J* = 15.6, 1.6 Hz, 1H, H2), 5.26 (dt, *J* = 6.1, 2.0 Hz, 1H, H4´), 4.32-4.15 (m, 6H, OCH_2CH_3), 3.67 (dt, *J* = 9.5, 5.7 Hz, 1H, H1´), 2.70 (dt, *J* = 13.9, 5.9 Hz, 1H,

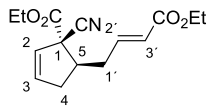
H4a), 2.44 (dt, *J* = 14.6, 9.0 Hz, 1H, H4b), 1.32-1.21 (m, 9H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 0.8 mL/min; τ_{major} = 54.00 min, τ_{minor} = 47.24 min (90% e.e. for the *cis* diastereomer) and τ_{major} = 52.98 min, τ_{minor} = 43.38 min (92% e.e. for the *trans* diastereomer).



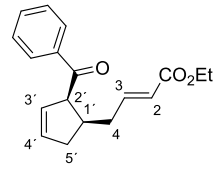
Diethyl (*R*,*E*)-5-(4-ethoxy-4-oxobut-2-en-1-yl)cyclopent-2-ene-1,1-dicarboxylate (VIII). Following the *general procedure P*, **VIII** (14.20 mg, 0.043 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 84% yield starting from aldehyde **6h** (13.30 mg, 0.052 mmol), (carbethoxymethylene)triphenylphosphorane (36.00 mg, 0.100 mmol) and THF (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.92 (ddd, *J* = 15.6, 8.1, 6.3 Hz, 1H, H2´), 5.99 (dt, *J* = 5.2, 2.4 Hz, 1H, H2), 5.88-5.79 (m, 2H, H3´, H3), 4.27-4.08 (m, 8H, OCH_2CH_3), 3.02 (ddd, *J* = 11.1, 6.8, 4.0 Hz, 1H, H5), 2.69-2.48 (m, 2H, H4), 2.24-2.15 (m, 2H, H1´), 1.33-1.20 (m, 12H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 16.69 min, τ_{minor} = 14.57 min (43% e.e.).



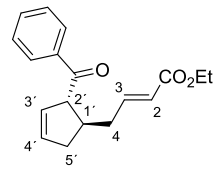
Ethyl (*R*,*E*)-4-(2,2-dicyanocyclopent-3-en-1-yl)but-2-enoate (IX). Following the *general procedure P*, **IX** (5.90 mg, 0.026 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 63% yield starting from aldehyde **6i** (6.50 mg, 0.041 mmol), (carbethoxymethylene)triphenylphosphorane (28.00 mg, 0.080 mmol) and THF (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.90 (dt, *J* = 15.0, 7.2 Hz, 1H, H3), 6.29 (dt, *J* = 5.4, 2.4 Hz, 1H, H3´), 6.02 (dt, *J* = 15.7, 1.6 Hz, 1H, H2), 5.81 (dt, *J* = 5.0, 2.0 Hz, 1H, H4´), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.04-2.90 (m, 1H, H1´), 2.90-2.71 (m, 2H, H5´), 2.71-2.53 (m, 1H, H4a), 2.35 (ddt, *J* = 17.1, 8.5, 2.3 Hz, 1H, H4b), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 39.12 min, τ_{minor} = 48.41 min (6% e.e.).



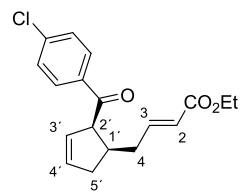
Ethyl (5*R*)-1-cyano-5-((*E*)-4-ethoxy-4-oxobut-2-en-1-yl)cyclopent-2-ene-1-carboxylate (X). Following the *general procedure P*, **X** (16.90 mg, 0.061 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 73% yield starting from aldehyde **6j** (14.70 mg, 0.084 mmol), (carbethoxymethylene)triphenylphosphorane (58.00 mg, 0.170 mmol) and THF (1.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.87 (dt, *J* = 15.0, 7.3 Hz, 1H, H2´), 6.13 (dt, *J* = 5.3, 2.5 Hz, 1H, H2), 5.95 (d, *J* = 15.5 Hz, 1H, H3´), 5.73 (dt, *J* = 5.2, 2.1 Hz, 1H, H3), 4.27 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.93 (td, *J* = 8.7, 6.3 Hz, 1H, H5), 2.79-2.63 (m, 2H, H4), 2.54 (dt, *J* = 15.2, 8.3 Hz, 1H, H1´a), 2.27 (ddt, *J* = 16.8, 8.3, 2.4 Hz, 1H, H1´b), 1.30 (dt, *J* = 11.6, 7.1 Hz, 6H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 28.40 min, τ_{minor} = 26.59 min (39% e.e.).



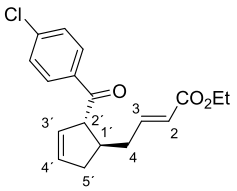
Ethyl (*E*)-4-((1*R*,2*S*)-2-benzoylcyclopent-3-en-1-yl)but-2-enoate (*cis*-XI). Following the *general procedure P*, ***cis*-XI** (7.00 mg, 0.021 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 65% yield starting from aldehyde ***cis*-6l** (7.20 mg, 0.033 mmol), (carbethoxymethylene)triphenylphosphorane (23.00 mg, 0.066 mmol) and THF (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.03-7.95 (m, 2H, C_{arom}-H), 7.51-7.45 (m, 3H, C_{arom}-H), 6.76 (dt, *J* = 14.7, 7.1 Hz, 1H, H3), 6.01-5.94 (m, 1H, H3´), 5.83-5.78 (m, 1H, H4´), 5.67 (d, *J* = 15.4 Hz, 1H, H2), 4.64 (d, *J* = 8.0 Hz, 1H, H2´), 4.11 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 2.94-2.81 (m, 1H, H1´), 2.59 (dd, *J* = 16.1, 7.5 Hz, 1H, H4a), 2.32 (d, *J* = 16.1 Hz, 1H, H4b), 2.23-2.05 (m, 2H, H5´), 0.92-0.81 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.31 min, τ_{minor} = 24.18 min (79% e.e.).



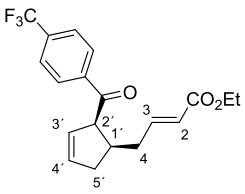
Ethyl (*E*)-4-((1*R*,2*R*)-2-benzoylcyclopent-3-en-1-yl)but-2-enoate (*trans*-XI). Following the *general procedure P*, ***trans*-XI** (6.00 mg, 0.021 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 64% yield starting from aldehyde ***trans*-6l** (7.00 mg, 0.033 mmol), (carbethoxymethylene)triphenylphosphorane (23.00 mg, 0.066 mmol) and THF (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.01-7.94 (m, 2H, C_{arom}-H), 7.62-7.54 (m, 1H, C_{arom}-H), 7.54-7.43 (m, 2H, C_{arom}-H), 6.92 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 5.89-5.80 (m, 2H, H3´, H4´), 5.72-5.64 (m, 1H, H2), 4.30-4.10 (m, 3H, H2´, OCH_2CH_3), 3.09-2.98 (m, 1H, H1´), 2.80-2.65 (m, 1H, H4a), 2.44-2.32 (m, 2H, H5´), 2.14 (ddd, *J* = 16.8, 5.0, 2.8 Hz, H4b), 1.34-1.21 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 16.77 min, τ_{minor} = 17.82 min (98% e.e.).



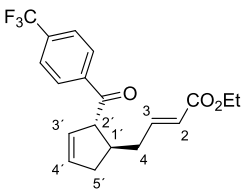
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-chlorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XII). Following the *general procedure P*, ***cis*-XII** (6.00 mg, 0.019 mmol) was isolated by FC (petroleum ether /EtOAc gradient from 9:1 to 7:3) in 42% yield starting from aldehyde ***cis*-6m** (11.10 mg, 0.044 mmol), (carbethoxymethylene)triphenylphosphorane (32.00 mg, 0.092 mmol) and THF (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.96-7.89 (m, 2H, C_{arom}-H), 7.47-7.44 (m, 2H, C_{arom}-H), 6.75 (dt, *J* = 14.7, 7.2 Hz, 1H, H3), 5.98 (dd, *J* = 5.8, 2.4 Hz, H3´), 5.78 (dd, *J* = 5.7, 2.2 Hz, H4´), 5.66 (d, *J* = 15.5 Hz, 1H, H2), 4.57 (d, *J* = 8.1 Hz, 1H, H2´), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.89-2.85 (m, 1H, H1´), 2.68-2.55 (m, 2H, H4), 2.36-2.31 (m, 2H, H5´), 1.26-1.21 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 11.97 min, τ_{minor} = 19.76 min (85% e.e.).



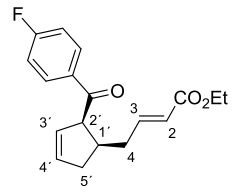
Ethyl (*E*)-4-((1*R*,2*R*)-2-(4-chlorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XII). Following the *general procedure P*, ***trans*-XII** (6.20 mg, 0.019 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 42% yield starting from aldehyde ***trans*-6m** (11.40 mg, 0.046 mmol), (carbethoxymethylene)triphenylphosphorane (32.00 mg, 0.092 mmol) and THF (0.7 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.94-7.89 (m, 2H, C_{arom}-H), 7.48-7.43 (m, 2H, C_{arom}-H), 6.90 (dt, *J* = 15.7, 7.2 Hz, 1H, H3), 5.92-5.84 (m, 2H, H3´, H2), 5.66-5.62 (m, 1H, H4´), 4.27-4.03 (m, 3H, OCH_2CH_3), H2´), 3.06-2.97 (m, 1H, H1´), 2.74 (ddt, *J* = 16.8, 8.3, 2.5 Hz, 1H, H4a), 2.46-2.32 (m, 2H, H5´), 2.20-2.08 (m, 1H, H4b), 1.34-1.21 (m, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.46 min, τ_{minor} = 13.70 min (96% e.e.).



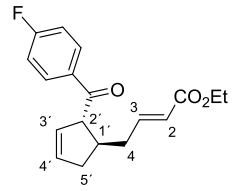
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-(trifluoromethyl)benzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XIII). Following the *general procedure P*, ***cis*-XIII** (1.70 mg, 0.005 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 46% yield starting from aldehyde ***cis*-6n** (3.10 mg, 0.011 mmol), (carbethoxymethylene)triphenylphosphorane (7.60 mg, 0.022 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.10 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 7.75 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 6.82-6.67 (m, 1H, H3), 6.01 (dd, *J* = 5.8, 2.4 Hz, 1H, H3´), 5.79 (dd, *J* = 5.8, 2.1 Hz, 1H, H4´), 5.69-5.62 (m, 1H, H2), 4.69-4.54 (m, 1H, H2´), 4.10 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.92-2.87 (m, 1H, H1´), 2.68-2.55 (m, 1H, H4a), 2.42-2.35 (m, 1H, H4b), 2.28-2.09 (m, 2H, H5´), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 12.16 min, τ_{minor} = 9.68 min (88% e.e.).



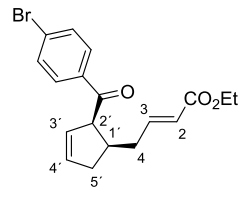
Ethyl (*E*)-4-((1*R*,2*R*)-2-(4-(trifluoromethyl)benzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XIII). Following the *general procedure P*, ***cis*-XIII** (2.00 mg, 0.006 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 75% yield starting from aldehyde ***cis*-6n** (2.30 mg, 0.008 mmol), (carbethoxymethylene)triphenylphosphorane (6.00 mg, 0.016 mmol) and THF (0.1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.07 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.75 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.99-6.83 (m, 1H, H3), 5.92-5.80 (m, 2H, H3´, H2), 5.65 (dd, *J* = 5.8, 2.3 Hz, 1H, H4´), 4.20-4.12 (m, 3H, H2´, OCH_2CH_3), 3.06-2.99 (m, 1H, H1´), 2.82-2.68 (m, 1H, H5´a), 2.43-2.34 (m, 2H, H4), 2.16 (ddd, *J* = 17.0, 4.8, 2.3 Hz, 1H, H5´b), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 12.51 min, τ_{minor} = 10.96 min (93% e.e.).



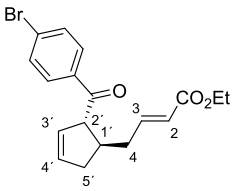
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-fluorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XIV). Following the *general procedure P*, ***cis*-XIV** (6.00 mg, 0.020 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 60% yield starting from aldehyde ***cis*-6o** (7.80 mg, 0.034 mmol), (carbethoxymethylene)triphenylphosphorane (23.00 mg, 0.068 mmol) and THF (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.08-7.97 (m, 2H, C_{arom}-H), 7.20-7.11 (m, 2H, C_{arom}-H), 6.75 (ddd, *J* = 15.6, 7.6, 6.7 Hz, 1H, H3), 5.98 (d, *J* = 6.6, 2.3 Hz, 1H, H3´), 5.78 (d, *J* = 6.0, 2.1 Hz, 1H, H4´), 5.67 (dt, *J* = 15.6, 1.5 Hz, 1H, H2), 4.58 (dt, *J* = 8.2, 2.1 Hz, 1H, H2´), 4.12 (q, *J* = 7.1 Hz, OCH_2CH_3), 2.85 (ddt, *J* = 13.4, 8.0, 3.9 Hz, 1H, H1´), 2.65-2.51 (m, 1H, H4a), 2.40-2.27 (m, 1H, H4b), 2.26-2.05 (m, 2H, H5´), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 24.29 min, τ_{minor} = 42.72 min (75% e.e.).



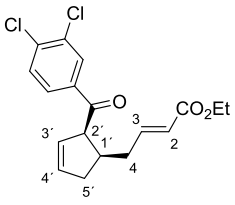
Ethyl (*E*)-4-((1*R*,2*R*)-2-(4-fluorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XIV). Following the *general procedure P*, ***trans*-XIV** (2.70 mg, 0.009 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 52% yield starting from aldehyde ***trans*-6o** (4.00 mg, 0.017 mmol), (carbethoxymethylene)triphenylphosphorane (12.00 mg, 0.034 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.05-7.97 (m, 2H, C_{arom}-H), 7.19-7.10 (m, 2H, C_{arom}-H), 7.00-6.82 (m, 1H, H3), 5.89-5.80 (m, 2H, H3´, H4´), 5.65 (dq, *J* = 4.7, 2.2 Hz, 1H, H2), 4.23-4.07 (m, 3H, H2´, OCH_2CH_3), 3.02 (qd, *J* = 7.7, 3.8 Hz, 1H, H1´), 2.74 (ddt, *J* = 16.9, 2.5 Hz, 1H, H4a), 2.42-2.32 (m, 2H, H5´), 2.14 (ddd, *J* = 16.9, 4.9, 2.7 Hz, 1H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 13.88 min, τ_{minor} = 12.40 min (98% e.e.).



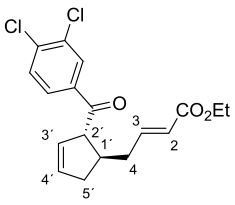
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-bromobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XV). Following the *general procedure P*, ***cis*-XV** (7.30 mg, 0.012 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 69% yield starting from aldehyde ***cis*-6p** (8.60 mg, 0.029 mmol), (carbethoxymethylene)triphenylphosphorane (20.00 mg, 0.058 mmol) and THF (0.5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.89-7.81 (m, 2H, C_{arom}-H), 7.66-7.58 (m, 2H, C_{arom}-H), 6.75 (dt, *J* = 15.8, 7.2 Hz, 1H, H3), 5.98 (dd, *J* = 5.6, 2.7 Hz, 1H, H3´), 5.82-5.73 (m, 1H, H4´), 5.66 (dt, *J* = 15.6, 1.5 Hz, H2), 4.56 (dt, *J* = 7.4 Hz, 1H, H2´), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.92-2.78 (m, 1H, H1´), 2.64-2.50 (m, 1H, H5a), 2.40-2.26 (m, 1H, H5b), 2.13 (tq, *J* = 15.2, 7.1 Hz, 2H, H4), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.98 min, τ_{minor} = 21.99 min (80% e.e.).



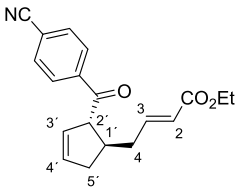
Ethyl (*E*)-4-((1*R*,2*R*)-2-(4-bromobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XV). Following the *general procedure P*, ***trans*-XV** (1.50 mg, 0.005 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 57% yield starting from aldehyde ***trans*-6p** (2.00 mg, 0.009 mmol), (carbethoxymethylene)triphenylphosphorane (6.00 mg, 0.018 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.90-7.86 (m, 2H, C_{arom}-H), 7.29-7.26 (m, 2H, C_{arom}-H), 6.92 (dt, *J* = 15.2, 7.7, 7.2 Hz, 1H, H3), 5.91-5.80 (m, 2H, H3´, H2), 5.67 (dd, *J* = 5.6, 2.4 Hz, 1H, H4´), 4.20-4.11 (m, 3H, OCH_2CH_3, H2´), 3.05-3.01 (m, 1H, H1´), 2.80-2.67 (m, 1H, H4a), 2.47-2.32 (m, 5H, CH_3, H5´), 2.19-2.07 (m, 11H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.92 min, τ_{minor} = 13.62 min (97% e.e.).



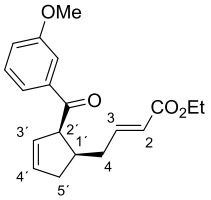
Ethyl (*E*)-4-((1*R*,2*S*)-2-(3,4-dichlorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XVI). Following the *general procedure P*, ***cis*-XVI** (4.00 mg, 0.010 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3 in 55% yield starting from aldehyde ***cis*-6q** (5.60 mg, 0.020 mmol), (carbethoxymethylene)triphenylphosphorane (14.00 mg, 0.040 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.06 (d, *J* = 2.1 Hz, 1H, C_{arom}-H), 7.81 (dd, *J* = 8.4, 2.1 Hz, 1H, C_{arom}-H), 7.56 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.75 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 6.00 (dd, *J* = 5.8, 2.3 Hz, 1H, H3´), 5.79-5.72 (m, 1H, H4´), 5.66 (dt, *J* = 15.6, 1.5 Hz, 1H, H2), 4.53 (dt, *J* = 8.1, 2.1 Hz, 1H, H2´), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.90-2.81 (m, 1H, H1´), 2.64-2.56 (m, 1H, H4a), 2.33 (ddd, *J* = 16.3, 5.5, 2.2 Hz, 1H, H4b), 2.27-2.02 (m, 2H, H5´), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 22.21 min, τ_{minor} = 26.96 min (76% e.e.).



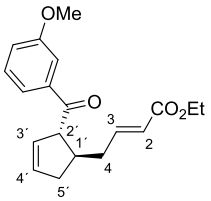
Ethyl (*E*)-4-((1*R*,2*R*)-2-(3,4-dichlorobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XVI). Following the *general procedure P*, ***trans*-XVI** (1.50 mg, 0.004 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 61% yield starting from aldehyde ***trans*-6q** (2.00 mg, 0.007 mmol), (carbethoxymethylene)triphenylphosphorane (5.00 mg, 0.014 mmol) and THF (0.1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.04 (d, *J* = 2.0 Hz, 1H, C_{arom}-H), 7.79 (dd, *J* = 8.4, 2.1 Hz, 1H, C_{arom}-H), 7.56 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.90 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 5.92-5.79 (m, 2H, H3´, H2), 5.68-5.59 (m, 1H, H4´), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.06 (dt, *J* = 4.8, 2.5 Hz, 1H, H2´), 3.09-2.96 (m, 1H, H1´), 2.80-2.68 (m, 1H, H4a), 2.42-2.30 (m, 2H, H5´), 2.15 (ddd, *J* = 17.0, 5.0, 2.3 Hz, 1H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak OD3 column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 12.27 min, τ_{minor} = 14.01 min (94% e.e.).



Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-cyanobenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XVII). Following the *general procedure P*, ***trans*-XVII** (2.20 mg, 0.007 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 76% yield starting from aldehyde ***cis*-6r** (2.20 mg, 0.009 mmol), (carbethoxymethylene)triphenylphosphorane (0.006 g, 0.018 mmol) and THF (0.2 mL) for *cis* diastereoisomer. The same procedure was carried out for *trans* diastereoisomer (0.08 mg, 0.02 mmol) in 80% yield starting from aldehyde ***trans*-6r** (0.80 mg, 0.003 mmol), (carbethoxymethylene)triphenylphosphorane (0.02 mg, 0.007 mmol) and THF (0.05 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.05 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.78 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.99-6.82 (m, 1H, H3), 5.94-5.79 (m, 2H, H2, H3´), 5.62 (dd, *J* = 5.7, 2.4 Hz, 1H, H4´), 4.21-4.09 (m, 3H, H2´, OCH_2CH_3), 3.06-3.00 (m, 1H, H1´), 2.81-2.68 (m, 1H, H4a), 2.38 (t, *J* = 7.2 Hz, 2H, H5), 2.26-2.11 (m, 1H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.7 mL/min; τ_{major} = 31.47 min, τ_{minor} = 34.51 min (68% e.e. for the *cis* diastereomer) and τ_{major} = 33.94 min, τ_{minor} = 37.50 min (95% e.e. for the *trans* diastereomer).

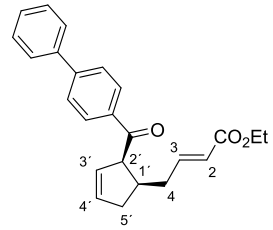


Ethyl (*E*)-4-((1*R*,2*S*)-2-(3-methoxybenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XVIII). Following the *general procedure P*, ***cis*-XVIII** (0.50 mg, 0.002 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 14% yield starting from aldehyde ***cis*-6t** (2.60 mg, 0.011 mmol), (carbethoxymethylene)triphenylphosphorane (7.00 mg, 0.021 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.58 (dt, *J* = 7.7, 1.2 Hz, 1H, C_{arom}-H), 7.51 (dd, *J* = 2.7, 1.6 Hz, 1H, C_{arom}-H), 7.39 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.12 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, C_{arom}-H), 6.76 (ddd, *J* = 15.5, 7.6, 6.7, 1H, H3), 5.96 (dq, *J* = 6.6, 2.3 Hz, 1H, H3´), 5.79 (dq, *J* = 6.0, 2.1 Hz, 1H, H4´), 5.68 (dt, *J* = 15.6, 1.5 Hz, 1H, H2), 4.61 (dp, *J* = 8.3, 2.1 Hz, 1H, H2´), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 2.94-2.81 (m, 1H, H1´), 2.65-2.52 (m, 1H, H4a), 2.38-2.27 (m, 1H, H4b), 2.21-2.08 (m, 2H, H5´), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 59.86 min, τ_{minor} = 51.54 min (81% e.e.).

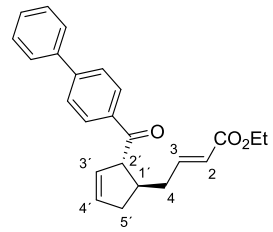


Ethyl (*E*)-4-((1*R*,2*R*)-2-(3-methoxybenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XVIII). Following the *general procedure P*, ***trans*-XVIII** (0.30 mg, 0.001 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 14% yield starting from aldehyde ***trans*-6t** (1.70 mg, 0.007 mmol), (carbethoxymethylene)triphenylphosphorane (5.00 mg, 0.014 mmol) and THF (0.1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.56 (dt, *J* = 7.7, 1.2 Hz, 1H, C_{arom}-H), 7.49 (dd, *J* = 2.7, 1.6 Hz, 1H, C_{arom}-H), 7.39 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.12 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, C_{arom}-H), 6.92 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 5.88-5.81 (m, 2H, H3´, H4´), 5.72-5.64 (m, 1H, H2), 4.23-4.09 (m, 3H, H2´, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 3.09-2.95 (m, 1H, H1´), 2.73 (ddq, *J* = 16.1, 8.1, 2.5 Hz, 1H, H4a), 2.46-2.27 (m, 2H, H5´), 2.14 (ddt, *J* = 16.8, 5.0, 2.3 Hz, 1H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using

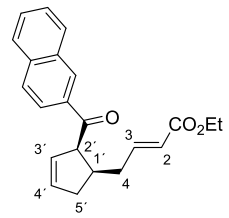
a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 11.69 min, τ_{minor} = 10.47 min (72% e.e.).



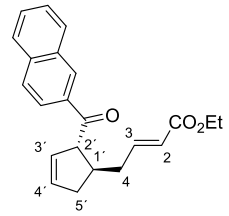
Ethyl (*E*)-4-((1*R*,2*S*)-2-([1,1'-biphenyl]-4-carbonyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XIX). Following the *general procedure P*, ***cis*-XIX** (2.60 mg, 0.007 mmol) was isolated by FC (petroleum ether /EtOAc gradient from 9:1 to 7:3) in 46% yield starting from aldehyde ***cis*-6u** (4.90 mg, 0.017 mmol), (carbethoxymethylene)triphenylphosphorane (11.00 mg, 0.034 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.10-8.04 (m, 2H, C_{arom}-H), 7.74-7.68 (m, 2H, C_{arom}-H), 7.68-7.60 (m, 2H, C_{arom}-H), 7.51-7.36 (m, 3H, C_{arom}-H), 6.79 (dt, *J* = 15.6, 7.2 Hz, 1H, H3), 5.99 (dd, *J* = 5.8, 2.4 Hz, 1H, H3´), 5.87-5.79 (m, 1H, H4´), 5.70 (dt, *J* = 15.6, 1.5 Hz, 1H, H2), 4.67 (dt, *J* = 8.2, 2.1 Hz, 1H, H2´), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.92-2.85 (m, 1H, H1´), 2.61 (ddd, *J* = 16.3, 7.7, 2.2 Hz, 1H, H4a), 2.34 (ddd, *J* = 16.3, 4.9, 2.2 Hz, 1H, H4b), 2.23-2.12 (m, 2H, H5´), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 20.11 min, τ_{minor} = 29.28 min (89% e.e.).



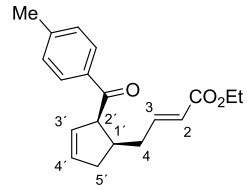
Ethyl (*E*)-4-((1*R*,2*R*)-2-([1,1'-biphenyl]-4-carbonyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XIX). Following the *general procedure P*, ***trans*-XIX** (0.90 mg, 0.002 mmol) was isolated by FC (petroleum ether /EtOAc gradient from 9:1 to 7:3) in 38% yield starting from aldehyde ***trans*-6u** (1.70 mg, 0.006 mmol), (carbethoxymethylene)triphenylphosphorane (4.00 mg, 0.011 mmol) and THF (0.1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.06 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.72-7.60 (m, 4H, C_{arom}-H), 7.52-7.38 (m, 3H, C_{arom}-H), 6.97-6.88 (m, 1H, H3), 5.90-5.82 (m, 2H, H3´, H4´), 5.76-5.66 (m, 1H, H2), 4.21-4.13 (m, 3H, H2´, OCH_2CH_3), 3.18-2.96 (m, 1H, H1´), 2.78-2.61 (m, 1H, H4a), 2.42-2.38 (m, 2H, H5´), 2.22-2.15 (m, 1H, H4), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 25.49 min, τ_{minor} = 20.38 min (64% e.e.).



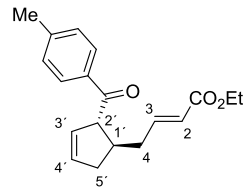
Ethyl (*E*)-4-((1*R*,2*S*)-2-(2-naphthoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XX). Following the *general procedure P*, ***cis*-XX** (5.20 mg, 0.016 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 78% yield starting from aldehyde ***cis*-6v** (5.40 mg, 0.020 mmol), (carbethoxymethylene)triphenylphosphorane (14.00 mg g, 0.040 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.53 (s, 1H, C_{arom}-H), 8.09-7.96 (m, 2H, C_{arom}-H), 7.96-7.85 (m, 2H, C_{arom}-H), 7.68-7.52 (m, 2H, C_{arom}-H), 6.76 (dt, *J* = 15.0, 7.2 Hz, 1H, H3), 6.01 (dd, *J* = 5.8, 2.3 Hz, 1H, H3´), 5.92-5.81 (m, 1H, H4´), 5.72-5.60 (m, 1H, H2), 4.89-4.76 (m, 1H, H2´), 4.04 (qd, *J* = 7.1, 2.0 Hz, 2H, OCH_2CH_3), 2.97-2.90 (m, 1H, H1´), 2.71-2.56 (m, 1H, H4a), 2.42-2.31 (m, 2H, H5´), 2.29-2.09 (m, 1H, H4b), 1.15 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 20.87 min, τ_{minor} = 33.97 min (78% e.e.).



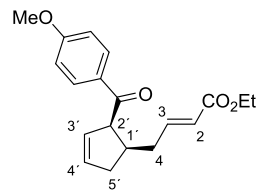
Ethyl (*E*)-4-((1*R*,2*R*)-2-(2-naphthoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XX). Following the *general procedure P*, ***trans*-XX** (2.10 mg, 0.006 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 70% yield starting from aldehyde ***trans*-6v** (2.50 mg, 0.009 mmol), (carbethoxymethylene)triphenylphosphorane (7.00 mg, 0.018 mmol) and THF (0.1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.50 (s, 1H, C_{arom}-H), 8.07-7.94 (m, 2H, C_{arom}-H), 7.95-7.84 (m, 2H, C_{arom}-H), 7.68-7.49 (m, 2H, C_{arom}-H), 6.96 (dt, *J* = 14.8, 7.3 Hz, 1H, H3), 5.93-5.83 (m, 2H, H2, H3′), 5.74 (dd, *J* = 5.7, 2.2 Hz, 1H, H4′), 4.39-4.30 (m, 1H, H2′), 4.14 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.16-3.04 (m, 1H, H1′), 2.85-2.69 (m, 1H, H4a), 2.46-2.39 (m, 2H, H5′), 2.24-2.11 (m, 1H, H4b), 1.15 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 0.7 mL/min; τ_{major} = 47.96 min, τ_{minor} = 40.76 min (97% e.e.).



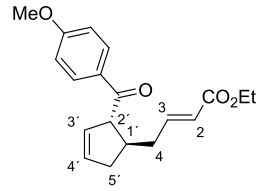
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-methylbenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XXI). Following the *general procedure P*, ***cis*-XXI** (5.10 mg, 0.017 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 32% yield starting from aldehyde ***cis*-6w** (13.60 mg, 0.058 mmol), (carbethoxymethylene)triphenylphosphorane (37.00 mg, 0.126 mmol) and THF (0.8 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.95-7.85 (m, 2H, C_{arom}-H), 7.32-7.21 (m, 2H, C_{arom}-H), 6.76 (ddd, *J* = 14.1, 10.3, 6.5 Hz, 1H, H3), 5.96 (dq, *J* = 5.9, 2.3 Hz, 1H, H3′), 5.79 (dq, *J* = 6.0, 2.1 Hz, 1H, H4′), 5.67 (dt, *J* = 15.6, 1.6 Hz, 1H, H2), 4.61 (dq, *J* = 6.2, 2.2 Hz, 1H, H2′), 4.12 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.990-2.80 (m, 1H, H1′), 2.65-2.52 (m, 1H, H4a), 2.42 (s, 3H, CH_3), 2.31 (ddt, *J* = 16.2, 4.7, 2.1 Hz, 1H, H4b), 2.24-2.02 (m, 2H, H5′), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.28 min, τ_{minor} = 34.58 min (79% e.e.).



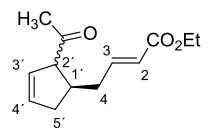
Ethyl (*E*)-4-((1*R*,2*R*)-2-(4-methylbenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XXI). Following the *general procedure P*, ***trans*-XXI** (1.50 mg, 0.005 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 57% yield starting from aldehyde ***trans*-6w** (2.00 mg, 0.009 mmol), (carbethoxymethylene)triphenylphosphorane (6.00 mg, 0.018 mmol) and THF (0.2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) 7.90-7.86 (m, 2H, C_{arom}-H), 7.29-7.26 (m, 2H, C_{arom}-H), 6.92 (dt, *J* = 15.2, 7.7, 7.2 Hz, 1H, H3), 5.91-5.80 (m, 2H, H3′, H2), 5.67 (dd, *J* = 5.6, 2.4 Hz, 1H, H4′), 4.20-4.11 (m, 3H, OCH_2CH_3, H2′), 3.05-3.01 (m, 1H, H1′), 2.80-2.67 (m, 1H, H4a), 2.47-2.32 (m, 5H, CH_3, H5′), 2.19-2.07 (m, 11H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IE-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.89 min, τ_{minor} = 22.91 min (77% e.e.).



Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-methoxybenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*cis*-XXII). Following the *general procedure P*, ***cis*-XXII** (3.50 mg, 0.011 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 65% yield starting from aldehyde ***cis*-6x** (4.20 mg, 0.017 mmol), (carbethoxymethylene)triphenylphosphorane (12.00 mg, 0.034 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.03-7.94 (m, 2H, C_{arom}-H), 6.98-6.90 (m, 2H, C_{arom}-H), 6.84-6.70 (m, 1H, H3), 5.95 (dd, *J* = 5.8, 2.5 Hz, 1H, H3′), 5.83-5.75 (m, 1H, H4′), 5.68 (dt, *J* = 15.6, 1.5 Hz, 1H, H2), 4.63-4.54 (m, 1H, H2′), 4.18-4.06 (m, 2H, OCH_2CH_3), 3.88 (s, 3H, OCH_3), 2.86-2.83 (m, 1H, H1′), 2.62-2.53 (m, 1H, H4a), 2.37-2.25 (m, 1H, H4b), 2.23-2.04 (m, 2H, H5′), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 30.27 min, τ_{minor} = 51.70 min (80% e.e.).



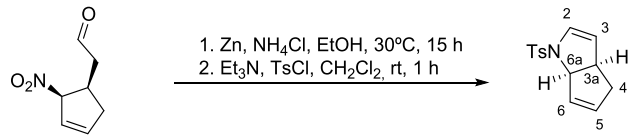
Ethyl (*E*)-4-((1*R*,2*S*)-2-(4-methoxybenzoyl)cyclopent-3-en-1-yl)but-2-enoate (*trans*-XXII). Following the *general procedure P*, ***trans*-XXII** (1.30 mg, 0.004 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 25% yield starting from aldehyde ***trans*-6x** (3.90 mg, 0.016 mmol), (carbethoxymethylene)triphenylphosphorane (11.00 mg, 0.032 mmol) and THF (0.3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 8.01-7.92 (m, 2H, C_{arom}-H), 6.98-6.86 (m, 3H, C_{arom}-H, H3), 5.88-5.77 (m, 2H, H2, H3′), 5.68-5.64 (m, 1H, H4′), 4.20-4.13 (m, 3H, OCH_2CH_3), H2′), 3.88 (s, 3H, OCH_3), 3.09-2.97 (m, 1H, H1′), 2.80-2.66 (m, 1H, H4a), 2.41-2.33 (m, 2H, H5′), 2.19-2.06 (m, 1H, H4b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 46.46 min, τ_{minor} = 38.29 min (94% e.e.).



Ethyl (*E*)-4-((1*R*)-2-acetylcyclopent-3-en-1-yl)but-2-enoate (cis/*trans*-XXIII). cis/*trans*-XXIII (6.50 mg, 0.029 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) in 29% yield starting from aldehyde **4y** (15.00 mg, 0.099 mmol), catalyst **5m** (8.90 mg, 0.198 mmol), (carbethoxymethylene)triphenylphosphorane (68.00 mg, 0.200 mmol) and $CDCl_3$ (1.0 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) (* denotes *trans* diastereoisomer resonances; d.r.: 3:1): 6.97-6.79 (m, 1H, H3), 6.00-5.97* (2H, H3′, H4′), 5.89-5.80 (m, 2H, H3′, H4′), 5.76-5.73* (m, 1H, H2), 5.70-5.66 (m, 1H, H2), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.66* (d, *J* = 8.4 Hz, H2′), 3.28-3.26 (m, 1H, H2′), 2.82-2.49 (m, 2H, H4), 2.42-2.19 (m, 2H, H5′), 2.13-2.01 (m, 1H, H1′), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 208.5 (C=O), 166.5 (C=O), 147.4* (C3), 146.7 (C3), 134.3* (C3′), 133.4 (C3′), 129.4* (C4′), 127.6 (C4′), 123.1 (C2), 122.9* (C2), 65.4 (C2′), 61.2* (OCH_2CH_3), 60.4 (OCH_2CH_3), 40.8 (C1′), 38.4*(C4), 38.3 (C4), 38.0* (C5′), 33.5 (C5′), 30.8* (C5′), 28.4 (CH_3), 14.4 (OCH_2CH_3). **IR** (ATR): 3016 (=CH st), 1738 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 222 (M^+, 1), 180 (M^+-C_2H_3O, 1), 133 (22), 114 (100), 105 (61), 91 (16), 86 (29), 79 (23), 77 (16), 68 (20), 66 (19). **HRMS**: Calculated for $[C_{13}H_{18}NaO_3]^+$: 245.1154 [$(M+Na)^+$]; found: 245.1161. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 7.75 min, τ_{minor} = 8.81 min (85% e.e. for the *cis* diastereomer) and τ_{major} = 11.33 min, τ_{minor} = 5.97 min (96% e.e. for the *trans* diastereomer).

2.4. Transformation of the adducts

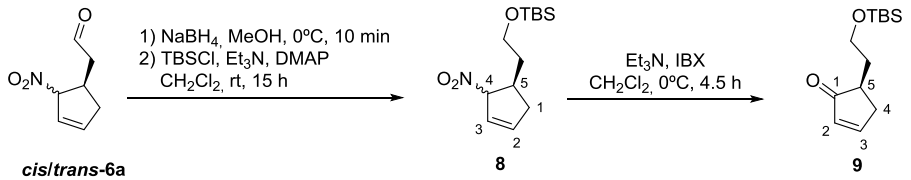
2.4.1. Synthesis of (3a*R*,6a*R*)-1-tosyl-1,3a,4,6a-tetrahydrocyclopenta[b]pyrrole 7



***cis*-6a** **7**

To a stirred solution of ***cis*-6a** (0.05 g, 0.3 mmol, 1.0 eq) in EtOH (3 mL, 0.1 *M*) was added zinc powder (0.10 g, 1.5 mmol, 5.0 eq) and ammonium chloride (0.08 g, 1.5 mmol, 5.0 eq) at room temperature and it was stirred at 30ºC for 15 hours. The reaction mixture was filtered and the solvent was removed in vacuo. The crude was dissolved in CH_2Cl_2 (3 mL, 0.1 *M*) and triethylamine (0.36 mmol, 1.2 eq) and *p*-Toluenesulfonyl chloride (0.36 mmol, 1.2 eq) were added. The reaction mixture was stirred at room temperature for 1 hour. Once the reaction was finished, the reaction mixture was quenched with H_2O (10 mL) and it was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (2 x 20 mL) dried over Na_2SO_4 and concentrated in vacuo to give **7** (0.02 g, 0.1 mmol) in 37% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.73-7.71 (m, 2H, C_{arom}-H), 7.31 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 5.84-5.80 (m, 1H, H6), 5.75-5.71 (m, 1H, H5), 4.58-4.54 (m, 1H, H2), 3.36 (ddd, *J* = 9.9, 6.8, 4.5 Hz, 1H, H3), 3.26-3.18 (m, 1H, H6a), 2.62 (td, *J* = 8.0, 2.1 Hz, 1H, H3a), 2.43 (s, 3H, CH_3), 2.10 (dq, *J* = 16.6, 2.1 Hz, 1H, H4a), 1.85 (dddd, *J* = 12.6, 8.1, 6.4, 4.6 Hz, 1H, H4b). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 143.4 (C_{arom}-C), 135.0 (C_{arom}-C), 132.0 (C6), 131.4 (C2), 129.7 (C_{arom}-H), 127.8 (C_{arom}-H), 127.2 (C5), 70.2 (C6a), 48.4 (C4), 40.0 (C3a), 21.7 (CH_3). **IR** (ATR): 2922 (C-H st), 1741 (C=C st) cm^{-1}. **$[\alpha]_D^{rt}$**: +35.6 (*c* = 0.2, CH_2Cl_2). The e.e. was determined by HPLC using a Chiralpak IE3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 58.64 min, τ_{minor} = 67.92 min (80% e.e.).

2.4.2. Synthesis of 9 by a Nef reaction



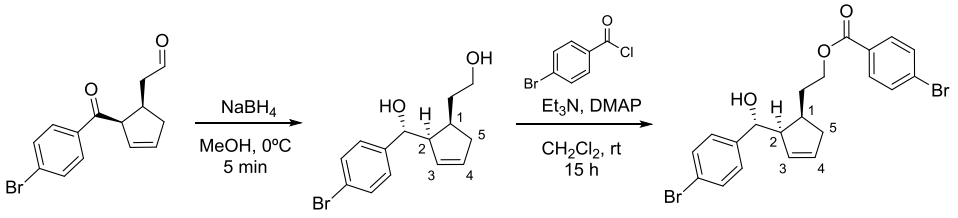
***cis*/*trans*-6a** **8** **9**

To a stirred solution of ***cis*/*trans*-6a** (0.05 g, 0.3 mmol, 1.0 eq) in MeOH (3 mL, 0.1 *M*), $NaBH_4$ (0.012 g, 0.3 mmol, 1.1 eq) was added at 0ºC and the reaction mixture was stirred at that temperature for 10 minutes. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) was added. Once the phases were separated, the aqueous phase was extracted with EtOAc (3 x 10

mL). The combined organic phases were washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was dissolved in CH_2Cl_2 (2 mL, 0.17 *M*), DMAP (0.02 g, 0.2 mmol, 0.4 eq), Et_3N (0.21 mL, 1.5 mmol, 4.05 eq) and *tert*-butyldimethylsilyl chloride (0.09 g, 0.6 mmol, 1.5 eq) were added and the reaction mixture was stirred at room temperature for 15 hours. When the reaction was completed, the crude was diluted with H_2O (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford pure **8** (0.02 g, 0.08 mmol) in 28% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.23-6.20 (m, 1H, H2), 5.85-5.80 (m, 1H, H3), 5.31-5.28 (m, 1H, H4), 3.75-3.69 (m, 2H, OTBSC*H*$_2$CH$_2$CH), 3.01-2.92 (m, 1H, H1a), 2.90-2.80 (m, 1H, H1b), 2.21-2.13 (m, 1H, OTBSCH$_2$CH$_2$C*H*), 1.89-1.78 (m, 1H, OTBSCH$_2$C*H*$_2$-CH), 1.75-1.64 (m, 1H, OTBSCH$_2$C*H*$_2$CH), 0.89 (s, 9H, 3 x CH_3), 0.04 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 139.8 (C2), 125.7 (C3), 97.2 (C4), 61.2 (OTBS*C*H$_2$CH$_2$CH), 40.8 (OTBSCH$_2$CH$_2$*C*H), 38.6 (C1), 37.4 (OTBSCH$_2$*C*H$_2$CH), 26.1 (3 x CH_3), 18.4 (Si*C*(CH$_3$)$_3$), -5.3 (2 x CH_3). **IR** (ATR): 2926 (C-H st), 2855 (C-H st), 1741 (C=C st), 1547 (NO_2 st as), 1372 (NO_2 st sim), 1103 (O-Si st) cm^{-1}. **MS** (EI) m/z (%): 183 (15), 167 (39), 93 (100), 92 (24), 91 (36), 89 (17), 77 (26), 75 (40), 73 (28). **[α]**$_D^{rt}$: +81.3 (*c* = 0.7, CH_2Cl_2).

To a stirred solution of **8** (8.00 mg, 0.030 mmol, 1.0 eq) in CH_2Cl_2 (0.4 mL, 0.075 *M*), Et_3N (0.016 mL, 0.132 mmol, 4.4 eq) and IBX (22.00 mg, 0.080 mmol, 2.7 eq) were added and the reaction mixture was stirred at room temperature for 4.5 hours. Once the reaction was completed, the reaction mixture was poured into NaOH 0.5 *N* (5 mL) and the organic layer was washed with HCl 1 *M* (5 mL) and H_2O (5 mL). It was dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 8:2) to afford pure **9** (6.40 mg, 0.027 mmol) in 89% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.67 (dd, *J* = 5.7, 2.9 Hz, 1H, H3), 6.18 (d, *J* = 5.8 Hz, 1H, H2), 3.78-3.72 (m, 2H, OTBSC*H*$_2$CH$_2$), 2.93-2.84 (m, 1H, H5), 2.52-2.41 (m, 2H, H4), 2.13-2.02 (m, 2H, OTBSCH$_2$C*H*$_2$), 0.89 (s, 9H, 3 x CH_3), 0.05 (s, 6H, 2 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 212.6 (C1), 163.6 (C3), 133.9 (C2), 61.6 (OTBS*C*H$_2$CH$_2$), 42.6 (C5), 36.2 (C4), 34.3 (OTBSCH$_2$*C*H$_2$), 29.8 (Si*C*(CH$_3$)$_3$), 26.1 (3 x CH_3), -5.2 (CH_3), -5.3 (CH_3). **IR** (ATR): 2969 (C-H st), 1741 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 184 (10), 183 (73), 109 (M$^+$-OTBS, 4), 75 (100), 59 (10), 56 (22), 55 (13), 53 (10). **HRMS**: Calculated for [$C_{13}H_{25}O_2Si$]$^+$: 241.1624 [(M+H)$^+$]; found: 241.1628. **[α]**$_D^{rt}$: +35.6 (*c* = 0.2, CH_2Cl_2). The e.e. was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (99:01)]; flow rate 0.7 mL/min; τ_{major} = 10.58 min, τ_{minor} = 11.49 min (81% e.e.).

2.4.3. Synthesis of 14 for the determination of absolute configuration



***cis*-6p** **13** **14**

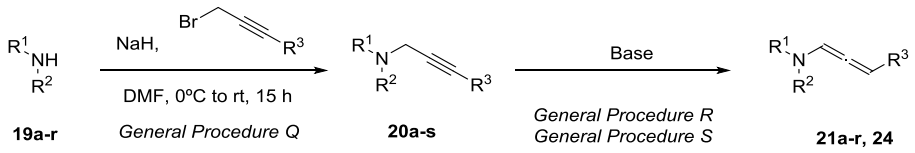
To a stirred solution of ***cis*-6p** (6.00 mg, 0.020 mmol, 1.0 eq) in MeOH (0.1 mL, 0.2 *M*) $NaBH_4$ (4.00 mg, 0.300 mmol, 5.0 eq) was added at 0ºC and the reaction mixture was stirred at that temperature for 5 minutes. The reaction mixture was diluted with EtOAc (2 mL) and H_2O (2 mL) was added. Once the phases were separated, the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (2x 10 mL) dried over Na_2SO_4 and concentrated in vacuo and the crude was then purified by flash column chromatography (petroleum ether/EtOAc gradient from 7:3 to 1:1) to afford pure **13** (0.004 g, 0.016 mmol) in 73% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.48-7.44 (m, 2H, C_{arom}-H), 7.22-7.17 (m, 2H, C_{arom}-H), 5.74-5.67 (m, 1H, H3), 4.99-4.92 (m, 1H, H4), 4.50 (d, *J* = 9.3 Hz, 1H, OHC*H*), 3.88 (dt, *J* = 10.2, 4.6 Hz, 1H, $CH_2CH_aH_bOH$), 3.70 (td, *J* = 9.8, 5.3 Hz, 1H, $CH_2CH_aH_bOH$), 3.02-2.96 (m, 1H, H2), 2.52-2.46 (m, 2H, H5), 2.40-2.37 (m, 1H, H1), 2.24-2.14 (m, 2H, CH_2CH_2OH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 143.2 (C_{arom}-C), 132.5 (C3), 131.5 (C4), 131.5 (C_{arom}-H), 128.8 (C_{arom}-H), 121.5 (C_{arom}-C), 73.2 (OH*C*H), 63.4 ($OHCH_2CH_2$), 54.9 (C2), 40.0 (C1), 38.3 (C5), 32.2 ($OHCH_2CH_2$). **IR** (ATR): 3461 (O-H st), 3020 (=CH st), 2972 (C-H st), 1741 (C=C st), 772 (C-Br st) cm^{-1} **HRMS**: Calculated for $[C_{14}H_{17}O_2BrNa]^+$: 319.0310 $[(M+Na)^+]$; found: 319.0310. **[α]**$_D^{rt}$: -24-4 (*c* = 0.3, CH_2Cl_2).

To a stirred solution of **13** (4.00 mg, 0.016 mmol, 1.0 eq) in CH_2Cl_2 (0.3 mL, 0.05 *M*) Et_3N (2.30 mg, 0.017 mmol, 1.1 eq) and 4-bromobenzoyl chloride (3.6 mg, 0.017 mmol, 1.1 eq) were added at room temperature and it was stirred for 15 hours. The reaction mixture was quenched with H_2O (5 mL). Once the phases were separated, the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL) dried over Na_2SO_4 and concentrated in vacuo and the crude was then purified by flash column chromatography to afford pure **14** (3.30 mg, 0.007 mmol) in 46% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm) 7.94-7.88 (m, 2H, C_{arom}-H), 7.61-7.56 (m, 2H, C_{arom}-H), 7.50-7.45 (m, 2H, C_{arom}-H), 7.25-7.20 (m, 1H, C_{arom}-H), 5.74 (dd, *J* = 5.9, 2.3 Hz, 1H, H3), 5.03 (dq, *J* = 6.1, 2.1 Hz, 1H, H4), 4.56 (d, *J* = 9.2 Hz, 1H, C*H*OH), 4.49-4.35 (m, 2H, CH_2CH_2O), 3.06-3.00 (m, 1H, H2), 2.66-2.56 (m, 1H, H5a), 2.54-2.43 (m, 1H, H5b), 2.41-2.29 (m, 1H, $CH_aH_bCH_2O$), 2.27-2.16 (m, 1H, $CH_aH_bCH_2O$), 1.92-1.90 (m, 1H, H1). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 166.2 (C=O), 143.2 (C_{arom}-C), 131.9 (C3), 131.8 (C_{arom}-H), 131.7 (C_{arom}-H), 131.6 (C3), 131.3 (C_{arom}-H), 129.5 (C_{arom}-C), 128.6 (C_{arom}-H), 128.1 (C_{arom}-C), 121.7 (C_{arom}-C), 73.7 (*C*H-OH), 65.2 (CH_2CH_2O), 55.0 (C2), 38.1 (C1), 37.7 (C5), 29.3 (CH_2CH_2O) . **IR** (ATR): 2922 (C-H st), 1741 (C=O st) cm^{-1} **[α]**$_D^{rt}$: -32.6 (*c* = 0.2,

CH_2Cl_2). The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 0.8 mL/min; τ_{major} = 16.48 min, τ_{minor} = 18.73 min (79% e.e.).

3. TRANSITION METAL-FREE STEREOSELECTIVE BORYLATION OF ALLENYLAMIDES

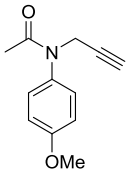
3.1. Synthesis of allenylamides 21a-r, 23, 24



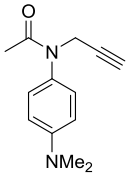
Compounds **19a-r** were prepared following the procedure described in the literature. Spectroscopic data were consistent with those reported in the literature.[17]

General Procedure Q: To a cooled (0ºC) solution of the corresponding protected amines **19a-r** (20.0 mmol, 1.0 eq) in dry DMF (60 mL, 0.33 *M*), NaH (60 wt.% in mineral oil, 24.0 mmol, 1.2 eq) was added in one portion. After stirring for 30 min at 0ºC, the corresponding propargyl bromide (28.0 mmol, 1.4 eq) was added and the mixture was stirred at room temperature for 15 hours. The resulting mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). Organic extracts were washed with brine (2 x 20 mL), dried over Na_2O_4 and concentrated in vacuo. The crude was then purified by flash column chromatography to afford pure **20a-r**.

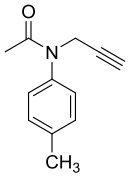
[17] (a) Tayama, E.; Sugai, S. *Tetrahedron Lett*. **2007**, *48*, 6163. (b) Murayama, T.; Shibuya, M.; Yamamoto, Y. *J. Org. Chem*. **2016**, *81*, 11940. (c) Xiong, X.; Yeung, Y. *Angew. Chem. Int. Ed*. **2016**, *55*, 16101. (d) Panahi, F.; Khajeh Dongolani, S.; Khalafi-Nezhad, A. *ChemistrySelect*, **2016**, *1*, 3541. (e) Obata, A.; Ano, Y.; Chatani, N. *Chem. Sci*. **2017**, *8*, 6650. (f) Kathiravan, S.; Nicholls, I. A. *Tetrahedron Lett*. **2017**, *58*, 1. (g) Ballenbach, M.; Aquino, P. G. V.; de Araújo-Junior, J. X.; Bourguignon, J.; Bihel, F.; Salomé, C.; Wagner, P.; Schmitt, M. *Chem. Eur. J*. **2017**, *23*, 13676. (h) Nie, Q.; Yi, F.; Huang, B.; *Adv. Synth. Catal*. **2017**, *359*, 3968. (i) Youn, S. W.; Ko, T. Y.; Jang, Y. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 6636.



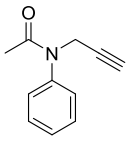
***N*-(4-methoxyphenyl)-*N*-(prop-2-yn-1-yl)acetamide (20a).** Following the *general procedure Q*, **20a** (4.70 g, 23.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 92% yield as a yellow oil starting from amide **19a** (4.00 g, 25.0 mmol), NaH (1.20 g, 30.0 mmol), propargyl bromide (4.00 mL, 35.0 mmol) and DMF (75 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.18 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 4.42 (d, *J* = 2.4 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 2.17 (t, *J* = 2.4 Hz, 1H, C≡CH), 1.83 (s, 3H, CH_3C=O). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 170.6 (C=O), 159.4 (C_{arom}-C), 135.0 (C_{arom}-C), 129.3 (C_{arom}-H), 114.9 (C_{arom}-H), 79.4 (*C*≡CH), 72.0 (C≡*C*H), 55.6 (OCH_3), 38.4 (CH_2), 22.4 (CH_3C=O). **HRMS** (ESI) for $C_{12}H_{14}NO_2$ $[M]^+$: calculated: 204.1025, found: 204.1030.



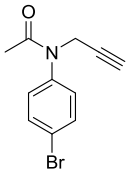
***N*-(4-(Dimethylamino)phenyl)-*N*-(prop-2-yn-1-yl)acetamide (20b).** Following the *general procedure Q*, **20b** (3.70 g, 17.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 72% yield as a brown solid starting from amide **19b** (4.30 g, 24.0 mmol), NaH (1.15 g, 29.0 mmol), propargyl bromide (3.74 mL, 34.0 mmol) and DMF (73 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.13-7.06 (m, 2H, C_{arom}-H), 6.73-6.65 (m, 2H, C_{arom}-H), 4.42 (d, *J* = 2.5 Hz, 2H, CH_2), 2.98 (s, 6H, NCH_3), 2.17 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.85 (s, 3H, CH_3C=O). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 171.1 (C=O), 150.2 (C_{arom}-C), 131.1 (C_{arom}-C), 128.7 (C_{arom}-H), 112.7 (C_{arom}-H), 79.8 (*C*≡CH), 71.7 (C≡*C*H), 40.6 (CH_2), 38.5 (NCH_3), 22.4 (CH_3C=O). **HRMS** (ESI) for $C_{13}H_{17}N_2O$ $[M+H]^+$: calculated: 217.1341, found: 217.1354.



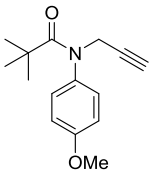
***N*-(Prop-2-yn-1-yl)-*N*-(*p*-tolyl)acetamide (20c).** Following the *general procedure Q*, **20c** (3.90 g, 20.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 63% yield as a yellow solid starting from amide **19c** (5.00 g, 33.0 mmol), NaH (1.60 g, 40.0 mmol), propargyl bromide (5.20 mL, 46.0 mmol) and DMF (100 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.17 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.12-7.07 (m, 2H, C_{arom}-H), 4.38 (d, *J* = 2.5 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3C=O), 2.14 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.79 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 170.0 (C=O), 139.5 (C_{arom}-C), 138.2 (C_{arom}-C), 130.2 (C_{arom}-H), 127.7 (C_{arom}-H), 79.2 (*C*≡CH), 71.9 (C≡*C*H), 38.1 (CH_2), 22.3 (CH_3C=O), 21.0 (C_{arom}-CH_3). **HRMS** (ESI) for $C_{12}H_{14}NO$ $[M+H]^+$: calculated: 188.1075, found: 188.1086.



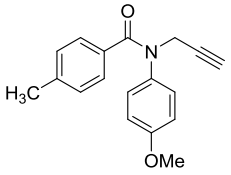
***N*-Phenyl-*N*-(prop-2-yn-1-yl)acetamide (20d).** Following the *general procedure Q*, **20d** (2.80 g, 16.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 70% yield as a brown solid starting from amide **19d** (3.00 g, 24.0 mmol), NaH (1.10 g, 28.0 mmol), propargyl bromide (3.70 mL, 33.6 mmol) and DMF (73 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.49-7.32 (m, 3H, C_{arom}-H), 7.32-7.19 (m, 2H, C_{arom}-H), 4.47 (d, *J* = 2.6 Hz, 2H, CH_2), 2.19 (t, *J* = 2.6 Hz, 1H, C≡CH), 1.86 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 170.1 (C=O), 142.3 (C_{arom}-C), 129.7 (C_{arom}-H), 128.4 (C_{arom}-H), 128.1 (C_{arom}-H), 79.2 (*C*≡CH), 72.0 (C≡*C*H), 38.3 (CH_2), 22.5 (CH_3). **HRMS** (ESI) for $C_{11}H_{12}NO$ $[M+H]^+$: calculated: 174.0923, found: 174.0919.



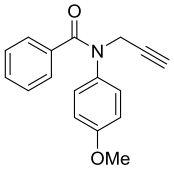
***N*-(4-Bromophenyl)-*N*-(prop-2-yn-1-yl)benzamide (20e).** Following the *general procedure Q*, **20e** (6.00 g, 23.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 99% yield as a brown oil starting from amide **19e** (5.00 g, 23.0 mmol), NaH (1.10 g, 27.6 mmol), propargyl bromide (3.60 mL, 32.2 mmol) and DMF (70 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.49 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.17-7.06 (m, 2H), 4.37 (d, *J* = 2.5 Hz, 2H, C_{arom}-H), 2.17 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.78 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 169.5 (C=O), 141.0 (C_{arom}-C), 132.8 (C_{arom}-H), 129.7 (C_{arom}-H), 122.2 (C_{arom}-C), 78.8 (*C*≡CH), 72.4 (C≡*C*H), 37.9 (CH_2), 22.3 (CH_3). **HRMS** (ESI) for $C_{11}H_{11}NOBr$ $[M+H]^+$: calculated: 252.0024, found: 252.0029.



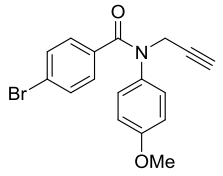
***N*-(4-Methoxyphenyl)-*N*-(prop-2-yn-1-yl)pivalamide (20f).** Following the *general procedure Q*, **20f** (5.40 g, 22.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 49% yield as a brown oil starting from amide **19f** (9.30 g, 45.0 mmol), NaH (2.16 g, 54.0 mmol), propargyl bromide (5.61 mL, 63.0 mmol) and DMF (136 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.18 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.86 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 4.29 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 2.15 (s, 1H, C≡CH), 0.99 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 177.7 (C=O), 159.3 (C_{arom}-C), 135.5 (C_{arom}-C), 130.9 (C_{arom}-H), 114.1 (C_{arom}-H), 79.9 (*C*≡CH), 71.8 (C≡*C*H), 55.4 (OCH_3), 42.2 (CH_2), 40.8 ($C(CH_3)_3$), 29.3 (3 x CH_3). **HRMS** (ESI) for $C_{15}H_{20}NO_2$ $[M+H]^+$: calculated: 246.1494, found: 246.1496.



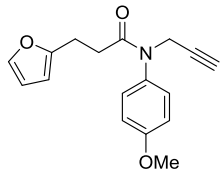
***N*-(4-Methoxyphenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzamide (20g).** Following the *general procedure Q*, **20g** (2.40 g, 8.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 62% yield as a yellow solid starting from amide **19g** (3.35 g, 13.9 mmol), NaH (0.67 g, 16.7 mmol), propargyl bromide (2.17 mL, 19.5 mmol) and DMF (42 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.22 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.10-6.98 (m, 2H, C_{arom}-H), 6.94 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.80-6.68 (m, 2H, C_{arom}-H), 4.60 (d, *J* = 2.5 Hz, 2H, CH_2), 3.70 (s, 3H, OCH_3), 2.21 (m, 4H, C_{arom}-CH_3, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 170.2 (C=O), 158.3 (C_{arom}-C), 140.0 (C_{arom}-C), 135.8 (C_{arom}-C), 132.3 (C_{arom}-C), 128.9 (C_{arom}-H), 128.4 (C_{arom}-H), 114.3 (C_{arom}-H), 79.3 (*C*≡CH), 72.2 (C≡*C*H), 55.3 (OCH_3), 40.0 (CH_2), 21.3 (C_{arom}-CH_3). **HRMS** (ESI) for $C_{18}H_{18}NO_2$ $[M+H]^+$: calculated: 280.1338, found: 280.1348.



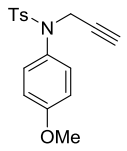
***N*-(4-Methoxyphenyl)-*N*-(prop-2-yn-1-yl)benzamide (20h).** Following the *general procedure Q*, **20h** (0.90 g, 3.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 90% yield as a brown solid starting from amide **19h** (1.00 g, 3.7 mmol), NaH (0.18 g, 4.5 mmol), propargyl bromide (0.60 mL, 5.2 mmol) and DMF (12 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.34 (d, *J* = 7.4 Hz, 2H, C_{arom}-H), 7.21 (m, 3H, C_{arom}-H), 7.06 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.76 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 4.64 (d, *J* = 2.6 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 2.25 (t, *J* = 2.6 Hz, 1H, C≡CH). **^{13}C NMR** (300 MHz, $CDCl_3$) (δ, ppm): 170.4 (C=O), 158.6 (C_{arom}-C), 135.7 (C_{arom}-C), 135.4 (C_{arom}-C), 129.9 (C_{arom}-H), 129.1 (C_{arom}-H), 128.9 (C_{arom}-H), 127.9 (C_{arom}-H), 114.5 (C_{arom}-H), 79.3 (*C*≡CH), 72.3 (C≡*C*H), 55.5 (OCH_3), 40.1 (CH_2). **HRMS** (ESI) for $C_{17}H_{16}NO_2$ $[M+H]^+$: calculated: 266.1181, found: 266.1183.



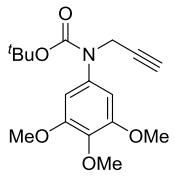
4-Bromo-*N*-(4-methoxyphenyl)-*N*-(prop-2-yn-1-yl)benzamide (20i). Following the *general procedure Q*, **20i** (0.55 g, 1.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 88% yield as a grey solid starting from amide **19i** (0.55 g, 1.8 mmol), NaH (0.90 g, 2.2 mmol), propargyl bromide (0.30 mL, 2.5 mmol) and DMF (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.23 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.14 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.99 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.70 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 4.54 (d, *J* = 2.5 Hz, 2H, CH_2), 3.64 (s, 3H, OCH_3), 2.22 (t, *J* = 2.5 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 168.6 (C=O), 158.4 (C_{arom}-C), 134.9 (C_{arom}-C), 134.0 (C_{arom}-C), 130.8 (C_{arom}-H), 130.3 (C_{arom}-H), 128.8 (C_{arom}-C), 124.1 (C_{arom}-H), 114.3 (C_{arom}-H), 78.8 (*C*≡CH), 72.4 (C≡*C*H), 55.1 (OCH_3), 39.8 (CH_2). **HRMS** (ESI) for $C_{17}H_{15}NO_2Br$ $[M+H]^+$: calculated: 344.0286, found: 344.0295.



3-(furan-2-yl)-*N*-(4-methoxyphenyl)-*N*-(prop-2-yn-1-yl)propanamide (20j). Following the *general procedure Q*, **20j** (0.58 g, 2.5 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 99% yield as a yellow oil starting from amide **19j** (0.50 g, 2.0 mmol), NaH (0.98 g, 2.5 mmol), propargyl bromide (0.32 mL, 2.9 mmol) and DMF (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.21 (d, *J* = 1.8 Hz, 1H, C*H*=CH-CH), 7.08 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.88 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.20 (t, *J* = 2.5 Hz, 1H, CH=C*H*CH), 5.90 (d, *J* = 3.1 Hz, 1H, CH=CHC*H*), 4.42 (d, *J* = 2.5 Hz, 2H, CH_2C≡CH), 3.79 (s, 3H, OCH_3), 2.90 (t, *J* = 7.6 Hz, 2H, CH_2CH_2C=O), 2.35 (t, *J* = 7.6 Hz, 2H, CH_2CH_2C=O), 2.18 (t, *J* = 2.5 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 171.6 (C=O), 159.4 (C_{arom}-C), 154.7 (C_{arom}-C), 140.9 (*C*H=CH-CH), 134.1 (C_{arom}-C), 129.3 (C_{arom}-H), 114.8 (C_{arom}-H), 110.1 (CH=*C*HCH), 105.2 (CH=CH*C*H), 79.3 (C≡*C*H), 72.0 (*C*≡CH), 55.4 (OCH_3), 38.5 (*C*H_2C≡CH), 32.6 (*C*H_2CH_2C=O), 23.7 (CH_2*C*H_2C=O). **HRMS** (ESI) for $C_{17}H_{18}NO_3$ $[M+H]^+$: calculated: 284.1287, found: 284.1293.

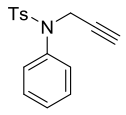


***N*-(4-Methoxyphenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (20k).** Following the *general procedure Q*, **20k** (1.10 g, 3.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 90% yield as a white solid starting from amide **19k** (1.13 g, 4.0 mmol), NaH (0.20 g, 4.8 mmol), propargyl bromide (0.62 mL, 5.6 mmol) and DMF (12 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.54 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.22 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.10 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.80 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 4.39 (d, *J* = 2.3 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 2.40 (s, 3H, C_{arom}-CH_3), 2.16 (t, *J* = 2.3 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 159.4 (C_{arom}-C), 143.7 (C_{arom}-C), 135.6 (C_{arom}-C), 131.7 (C_{arom}-C), 130.1 (C_{arom}-H), 129.3 (C_{arom}-H), 128.1 (C_{arom}-H), 114.2 (C_{arom}-H), 78.2 (*C*≡CH), 73.8 (C≡*C*H), 55.4 (OCH_3), 41.4 (CH_2), 21.6 (C_{arom}-*C*H_3). **HRMS** (ESI) for $C_{17}H_{18}NO_3S$ $[M+H]^+$: calculated: 316.1007, found: 316.1009.

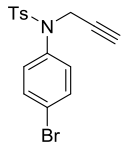


***tert*-butyl prop-2-yn-1-yl-(3,4,5-trimethoxyphenyl)carbamate (20l).** Following the *general procedure Q*, **20l** (2.40 g, 7.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 99% yield as an orange solid starting from carbamate **19l** (2.10 g, 7.5 mmol), NaH (0.36 g, 8.9 mmol), propargyl bromide (1.15 mL, 10.4 mmol) and DMF (25 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 6.47 (s, 2H, C_{arom}-H), 4.21 (d, *J* = 2.5 Hz, 2H, CH_2), 3.72 (s, 6H, OCH_3), 3.71 (s, 3H, OCH_3), 2.21 (t, *J* = 2.4 Hz, 1H, C≡CH), 1.36 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4

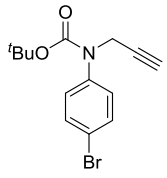
MHz, $CDCl_3$) (δ, ppm): 153.7 (C=O), 152.7 (C_{arom}-C), 137.6 (C_{arom}-C), 136.2 (C_{arom}-C), 103.9 (C_{arom}-H), 80.7 ($C(CH_3)_3$), 79.9 (*C*≡CH), 76.6 (C≡*C*H), 60.4 (OCH_3), 55.7 (OCH_3), 39.7 (CH_2), 28.0 (3 x CH_3)**. HRMS** (ESI) for $C_{17}H_{24}NO_5$ $[M+H]^+$: calculated: 322.1654, found: 322.1660.



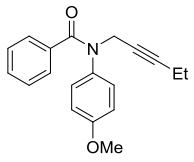
4-Methyl-*N*-phenyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (20m). Following the *general procedure Q*, **20m** (1.30 g, 4.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 95% yield as a white solid starting from amide **19m** (1.20 g, 5.0 mmol), NaH (0.24 g, 6.0 mmol), propargyl bromide (0.78 mL, 7.0 mmol) and DMF (15 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.55 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.34-7.29 (m, 3H, C_{arom}-H), 7.26-7.22 (m, 4H, C_{arom}-H), 4.44 (d, *J* = 2.5 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.17 (t, *J* = 2.5 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 143.8 (C_{arom}-C), 139.5 (C_{arom}-C), 135.7 (C_{arom}-C), 129.4 (C_{arom}-H), 129.2 (C_{arom}-H), 128.6 (C_{arom}-H), 128.3 (C_{arom}-H), 128.2 (C_{arom}-H), 78.2 (*C*≡CH), 73.9 (C≡*C*H), 41.2 (CH_2), 21.7 (CH_3). **HRMS** (ESI) for $C_{16}H_{16}NO_2S$ $[M+H]^+$: calculated: 286.0902, found: 286.0910.



***N*-(4-Bromophenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (20n).** Following the *general procedure Q*, **20n** (1.20 g, 3.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 93% yield as a white solid starting from amide **19n** (1.10 g, 3.5 mmol), NaH (0.17 g, 4.2 mmol), propargyl bromide (0.54 mL, 4.9 mmol) and DMF (11 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.52 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.46-7.40 (m, 2H, C_{arom}-H), 7.26-7.22 (m, 2H, C_{arom}-H), 7.13-7-08 (m, 2H, C_{arom}-H), 4.40 (d, *J* = 2.5 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.18 (t, *J* = 2.5 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 144.2 (C_{arom}-C), 138.5 (C_{arom}-C), 135.2 (C_{arom}-C), 132.4 (C_{arom}-H), 130.1 (C_{arom}-H), 129.6 (C_{arom}-H), 128.1 (C_{arom}-H), 122.3 (C_{arom}-C), 77.8 (*C*≡CH), 74.4 (C≡*C*H), 41.0 (CH_2), 21.7 (CH_3). **HRMS** (ESI) for $C_{16}H_{15}NO_2SBr$ $[M+H]^+$: calculated: 364.0007, found: 364.0015.



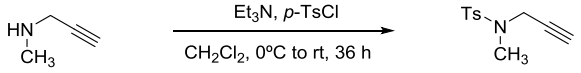
***tert*-butyl (4-bromophenyl)(prop-2-yn-1-yl)carbamate (20p).** Following the *general procedure Q*, **20p** (0.54 g, 1.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 47% yield as a yellow solid starting from carbamate **19p** (1.00 g, 3.7 mmol), NaH (0.20 g, 4.4 mmol), propargyl bromide (0.57 mL, 5.1 mmol) and DMF (12 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.42 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.18 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 4.30 (d, *J* = 2.5 Hz, 2H, CH_2), 2.23 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.42 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 153.6 (C=O), 141.1 (C_{arom}-C), 131.7 (C_{arom}-H), 127.9 (C_{arom}-H), 119.6 (C_{arom}-C), 81.4 ($C(CH_3)_3$), 79.6 (*C*≡CH), 72.2 (C≡*C*H), 39.6 (CH_2), 28.2 (3 x CH_3). **HRMS** (ESI) for $C_{14}H_{16}NO_2BrNa$ $[M+Na]^+$: calculated: 332.0262, found: 332.0261.



***N*-(4-Methoxyphenyl)-*N*-(pent-2-yn-1-yl)benzamide (20s).** Following the *general procedure Q*, **20s** (0.35 g, 1.2 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 50% yield as a yellow oil starting from amide **19h** (0.67 g, 2.4 mmol), NaH (0.12 g, 2.9 mmol), propargyl bromide (0.35 mL, 3.4 mmol) and DMF (8 mL). **^{1}H NMR (**300 MHz, $CDCl_3$) (δ, ppm): 7.33 (d, *J* = 7.3 Hz, 2H, C_{arom}-H), 7.23-7.14 (m, 3H, C_{arom}-H), 7.05 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.75 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 4.60 (s, 2H, CH_2), 3.75 (s,

3H, OCH_3), 2.16 (qt, *J* = 7.5, 2.2 Hz, 2H, CH_2CH_3), 1.09 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 170.2 (C=O), 158.3 (C_{arom}-C), 135.7 (C_{arom}-C), 129.5 (C_{arom}-H), 129.1 (C_{arom}-H), 128.7 (C_{arom}-H), 127.7 (C_{arom}-C), 114.1 (C_{arom}-H), 86.0 (*C*≡C), 74.6 (C≡*C*), 55.3 (OCH_3), 40.3 (CH_2), 13.8 (CH_2CH_3), 12.4 (CH_2CH_3). **HRMS** (ESI) for $C_{19}H_{20}NO_2$ $[M+H]^+$: calculated: 294.1494, found: 294.1507.

Synthesis of *N*,4-dimethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (20o)[18]



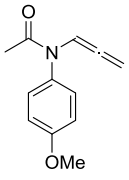
20o

To a solution of *p*-toluenesulfonyl chloride (0.76 mL, 4.0 mmol) in CH_2Cl_2 (10 mL, 0.4 *M*) at 0ºC, *N*-methylpropargylamine (0.33 mL, 4.0 mmol) was added. Then, Et_3N (1.11 mL, 8.0 mmol) was added dropwise at the same temperature. The reaction mixture was stirred at room temperature for 36 hours. Wen the reaction was finished, H_2O (20 mL) and CH_2Cl_2 (20 mL) were added. The phases were separated and the organic layer was washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) to afford pure **20o** (0.90 g, 4.0 mmol) in 99% yield as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.68 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.29 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 3.99 (d, *J* = 2.5 Hz, 2H, CH_2), 2.80 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3), 2.08 (t, *J* = 2.5 Hz, 1H, C≡CH). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 143.8 (C_{arom}-C), 134.2 (C_{arom}-C), 129.6 (C_{arom}-H), 128.0 (C_{arom}-H), 76.4 (*C*≡CH), 74.1 (C≡*C*H), 39.8 (CH_2), 34.4 (NCH_3), 21.6 (CH_3). **HRMS** (ESI) for $C_{11}H_{14}NO_2S$ $[M+H]^+$: calculated: 224.0745, found: 224.0755.

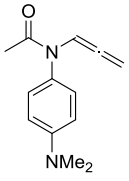
General Procedure R: Corresponding propargyl amide **20e-f, h, j-p** (5.0 mmol, 1.0 eq) was dissolved in THF (15 mL, 0.33 *M*). The mixture was cooled to 0ºC and KO^{t}Bu (1.5 mmol, 30 mol%) was added in three portions. It is observed that the reaction turned dark. The reaction was monitored by TLC after 15 hours and more base was added if necessary. It was diluted with Et_2O (20 mL) and filtered by celite®. After removal of the solvent the residue was purified by flash column chromatography to afford pure **21e-f, h, j-p**.[19]

General Procedure S: Corresponding propargyl amide **20a-d, g, i** (5.0 mmol, 1.0 eq) was dissolved in CH_3CN (50 mL, 0.1 *M*) and $CsOH{\cdot}H_2O$ (1.0 mmol, 0.2 eq) was added. The reaction mixture was stirred at 60ºC for 15 hours hours. The solvent was evaporated and the residue was purified by flash column chromatography to afford pure **21a-d, g, i**.[20]

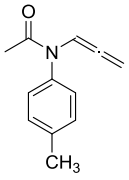
[18] Zhou, Y.; Porco, J. A.; Snyder, J. K. *Org. Lett*. **2007**, *9*, 393.
[19] Ballesteros, A.; Morán-Poladura, P.; González, J. M. *Chem. Commun*. **2016**, *52*, 2905.
[20] Li, Y.; Chen, J.; Qiu, R.; Wang, X.; Long, J.; Zhu, L.; Au, C.; Xu, X., *Tetrahedron Lett*. **2015**, *56*, 5504.



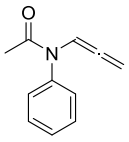
***N*-(4-Methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)acetamide (21a).** Following the *general procedure S*, **21a** (1.60 g, 8.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 60% yield as a brown solid starting from propargyl amide **20a** (2.70 g, 13.0 mmol), $CsOH{\cdot}H_2O$ (0.45 g, 2.7 mmol) and CH_3CN (130 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.66 (t, *J* = 6.3 Hz, 1H, C*H*=C=CH_2), 7.07 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.99 (d, *J* = 6.3 Hz, 2H, CH=C=CH_2), 3.82 (s, 3H, OCH_3), 1.88 (s, 3H, CH_3C=O). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.8 (CH=*C*=CH_2), 169.0 (C=O), 159.4 (C_{arom}-C), 133.0 (C_{arom}-C), 129.5 (C_{arom}-H), 114.6 (C_{arom}-H), 101.2 (*C*H=C=CH_2), 86.4 (CH=C=*C*H_2), 55.5 (OCH_3), 23.0 (*C*H_3C=O). **HRMS** (ESI) for $C_{12}H_{14}NO_2$ $[M+H]^+$: calculated: 204.1025, found: 204.1028.



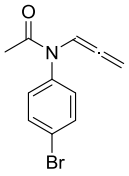
***N*-[4-(dimethylamino)phenyl]-*N*-(propa-1,2-dien-1-yl)acetamide (21b).** Following the *general procedure S*, **21b** (0.70 g, 3.9 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 70% yield as a orange solid starting from propargyl amide **20b** (1.00 g, 5.6 mmol), $CsOH{\cdot}H_2O$ (0.28 g, 1.9 mmol) and CH_3CN (56 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.66 (t, *J* = 6.4 Hz, 1H, C*H*=C=CH_2), 7.04-6.90 (m, 2H, C_{arom}-H), 6.77-6.64 (m, 2H, C_{arom}-H), 5.00 (d, *J* = 6.4 Hz, 2H, CH=C=CH_2), 2.98 (s, 6H, $N(CH_3)_2$), 1.88 (s, 3H, CH_3C=O). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.0 (CH=*C*=CH_2), 169.5 (C=O), 150.1 (C_{arom}-C), 129.0 (C_{arom}-C), 128.9 (C_{arom}-H), 112.3 (C_{arom}-H), 101.4 (*C*H=C=CH_2), 86.1 (CH=C=*C*H_2), 40.5 ($N(CH_3)_2$), 22.9 (*C*H_3C=O). **HRMS** (ESI) for $C_{13}H_{17}N_{2O}$ $[M+H]^+$: calculated: 217.1341, found: 217.1344.



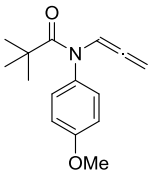
***N*-(Propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)acetamide (21c).** Following the *general procedure S*, **21c** (0.67 g, 3.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 68% yield as a pink solid starting from propargyl amide **20c** (1.00 g, 5.3 mmol), $CsOH{\cdot}H_2O$ (0.27 g, 1.6 mmol) and CH_3CN (53 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.66 (t, *J* = 6.4 Hz, 1H, C*H*=C=CH_2), 7.25-7.15 (m, 2H, C_{arom}-H), 7.09-6.98 (m, 2H, C_{arom}-H), 4.98 (d, *J* = 6.4 Hz, 2H, CH=C=CH_2), 2.37 (s, 3H, CH_3C=O), 1.87 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.8 (CH=*C*=CH_2), 168.9 (C=O), 138.6 (C_{arom}-C), 137.7 (C_{arom}-C), 130.2 (C_{arom}-H), 128.3 (C_{arom}-H), 101.1 (*C*H=C=CH_2), 86.5 (CH=C=*C*H_2), 23.1 (*C*H_3C=O), 21.4 (C_{arom}-*C*H_3). **HRMS** (ESI) for $C_{12}H_{13}NONa$ $[M+Na]^+$: calculated: 210.0895, found: 210.0896.



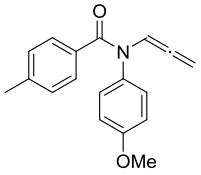
***N*-Phenyl-*N*-(propa-1,2-dien-1-yl)acetamide (21d).** Following the *general procedure S*, **21d** (0.23 g, 1.3 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 46% yield as a orange oil starting from propargyl amide **20d** (0.50 g, 2.9 mmol), $CsOH{\cdot}H_2O$ (0.15 g, 0.9 mmol) and CH_3CN (29 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.64 (br s, *J* = 6.3 Hz, 1H, C*H*=C=CH_2), 7.44-7.27 (m, 3H, C_{arom}-H), 7.14 (dd, *J* = 7.0, 2.0 Hz, 2H, C_{arom}-H), 4.93 (d, *J* = 6.3 Hz, 2H, CH=C=CH_2), 1.85 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.6 (CH=*C*=CH_2), 168.4 (C=O), 140.0 (C_{arom}-C), 129.4 (C_{arom}-H), 128.5 (C_{arom}-H), 128.4 (C_{arom}-H), 100.9 (*C*H=C=CH_2), 86.3 (CH=C=*C*H_2), 22.9 (CH_3). **HRMS** (ESI) for $C_{11}H_{12}NO$ $[M+H]^+$: calculated: 174.0919, found: 174.0927.



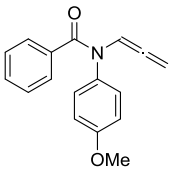
***N*-(4-Bromophenyl)-*N*-(propa-1,2-dien-1-yl)acetamide (21e).** Following the *general procedure R*, **21e** (1.62 g, 6.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 80% yield as a brown solid starting from propargyl amide **20e** (2.00 g, 7.9 mmol), KO^{t}Bu (0.27 g, 2.4 mmol) and THF (24 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.68-7.59 (br s, 1H, C*H*=C=CH_2), 7.55 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.06 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 5.02 (d, *J* = 6.5 Hz, 2H, CH=C=C*H*$_2$), 1.90 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.5 (CH=*C*=CH_2), 168.2 (C=O), 139.2 (C_{arom}-C), 132.8 (C_{arom}-H), 130.3 (C_{arom}-H), 122.5 (C_{arom}-C), 100.9 (*C*H=C=CH_2), 87.0 (CH=C=*C*H_2), 23.0 (CH_3). **HRMS** (ESI) for $C_{11}H_{11}NOBr$ $[M+H]^+$: calculated: 252.0024, found: 252.0033.



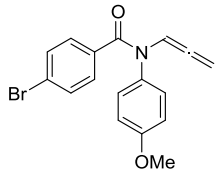
***N*-(4-Methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)pivalamide (21f).** Following the *general procedure R* **21f** (1.40 g, 5.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 94% yield as a brown oil starting from propargyl amide **20f** (1.50 g, 6.1 mmol), KO^{t}Bu (0.21 g, 1.8 mmol) and THF (19 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.68 (t, *J* = 6.4 Hz, 1H, C*H*=C=CH_2), 7.14-7.04 (m, 2H, C_{arom}-H), 6.90-6.81 (m, 2H, C_{arom}-H), 4.89 (d, *J* = 6.4 Hz, 2H, CH=C=C*H*$_2$), 3.82 (s, 3H, OCH_3), 1.06 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.0 (CH=*C*=CH_2), 176.2 (C=O), 159.3 (C_{arom}-C), 133.3 (C_{arom}-C), 131.3 (C_{arom}-H), 113.8 (C_{arom}-H), 104.6 (*C*H=C=CH_2), 86.0 (CH=C=*C*H_2), 55.5 (OCH_3), 41.2 (*C*$(CH_3)_3$), 29.4 (3 x CH_3). **HRMS** (ESI) for $C_{15}H_{20}NO_2$ $[M+H]^+$: calculated: 246.1494, found: 246.1498.



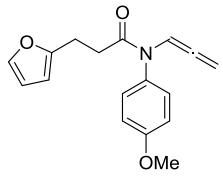
***N*-(4-Methoxyphenyl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzamide (21g).** Following the *general procedure S*, **21g** (0.17 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 33% yield as a yellow oil starting from propargyl amide **20g** (0.50 g, 1.8 mmol), $CsOH \cdot H_2O$ (0.15 g, 0.9 mmol) and CH_3CN (18 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.66 (t, *J* = 6.5 Hz, 1H, C*H*=C=CH_2), 7.23 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 6.97 (dd, *J* = 8.1, 5.0 Hz, 4H, C_{arom}-H), 6.78-6.68 (m, 2H, C_{arom}-H), 5.05 (d, *J* = 6.5 Hz, 2H, CH=C=C*H*$_2$), 3.72 (s, 3H, OCH_3), 2.24 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.8 (CH=*C*=CH_2), 167.6 (C=O), 157.5 (C_{arom}-C), 139.2 (C_{arom}-C), 132.3 (C_{arom}-C), 131.3 (C_{arom}-C), 128.5 (C_{arom}-H), 128.0 (C_{arom}-H), 127.5 (C_{arom}-H), 113.0 (C_{arom}-H), 101.4 (*C*H=C=CH_2), 85.7 (CH=C=*C*H_2), 54.3 (OCH_3), 20.5 (C_{arom}-CH_3). **HRMS** (ESI) for $C_{18}H_{18}NO_2$ $[M+H]^+$: calculated: 280.1338, found: 280.1335.



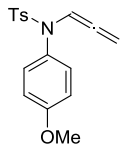
***N*-(4-Methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)benzamide (21h).** Following the *general procedure R*, **21h** (0.18 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 36% yield as a brown solid starting from propargyl amide **20h** (0.50 g, 1.9 mmol), KO^{t}Bu (0.06 g, 0.6 mmol) and THF (6 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.75-7.60 (br s, 1H, C*H*=C=CH_2), 7.34 (d, *J* = 6.9 Hz, 2H, C_{arom}-H), 7.28-7.16 (m, 3H, C_{arom}-H), 6.99 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.75 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 5.08 (d, *J* = 6.4 Hz, 2H, CH=C=C*H*$_2$), 3.74 (s, 3H, OCH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.9 (CH=*C*=CH_2), 168.7 (C=O), 158.6 (C_{arom}-C), 135.4 (C_{arom}-C), 133.2 (C_{arom}-C), 130.0 (C_{arom}-H), 129.6 (C_{arom}-H), 129.0 (C_{arom}-H), 127.9 (C_{arom}-H), 114.1 (C_{arom}-H), 102.4 (*C*H=C=CH_2), 86.8 (CH=C=*C*H_2), 55.4 (OCH_3). **HRMS** (ESI) for $C_{17}H_{16}NO_2$ $[M+H]^+$: calculated: 266.1181, found: 266.1181.



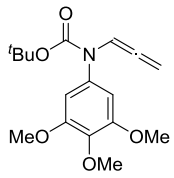
4-Bromo-*N*-(4-methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)benzamide (21i). Following the *general procedure S*, **21i** (0.26 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 52% yield as a orange oil starting from propargyl amide **20i** (0.50 g, 1.4 mmol), $CsOH{\cdot}H_2O$ (0.24 g, 1.4 mmol) and CH_3CN (15 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.69-7.56 (br s, 1H, C*H*=C=CH_2), 7.32 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.20 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.02-6.91 (m, 2H, C_{arom}-H), 6.82-6.72 (m, 2H, C_{arom}-H), 5.09 (d, *J* = 6.4 Hz, 2H, CH=C=CH_2), 3.77 (s, 3H, OCH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 203.1 (CH=*C*=CH_2), 167.6 (C=O), 159.0 (C_{arom}-C), 134.4 (C_{arom}-C), 133.0 (C_{arom}-C), 131.3 (C_{arom}-H), 130.7 (C_{arom}-H), 129.7 (C_{arom}-H), 124.7 (C_{arom}-H), 114.4 (C_{arom}-C), 102.4 (*C*H=C=CH_2), 87.1 (CH=C=*C*H_2), 55.6 (OCH_3). **HRMS** (ESI) for $C_{17}H_{15}BrNO_2$ $[M+H]^+$: calculated: 344.0286, found: 344.0290.



3-(furan-2-yl)-*N*-(4-methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)propanamide (21j). Following the *general procedure R*, **21j** (0.07 g, 0.02 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 69% yield as a brown oil starting from propargyl amide **20j** (0.10 g, 0.3 mmol), KO^{t}Bu (0.01 g, 0.1 mmol) and THF (1 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.68 (t, *J* = 6.5 Hz, 1H, C*H*=C=CH_2), 7.24 (s, 1H, C*H*=CH-CH), 7.03-6.94 (m, 2H, C_{arom}-H), 6.92-6.85 (m, 2H, C_{arom}-H), 6.23 (dd, *J* = 3.2, 2.9 Hz, 1H, CH=C*H*CH), 5.93 (d, *J* = 3.2 Hz, 1H, CH=CHC*H*), 4.99 (d, *J* = 6.5 Hz, 2H, CH=C=CH_2), 3.81 (s, 3H, OCH_3), 2.93 (t, *J* = 7.5 Hz, 2H, C$H_2$$CH_2$C=O), 2.40 (t, *J* = 7.5 Hz, 2H, CH_2CH_2C=O). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 202.3 (CH=*C*=CH_2), 170.3 (C=O), 159.4 (C_{arom}-C), 154.7 (*C*H=CH-CH=C), 141.1 (C_{arom}-C), 132.2 (CH=*C*HCH=C), 129.6 (C_{arom}-H), 114.7 (C_{arom}-H), 110.3 (CH=CH*C*H=C), 105.4 (CH=CHCH=*C*), 101.4 (*C*H=C=CH_2), 86.4 (CH=C=*C*H_2), 55.4 (OCH_3), 33.3 (*C*$H_2$$CH_2$C=O), 23.8 ($CH_2$*C*$H_2$C=O). **HRMS** (ESI) for $C_{17}H_{18}NO_3$ $[M+H]^+$: calculated: 284.1287, found: 284.1296.

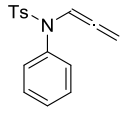


***N*-(4-Methoxyphenyl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (21k).** Following the *general procedure R*, **21k** (0.13 g, 0.4 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 63% yield as a brown solid starting from propargyl sulfonamide **20k** (0.20 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol) and THF (2 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.55 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.27 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.12 (t, *J* = 6.2 Hz, 1H, C*H*=C=CH_2), 6.93-6.85 (m, 2H, C_{arom}-H), 6.82-6.74 (m, 2H, C_{arom}-H), 5.03 (d, *J* = 6.2 Hz, 2H, CH=C=CH_2), 3.79 (s, 3H, OCH_3), 2.44 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.0 (CH=*C*=CH_2), 159.6 (C_{arom}-C), 143.9 (C_{arom}-C), 135.4 (C_{arom}-C), 130.9 (C_{arom}-H), 129.7 (C_{arom}-C), 129.6 (C_{arom}-H), 127.9 (C_{arom}-H), 114.0 (C_{arom}-H), 102.9 (*C*H=C=CH_2), 87.6 (CH=C=*C*H_2), 55.5 (OCH_3), 21.7 (C_{arom}-CH_3). **HRMS** (ESI) for $C_{17}H_{18}NO_3S$ $[M+H]^+$: calculated: 316.1018, found: 316.1019.

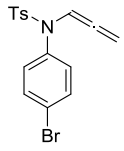


***tert*-butyl propa-1,2-dien-1-yl(3,4,5-trimethoxyphenyl)carbamate (21l).** Following the *general procedure R*, **21l** (0.32 g, 1.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 65% yield as a yellow solid starting from propargyl amide **20l** (0.50 g, 1.5 mmol), KO^{t}Bu (0.05 g, 0.5 mmol) and THF (5 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.12 (t, *J* = 6.4 Hz, 1H, C*H*=C=CH_2), 6.34 (s, 2H, C_{arom}-H), 4.98 (d, *J* = 6.4 Hz, 2H, CH=C=CH_2), 3.75 (s, 3H, OCH_3), 3.74 (s, 6H, OCH_3), 1.39 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ,

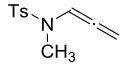
ppm): 201.2 (CH=*C*=CH_2), 152.8 (C_{arom}-C), 152.1 (C=O), 136.9 (C_{arom}-C), 134.7 (C_{arom}-C), 105.5 (C_{arom}-H), 101.9 (*C*H=C=CH_2), 86.3 (CH=C=*C*H_2), 81.4 (*C*$(CH_3)_3$), 60.7 (OCH_3), 56.0 (OCH_3), 28.1 (3 x CH_3). **HRMS** (ESI) for $C_{17}H_{24}NO_5$ $[M+H]^+$: calculated: 322.1654, found: 322.1660.



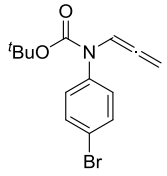
4-Methyl-*N*-phenyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (21m). Following the *general procedure R*, **21m** (0.20 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 67% yield as a brown solid starting from propargyl sulfonamide **20m** (0.30 g, 1.1 mmol), KO^{t}Bu (0.04 g, 0.3 mmol) and THF (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.56 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 7.32-7.22 (m, 5H, C_{arom}-H), 7.11 (t, *J* = 6.3 Hz, 1H, C*H*=C=CH_2), 7.06-6.96 (m, 2H, C_{arom}-H), 5.02 (d, *J* = 6.4 Hz, 2H, CH=C=C*H*$_2$), 2.44 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.2 (CH=*C*=CH_2), 144.0 (C_{arom}-C), 137.3 (C_{arom}-C), 135.4 (C_{arom}-C), 129.7 (C_{arom}-H), 129.6 (C_{arom}-H), 128.8 (C_{arom}-H), 128.7 (C_{arom}-H), 127.8 (C_{arom}-H), 102.5 (*C*H=C=CH_2), 87.6 (CH=C=*C*H_2), 21.7 (CH_3). **HRMS** (ESI) for $C_{16}H_{15}NO_2SNa$ $[M+Na]^+$: calculated: 308.0721, found: 308.0727.



***N*-(4-Bromophenyl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (21n).** Following the *general procedure R*, **21n** (0.27 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 89% yield as a white solid starting from propargyl sulfonamide **20n** (0.30 g, 0.8 mmol), KO^{t}Bu (0.03 g, 0.2 mmol) and THF (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.58-7.51 (m, 2H, C_{arom}-H), 7.44-7.38 (m, 2H, C_{arom}-H), 7.32-7.25 (m, 2H, C_{arom}-H), 7.08 (t, *J* = 6.3 Hz, 1H, C*H*=C=CH_2), 6.90-6.84 (m, 2H, C_{arom}-H), 5.05 (d, *J* = 6.3 Hz, 2H, CH=C=C*H*$_2$), 2.44 (s, 3H, CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 200.9 (CH=*C*=CH_2), 144.3 (C_{arom}-C), 136.7 (C_{arom}-C), 135.0 (C_{arom}-C), 132.2 (C_{arom}-H), 131.3 (C_{arom}-H), 129.8 (C_{arom}-H), 127.8 (C_{arom}-H), 122.8 (C_{arom}-C), 102.3 (*C*H=C=CH_2), 88.0 (CH=C=*C*H_2), 21.8 (CH_3). **HRMS** (ESI) for $C_{16}H_{15}NO_2SBr$ $[M+H]^+$: calculated: 364.0007, found: 364.0012.



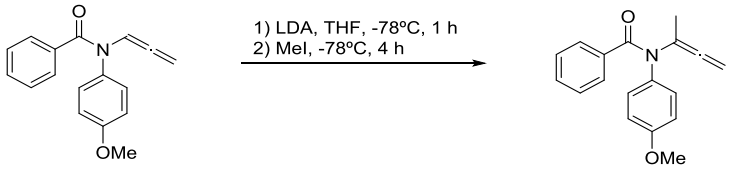
***N*,4-Dimethyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (21o).** Following the *general procedure R*, **21o** (0.27 g, 0.7 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 88% yield as a white solid starting from propargyl sulfonamide **20o** (0.30 g, 0.8 mmol), KO^{t}Bu (0.03 g, 0.2 mmol) and THF (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.65 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 7.30 (d, *J* = 8.0 Hz, C_{arom}-H), 6.87 (t, *J* = 6.2 Hz, 1H, C*H*=C=CH_2), 5.28 (d, *J* = 6.2 Hz, 2H, CH=C=C*H*$_2$), 2.69 (s, 3H, NCH_3), 2.41 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.5 (CH=*C*=CH_2), 143.9 (C_{arom}-C), 133.7 (C_{arom}-C), 129.8 (C_{arom}-H), 127.4 (C_{arom}-H), 101.7 (*C*H=C=CH_2), 87.8 (CH=C=*C*H_2), 33.3 (NCH_3), 21.6 (C_{arom}-CH_3). **HRMS** (ESI) for $C_{11}H_{14}NO_2S$ $[M+H]^+$: calculated: 224.0745, found: 224.0756.



***tert*-butyl (4-bromophenyl)(propa-1,2-dien-1-yl)carbamate (21p).** Following the *general procedure R*, **21p** (0.19 g, 0.6 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 1:1) in 63% yield as a yellow solid starting from propargyl amide **20p** (0.30 g, 1.0 mmol), KO^{t}Bu (0.03 g, 0.3 mmol) and THF (3 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.46 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.22 (t, *J* = 6.4 Hz, 1H, C*H*=C=CH_2), 7.06 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 5.05 (d, *J* = 6.4 Hz, 2H, CH=C=C*H*$_2$), 1.44 (s, 9H, 3 x CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 201.4 (CH=*C*=CH_2), 152.1 (C=O), 138.5 (C_{arom}-C), 132.0 (C_{arom}-H), 129.9 (C_{arom}-H), 120.8 (C_{arom}-C), 102.0

(*C*H=C=CH_2), 87.0 (CH=C=*C*H_2), 82.0 (*C*$(CH_3)_3$), 28.3 (3 x CH_3). **HRMS** (ESI) for $C_{14}H_{16}NO_2BrNa$ $[M+Na]^+$: calculated: 332.0262, found: 332.0264.

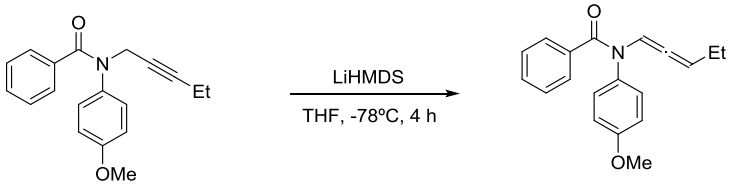
Synthesis of *N*-(buta-2,3-dien-2-yl)-*N*-(4-methoxyphenyl)benzamide (23)[21]



21h **23**

To a solution of iPr_2NH (0.35 mL, 2.5 mmol, 2.2 eq) in THF (5 mL, 0.2 *M*) at 0ºC was added dropwise *n*BuLi (0.90 mL, 2.3 mmol, 2.01 eq). After being stirred at 0ºC for 30 minutes, the solution was cooled to -78ºC. To this solution was added a solution of allenylamide **21h** (0.30 g, 1.1 mmol, 1.0 eq) in THF (8 mL, 0.14 *M*), and the resultant solution was stirred at -78ºC for 1 hour. To this solution was added dropwise MeI (0.35 mL, 5.6 mmol, 4.98 eq) and it was stirred at -78ºC for 4 hours. It was quenched with H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL), washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash column chromatography FC (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford pure **23** (0.20 g, 0.7 mmol) in 64% yield as a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.59-7.40 (m, 3H, C_{arom}-H), 7.37-7.24 (m, 2H, C_{arom}-H), 7.14 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.90-6.76 (m, 2H, C_{arom}-H), 4.79-4.58 (br s, 2H, C=C=CH_2), 3.76 (s, 3H, OCH_3), 1.97-1.89 (m, 3H, CH_3C). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 209.0 (C=*C*=CH_2), 170.5 (C=O), 158.1 (C_{arom}-H), 136.8 (C_{arom}-C), 130.0 (C_{arom}-H), 128.1 (C_{arom}-H), 127.9 (C_{arom}-H), 120.6 (C_{arom}-C), 114.3 (C_{arom}-H), 109.4 (*C*=C=CH_2), 80.3 (C=C=*C*H_2), 55.4 (OCH_3), 18.3 (CH_3C). **HRMS** (ESI) for $C_{18}H_{18}NO_2$ $[M+H]^+$: calculated: 280.1338, found: 280.1351.

Synthesis of *N*-(4-Methoxyphenyl)-*N*-(penta-1,2-dien-1-yl)benzamide (24)[22]

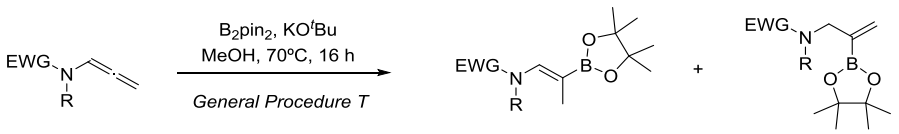


20s **24**

[21] Fuwa, H.; Sasaki, M. *Org. Biomol. Chem*. **2007**, *5*, 2214.
[22] Villar, L.; Uria, U.; Martinez, J. I.; Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed*. **2017**, *56*, 10535.

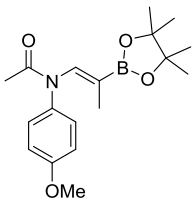
Propargyl amide **20s** (0.30 g, 1.0 mmol, 1.0 eq) was dissolved in dry THF (5 mL, 0.2 *M*) and cooled to -78°C. LiHMDS (1.0 *M* in THF, 1.50 mL, 1.5 mmol, 1.5 eq) was added dropwise and the reaction mixture was stirred at 0°C for 4 hours. The solvent was evaporated and the residue was purified by flash column chromatography on deactivated silica gel (acetone) (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford pure **24** (0.10 g, 0.3 mmol) in 35% yield as a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) (δ, ppm): 7.56-7.68 (br s, 1H, C*H*=C=CH), 7.34 (d, *J* = 7.4 Hz, 2H, C_{arom}-H), 7.30-7.11 (m, 3H, C_{arom}-H), 6.98 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.74 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 5.52 (q, *J* = 6.1 Hz, 1H, CH=C=C*H*), 3.74 (s, 3H, OCH_3), 1.88 (pd, *J* = 7.4, 2.8 Hz, 2H, CH_2CH_3), 0.82 (t, *J* = 7.4 Hz, 3H, CH_2CH_3). **^{13}C NMR** (75.4 MHz, $CDCl_3$) (δ, ppm): 196.4 (CH=*C*=CH), 168.7 (C=O), 158.6 (C_{arom}-C), 135.7 (C_{arom}-C), 133.6 (C_{arom}-C), 129.8 (C_{arom}-H), 129.7 (C_{arom}-H), 128.9 (C_{arom}-H), 127.9 (C_{arom}-H), 114.0 (C_{arom}-H), 104.7 (*C*H=C=CH), 103.0 (CH=C=*C*H), 55.4 (OCH_3), 23.0 (CH_2CH_3), 12.9 (CH_2CH_3). **HRMS** (ESI) for $C_{19}H_{20}NO_2$ $[M+H]^+$: calculated: 294.1494, found: 294.1509.

3.2. Metal-free borylation of allenylamides



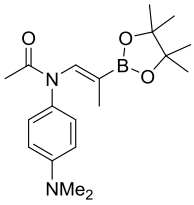
21a-r **22a-r** **25k-r**

General Procedure T: An oven-dried Schlenk tube, sealed with a rubber septum and equipped with a magnetic stirring bar, was charged with KO^{t}Bu (0.06 mmol, 0.3 eq) and bis(pinacolato)diboron (0.24 mmol, 1.2 eq) under argon followed by methanol (0.5 mL, 0.4 *M*). Then, allenylamide **21a-r** (0.2 mmol, 1.0 eq) was added and the reaction mixture was allowed to heat for 16 hours. The solvent was evaporated in vacuo and the NMR yield was calculated through comparison to an internal standard (naphthalene). The crude was then purified by flash column chromatography to afford pure **22a-r, 25k-r**.

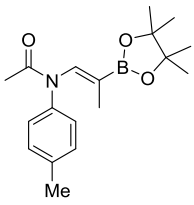


***N*-(4-Methoxyphenyl)-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]acetamide (22a).** Following the *general procedure T*, **22a** (47.00 mg, 0.140 mmol) was isolated by FC (pentane/EtOAc 4:1) in 71% yield as a colorless oil starting from allenylamide **21a** (41.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.24 mmol), KO^{t}Bu (6.70 mg, 0.06 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.97 (s, 1H, CH=C), 6.76 (m, 2H, C_{arom}-H), 6.54 (m, 2H, C_{arom}-H), 3.25 (s, 3H, OCH_3), 1.71 (s, 3H, CH_3C=O), 1.35 (d, *J* = 1.6 Hz, 3H, CH=CCH_3), 1.08 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz,

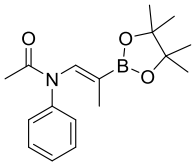
$CDCl_3$) (δ, ppm): 169.4, 137.4, 125.1, 114.3, 83.2, 54.7, 24.8 22.7, 13.2. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.8 (br s). **HRMS** (ESI) for $C_{18}H_{26}BNNaO_4$ $[M+Na]^+$: calculated: 354.1852, found: 354.1850.



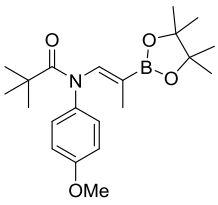
***N*-(4-(Dimethylamino)phenyl)-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]acetamide (22b).** Following the *general procedure T*, **22b** (54.00 mg, 0.160 mmol) was isolated by FC (pentane/EtOAc 4:1) in 78% yield as a colorless oil starting from allenylamide **21b** (43.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.49 (br s, 1H, CH=C), 7.02 (t, *J* = 6.0 Hz, 2H, C_{arom}-H), 6.66 (t, *J* = 7.3 Hz, 2H, C_{arom}-H), 2.96 (s, 6H, NCH_3), 1.91 (s, 3H, CH_3C=O), 1.22 (s, 12H, 4 x CH_3), 1.15 (d, *J* = 7.2 Hz, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.9, 149.5, 128.6, 127.9, 114.0, 112.4, 83.2, 40.5, 24.8, 22.9, 22.6, 12.0. **^{11}B NMR** (128.3 MHz, $CDCl_3$) (δ, ppm): 31.4 (br s). **HRMS** (ESI) for $C_{19}H_{29}BN_2NaO_3$ $[M+Na]^+$: calculated: 367.2163, found: 367.2168.



***N*-[(1*Z*)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]-*N*-(*p*-tolyl)acetamide (22c).** Following the *general procedure T*, **22c** (39.00 mg, 0.120 mmol) was isolated by FC (pentane/EtOAc 6:1) in 62% yield as a colorless oil starting from allenylamide **21c** (41.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.46 (m, 1H, CH=C), 7.18 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.10 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 2.37 (s, 3H, C_{arom}-CH_3), 1.94 (br s, 3H, CH_3C=O), 1.27 (s, 3H, CH=CCH_3), 1.25 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.6, 130.5, 129.5, 129.4, 129.0, 128.6, 119.9, 109.1, 83.1, 24.5, 21.1, 15.0. **^{11}B NMR** (128.3 MHz, $CDCl_3$) (δ, ppm): 30.9 (br s). **HRMS** (APCI-FIA-TOF) for $C_{18}H_{27}BNO_3$ $[M+H]^+$: calculated: 316.2079, found: 316.2079.

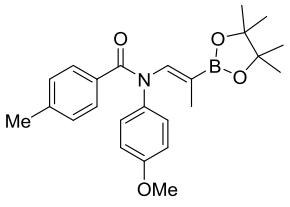


***N*-phenyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]acetamide (22d).** Following the *general procedure T*, **22d** (15.00 mg, 0.050 mmol) was isolated by FC (pentane/EtOAc 4:1) in 25% yield as a colorless oil starting from allenylamide **21d** (35.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.98 (br s, 1H, CH=C), 6.89 (m, 3H, C_{arom}-H), 6.80 (m, 2H, C_{arom}-H), 1.67 (s, 3H, CH_3C=O), 1.29 (s, 3H, CH=CCH_3), 1.07 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 169.3, 143.1, 139.3, 138.1, 137.5, 127.5, 83.6, 25.2, 23.0, 13.6. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.2 (br s). **HRMS** (APCI-FIA-TOF) for $C_{17}H_{25}BNO_3$ $[M+H]^+$: calculated: 302.1927, found: 302.1924.

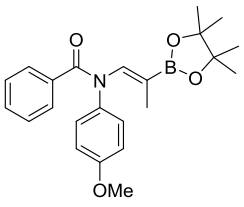


***N*-(4-Methoxyphenyl)-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]pivalamide (22f).** Following the *general procedure T*, **22f** (42.00 mg, 0.110 mmol) was isolated by FC (pentane/EtOAc 4:1) in 65% yield as a colorless oil starting from allenylamide **21f** (50.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.20 (s,

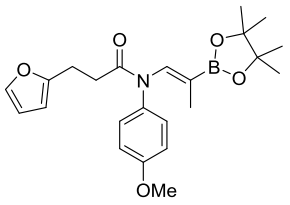
1H, CH=C), 7.05 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.78 (d, *J* = 9.0 Hz, 2H, C_{arom}-H), 3.74 (s, 3H, OCH_3), 1.19 (s, 12H, 4 x CH_3), 1.17 (s, 9H, 3 x CH_3), 1.14 (s, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 178.5, 158.3, 141.0, 135.3, 129.9, 113.9, 83.4, 55.4, 41.1, 28.8, 25.0, 24.7, 13.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) (δ, ppm): 30.5 (br s). **HRMS** (ESI) for $C_{21}H_{32}BNaNO_4$ $[M+Na]^+$: calculated: 396.2318, found: 396.2322.



***N*-(4-methoxyphenyl)-4-methyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]benzamide (22g**). Following the *general procedure T*, **22g** (30.00 mg, 0.070 mmol) was isolated by FC (pentane/EtOAc 7:1) in 74% yield as a colorless oil starting from allenylamide **21g** (56.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.66 (br s, 1H, CH=C), 7.23 (d, *J* = 7.6 Hz, 2H, C_{arom}-H), 6.99 (m, 4H, C_{arom}-H), 6.75 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.75 (s, 3H, OCH_3), 2.26 (s, 3H, C_{arom}-CH_3), 1.25 (br s, 12H, 4 x CH_3), 1.21 (br s, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 168.5, 158.4, 140.2, 133.3, 132.2, 130.1, 129.4, 129.0, 128.7, 128.4, 113.9, 83.5, 55.3, 29.7, 25.0, 21.4. **^{11}B NMR** (128.3 MHz, $CDCl_3$) (δ, ppm): 30.5 (br s). **HRMS** (ESI) for $C_{24}H_{30}BNNaO_3$ $[M+Na]^+$: calculated: 430.2164, found: 430.2165.

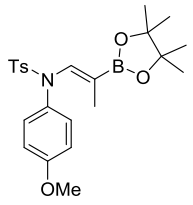


(*Z*)-*N*-(4-methoxyphenyl)-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)benzamide (22h). Following the *general procedure T*, **22h** (57.00 mg, 0.140 mmol) was isolated by FC (pentane/EtOAc 1:1) in 72% yield as a colorless oil starting from allenylamide **21h** (53.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.43 (d, *J* = 5.2 Hz, 2H, C_{arom}-H), 7.31 (t, *J* = 3.6 Hz, 1H, CH=C), 7.22 (d, *J* = 3 Hz, 2H, C_{arom}-H), 7.17 (s, 1H, C_{arom}-H), 7.02 (d, *J* = 5.2 Hz, 2H, C_{arom}-H), 6.76 (d, *J* = 1.0 Hz, 2H, C_{arom}-H), 3.76 (s, 3H, OCH_3), 1.25 (s, 3H, CH=CCH_3), 1.24 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.1, 157.8, 139.6, 135.7, 135.0, 130.2, 129.1, 128.5, 127.7, 114.1, 83.4, 55.3, 24.7, 13.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) (δ, ppm): 30.6 (br s). **HRMS** (APCI-FIA-TOF) for $C_{23}H_{29}BNO_4$ $[M+H]^+$: calculated: 394.2188, found: 394.2184.

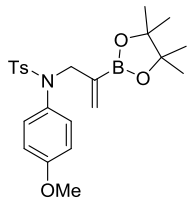


(*Z*)-3-(furan-2-yl)-*N*-(4-methoxyphenyl)-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)propanamide (22j). Following the *general procedure T*, **22j** (14.00 mg, 0.050 mmol) was isolated by FC (pentane/EtOAc 1:1) in 20% yield as a colorless oil starting from allenylamide **21j** (57.00 mg, 0.200 mmol), B_2pin_2 (37.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 8.17 (br s, 1H, CH=C), 6.96-6.97 (s, 1H, C*H*=CH-CH), 6.64 (br s, 2H, C_{arom}-H), 6.46-6.49 (m, 2H, C_{arom}-H), 5.98-6.0 (t, *J* =2.5 Hz, 1H, CH=C*H*CH), 5.61-5.83 (d, *J* = 3.0 Hz, 1H, CH=CHC*H*), 3.17 (s, 3H, OCH_3), 2.96-3.0 (t, *J* = 7.5 Hz, 2H, CH_2CH_2C=O), 2.29-2.35 (br s, 2H, CH_2CH_2C=O), 1.36-1.38 (m, 3H, CH=CCH_3), 1.07 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 170.6, 154.9, 140.6, 134.1, 129.7, 114.1, 110.0, 105.3, 82.8, 82.5, 54.3, 33.1, 30.0, 24.7, 24.5, 23.7, 12.8. **^{11}B NMR**

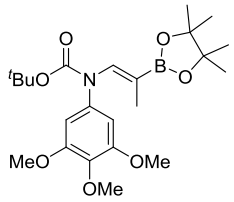
(128.3 MHz, toluene) (δ, ppm): 31.1 (br s) **HRMS** (ESI) for $C_{46}H_{60}B_2N_2NaO_{10}$ $[2M+Na]^+$: calculated: 845.4332, found: 845.4328.



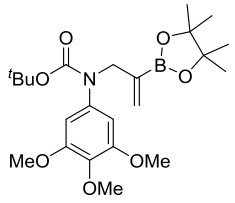
***N*-(4-methoxyphenyl)-4-methyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)]benzenesulfonamide (22k).** Following the *general procedure T*, **22k** (47.00 mg, 0.100 mmol) was isolated by FC (pentane/Et_2O 4:1) in 53% yield as a colorless oil starting from allenylamide **21k** (63.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.89 (s, 1H, CH=C), 7.46 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.97 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.59 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.46 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 3.17 (s, 3H, OCH_3), 1.84 (s, 3H, C_{arom}-CH_3), 1.38 (s, 3H, CH=CCH_3), 1.07 (s, 6H, 2 x CH_3), 1.01 (s, 6H, 2 x CH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 158.9, 142.8, 138.7, 135.7, 132.2, 130.8, 129.0, 127.8, 113.6, 82.9, 82.5, 54.3, 24.7, 24.6, 13.0 **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.5 (br s). **HRMS** (ESI) for $C_{23}H_{30}BNaNO_5S$ $[M+Na]^+$: calculated: 466.1835, found: 466.1834.



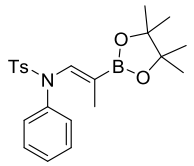
***N*-(4-methoxyphenyl)-4-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]benzenesulfonamide (25k).** Following the *general procedure T*, **25k** (25.00 mg, 0.050 mmol) was isolated by FC (pentane/Et_2O 4:1) in 28% yield as a colorless oil starting from allenylamide **21k** (63.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.50 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 7.00-6.96 (m, 2H, C_{arom}-H), 6.68 (d, *J* = 8.9, 2H, C_{arom}-H), 6.51 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.19-6.09 (m, 2H, C=CH_2), 4.52 (s, 2H, CH_2), 3.19 (s, 3H, OCH_3), 1.91 (s, 3H, C_{arom}-CH_3), 1.01 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 158.7, 143.1, 132.2, 132.1, 130.1, 129.3, 127.8, 125.7, 113.9, 83.6, 55.3, 54.0, 24.7, 21.9. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 29.9 (br s). **HRMS** (ESI) for $C_{23}H_{30}BNNaO_5S$ $[M-Na]^+$: calculated: 466.1835, found: 466.1837.



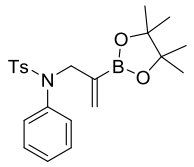
***tert*-Butyl [(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl](3,4,5-trimethoxyphenyl)carbamate (22l).** Following the *general procedure T*, **22l** (37.00 mg, 0.080 mmol) was isolated by FC (pentane/Et_2O 4:1) in 41% yield as a colorless oil starting from allenylamide **21l** (64.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.99 (br s, 1H, CH=C), 6.44 (s, 2H, C_{arom}-H), 3.75 (s, 3H, OCH_3), 3.28 (s, 6H, OCH_3), 1.53 (s, 3H, CH=CCH_3), 1.37 (s, 9H, 3 x CH_3), 1.09 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 13.2, 24.8, 28.0, 55.6, 60.4, 80.9, 83.1, 106.6, 129.1, 137.1, 139.5, 153.8, 153.3, 153.8. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 32.2 (br s). **HRMS** (ESI) for $C_{23}H_{36}BNNaO_5$ $[M+Na]^+$: calculated: 472.2482, found: 472.2480.



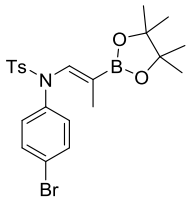
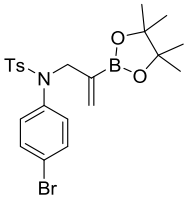
***tert*-Butyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl](3,4,5-trimethoxyphenyl)carbamate (25l).** Following the *general procedure T*, **25l** (11.00 mg, 0.020 mmol) was isolated by FC (pentane/Et_2O 4:1) in 12% yield as a colorless oil starting from allenylamide **21l** (64.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (* denotes product **22l**) (δ, ppm): 7.96* (s, 1H), 6.59 (s, 2H, C_{arom}-H), 6.44* (s, 2H), 6.20 (s, 1H, C=CH_aH$_b$), 5.98 (s, 1H, C=CH$_a$$H_b$), 4.61 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.74* (s, 3H), 3.41 (s, 6H, OCH_3), 3.28* (s, 6H), 1.44 (s, 9H, 3 x CH_3), 1.37* (s, 9H), 1.09* (s, 12H), 1.03 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (* denotes product **22l**) (δ, ppm): 12.9*, 24.2, 24.5*, 27.8*, 28.0, 53.8, 55.2*, 55.3, 59.9, 60.0*, 79.1, 80.6*, 80.8*, 83.1, 106.1, 128.7*, 136.7*, 137.6, 139.1*, 152.9*, 153.2, 153.4. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.9 (br s). **HRMS** (ESI) for $C_{23}H_{36}BNNaO_5$ [M-Na]$^+$: calculated: 472.2482, found: 472.2484.



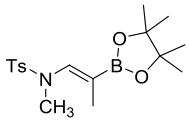
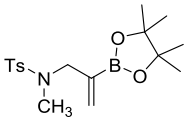
4-methyl-*N*-phenyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]benzenesulfonamide (22m). Following the *general procedure T*, **22m** (33.00 mg, 0.080 mmol) was isolated by FC (pentane/Et_2O 4:1) in 44% yield as a colorless oil starting from allenylamide **21m** (57.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.84 (s, 1H, CH=C), 7.43 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 7.06-7.08 (m, 2H, C_{arom}-H), 7.83-7.91 (m, 3H, C_{arom}-H), 6.52-6.57 (m, *J* = 7.9 Hz, 2H, C_{arom}-H), 1.81 (s, 3H, C_{arom}-CH_3), 1.04 (d, *J* = 1.6 Hz, 3H, C=CCH_3), 1.06 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 142.8, 139.9, 138.5, 135.6, 129.3, 129.0, 128.5, 128.4, 127.7, 127.1, 83.0, 24.7, 24.4, 13.2. **^{11}B NMR** (128 MHz, toluene) (δ, ppm): 31.3 (br s). **HRMS** (ESI) for $C_{44}H_{56}B_2N_2O_8S_2Na$ [2M+Na]$^+$: calculated: 849.3562, found: 849.3563.



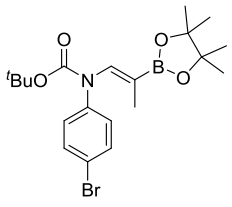
4-methyl-*N*-phenyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]benzenesulfonamide (25m). Following the *general procedure T*, **25m** (7.45 mg, 0.018 mmol) was isolated by FC (pentane/Et_2O 4:1) in 9% yield as a colorless oil starting from allenylamide **21m** (57.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (* denotes product **22m**) (δ, ppm): 7.82* (s, 1H), 7.43-7.40 (m, 2H*+2H, C_{arom}-H), 7.10-6.84 (m, 5H*+5H, C_{arom}-H), 6.70-6.64 (m, 2H, C_{arom}-H), 6.59-6.55* (m, 2H), 6.12 (s, 1H, C=CH_aH$_b$), 6.04 (s, 1H, C=CH$_a$$H_b$), 4.51 (s, 2H, CH_2), 1.92-1.90 (s, 3H, OCH_3), 1.83* (s, 3H), 1.33* (s, 3H), 1.02* (s, 12H), 1.0 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (* denotes product **22m**) (δ, ppm): 142.9*, 139.9*, 138.5*, 135.5, 132.1*, 129.2, 129.0, 128.9, 128.4*, 128.3, 127.1*, 83.0, 29.9, 24.7, 24.4, 24.3*, 13.2*. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 30.3 (br s). **HRMS** (ESI) for $C_{44}H_5{}_6B_2N_2O_8S_2Na$ [2M-Na]$^+$: calculated: 849.3562, found: 849.3565.

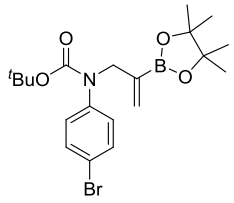
***N*-(4-bromophenyl)-4-methyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]benzenesulfonamide (22n) and *N*-(4-bromophenyl)-4-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]benzenesulfonamide (25n).** Following the *general procedure T*, **22n** and **25n** (74.00 mg, 0.150 mmol) were isolated by FC (pentane/Et_2O 4:1) in 47% (**22n**) and 28% (**25n**) yield as a colorless oil starting from allenylamide **21n** (73.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (* denotes product **22n**; $^+$ denotes product **25n**) (δ, ppm): 7.68* (s, 1H, CH=C), 7.56* (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.50$^+$ (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 7.10* (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.00-6.96$^+$ (m, 4H, C_{arom}-H), 6.85* (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 6.68$^+$ (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.64$^+$ (d, *J* = 8.2 Hz, 2H, C=CH_2), 4.40$^+$ (s, 2H, CH_2), 2.09$^+$ (s, 3H, C_{arom}-CH_3), 1.91$^+$ (s, 3H, C_{arom}-CH_3), 1.82* (s, 3H, C_{arom}-CH_3), 1.30* (s, 3H, CH=CCH_3), 1.06* (s, 6H, 3 x CH_3), 1.04* (s, 6H, 3 x CH_3), 1.03$^+$ (s, 6H, 3 x CH_3), 1.02$^+$ (s, 6H, 3 x CH_3). **^{11}B NMR** (128 MHz, toluene) (δ, ppm): 31.6 (br s). **HRMS** (ESI) for $C_{22}H_{27}BBrNO_4SNa$ $[M+Na]^+$: calculated: 514.0834, found: 514.0849.

***N*,4-dimethyl-*N*-[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]benzenesulfonamide (22o) and *N*,4-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]benzenesulfonamide (25o).** Following the *general procedure T*, **22o** and **25o** (22.00 mg, 0.060 mmol) were isolated by FC (pentane/Et_2O 4:1) in 20% (**22o**) and 11% (**25o**) yield as a colorless oil starting from allenylamide **21o** (44.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (* denotes product **22o**; $^+$ denotes product **25o**) (δ, ppm): 7.62-7.57*$^+$ (m, 4H, C_{arom}-H), 7.16* (s, 1H, C*H*=CCH_3), 6.78-6.75* (m, 2H, C_{arom}-H), 6.71-6.69$^+$ (m, 2H, C_{arom}-H), 6.15$^+$ (s, 1H, C=C$H_a$$H_b$), 5.91$^+$ (s, 1H, C=$CH_a$$H_b$), 3.82$^+$ (s, 2H, CH_2), 2.73*$^+$ (s, 6H, NCH_3), 2.46$^+$ (s, 3H, C_{arom}-CH_3), 1.94*(s, 3H, C_{arom}-CH_3), 1.83* (s, 3H, CH=CCH_3), 1.05*$^+$ (s, 24H, 8 x CH_3). **^{13}C NMR** (100 MHz, toluene) (* denotes product **22o**) (δ, ppm): 14.0*, 24.7*, 24.8, 25.1, 34.7, 36.1*, 53.8, 83.4*, 83.7, 127.6, 127.9, 129.5, 129.7, 131.3*, 136.1, 139.5*, 143.1. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.6 (br s). **HRMS** (ESI) for $C_{34}H_{52}B_2N_2O_8S_2Na$ $[2M+Na]^+$: calculated: 725.3249, found: 725.3262.

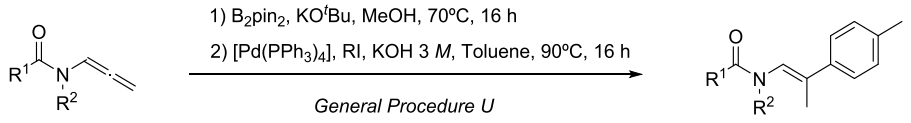


***tert*-butyl (4-bromophenyl)[(1*Z*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl]carbamate (22p).** Following the *general procedure T*, **22p** (45.00 mg, 0.100 mmol) was isolated by FC (pentane/Et_2O 4:1) in 51% yield as a colorless oil starting from allenylamide **21p** (62.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.75 (s, 1H, CH=C), 7.05 (d, *J* = 7.0 Hz, 2H, C_{arom}-H), 6.77 (d, *J* = 6.7 Hz, 2H, C_{arom}-H), 1.41 (s, 3H, CH=C-CH_3), 1.30 (s, 9H, 3 x CH_3), 1.08 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 13.5, 24.5, 27.5, 80.9, 82.9, 119.0, 129.0, 131.3, 131.5, 139.0, 140.5, 152.3. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 30.3 (br s). **HRMS** (ESI) for $C_{20}H_{29}BBrNO_4Na$ $[M-Na]^+$: calculated: 460.1270, found: 460.1277.



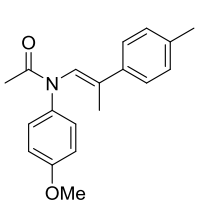
***tert*-butyl (4-bromophenyl)[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]carbamate (25p).** Following the *general procedure T*, **25p** (22.00 mg, 0.050 mmol) was isolated by FC (pentane/Et_2O 4:1) in 25% yield as a colorless oil starting from allenylamide **21p** (62.00 mg, 0.200 mmol), B_2pin_2 (61.00 mg, 0.240 mmol), KO^{t}Bu (6.70 mg, 0.060 mmol) and MeOH (0.5 mL). **^{1}H NMR** (400 MHz, toluene) (* denotes product **22p**) (δ, ppm): 7.72* (s, 1H), 7.04* (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.06 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.76* (d, *J* = 8.7 Hz, 2H), 6.12 (s, 1H, C=CH_aH_b), 5.99-5.95 (s, 2H, CH_2), 5.78 (s, 1H, C=CH_aH_b), 1.36 (s, 9H, 3 x CH_3), 1.29* (s, 9H), 1.32* (s, 3H), 1.08* (s, 12H), 1.05 (s, 12H, 4 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (* denotes product **22p**) (δ, ppm): 13.8 *, 24.88*, 24.9, 27.9*, 28.2, 53.6, 81.3, 79.9*, 83.2*, 83.5, 116.5, 119.4*, 129.3, 131.5, 131.7, 132.0, 139.3*, 140.8*, 142.7, 152.8*, 153.8. **^{11}B NMR** (128.3 MHz, toluene) (δ, ppm): 31.3 (br s). **HRMS** (ESI) for $C_{20}H_{29}BBrNO_4Na$ $[M-Na]^+$: calculated: 460.1270, found: 460.1283.

3.3. *One-pot* metal-free borylation/Pd-catalyzed Suzuki-Miyaura cross-coupling reaction

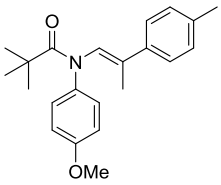


21a-b, f-h **26a-e**

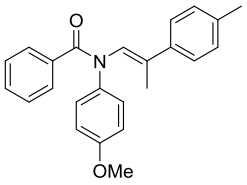
General procedure U: An oven-dried Schlenk tube, sealed with a rubber septum and equipped with a magnetic stirring bar, was charged with KO^{t}Bu (0.15 mmol, 0.3 eq) and bis(pinacolato)diboron (0.6 mmol, 1.2 eq) under argon followed by methanol (1.2 mL, 0.4 *M*). Then, allenylamide **21a-b, f-h** (0.5 mmol, 1.0 eq) was added and the reaction mixture was heated to 70ºC for 16 hours. The solvent was evaporated in vacuo and the crude was dissolved in toluene (0.6 mL, 0.8 *M*). A solution of $Pd(PPh_3)_4$ (0.015 mmol, 0.03 eq) in toluene, 1-iodo-4-methylbenzene (1.5 mmol, 3.0 eq) and a KOH 3 *M* solution (3.0 mmol, 6.0 eq) were added in sequence and the reaction was heated to 90ºC for 16 hours. After completion, the mixture was cooled to room temperature and diluted with CH_2Cl_2 (5 mL). The mixture was filtered through a small pad of Celite® and anhydrous $MgSO_4$. Afterwards, the solvent was concentrated in vacuo and the resulting crude was purified by flash column chromatography to afford pure **26a-e**.



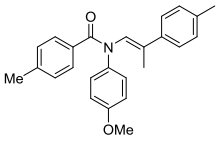
***N*-(4-methoxyphenyl)-*N*-[(1*E*)-2-(*p*-tolyl)prop-1-en-1-yl]acetamide (26a).** Following the *general procedure U*, **26a** (0.11 g, 0.4 mmol) was isolated by FC (pentane/EtOAc 4:1) in 72% yield as a yellow oil starting from allenylamide **21a** (0.10 g, 0.5 mmol), B_2pin_2 (0.15 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol), MeOH (1.2 mL), $Pd(PPh_3)_4$ (0.002 g, 0.02 mmol), 1-iodo-4-methylbenzene (0.33 g, 1.5 mmol), KOH 3 *M* (1.00 mL, 3.0 mmol) and toluene (0.6 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.44 (m, 1H, C=C), 7.06 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.96 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.74 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.65 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.84 (s, 3H, OCH_3), 3.74 (s, 3H, C_{arom}-CH_3), 1.83 (s, 3H, CH_3C=O), 1.61 (d, *J* = 5.1 Hz , 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 168.5, 159.4, 152.8, 139.6, 132.6, 129.8, 129.2, , 116.5, 115.0, 114.8, 109.1, 55.5, 29.7, 23.2, 15.1. **HRMS** (APCI-FIA-TOF) for $C_{19}H_{22}NO_2$ $[M+H]^+$: calculated: 296.1646, found: 296.1645.



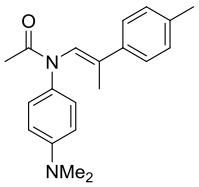
***N*-(4-methoxyphenyl)-N-[(1E)-2-(*p*-tolyl)prop-1-en-1-yl]pivalamide (26b).** Following the *general procedure U*, **26b** (0.04 g, 0.1 mmol) was isolated by FC (pentane/EtOAc 4:1) in 26% yield as a yellow oil starting from allenylamide **21f** (0.12 g, 0.5 mmol), B_2pin_2 (0.15 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol), MeOH (1.2 mL), $Pd(PPh_3)_4$ (0.002 g, 0.02 mmol), 1-iodo-4-methylbenzene (0.33 g, 1.5 mmol), KOH 3 *M* (1.00 mL, 3.0 mmol) and toluene (0.6 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.29 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.15 (m, 4H, C_{arom}-H), 6.87 (d, *J* = 9.0 Hz, 2H, C_{arom}-H), 6.75 (br s, 1H, CH=C), 3.80 (s, 3H, OCH_3), 2.34 (s, 3H, C_{arom}-CH_3), 1.87 (d, *J* = 1.4 Hz, 3H, CH=CCH_3), 1.29 (s, 3H, 3 x CH_3), 1.28 (s, 6H, 3 x CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 178.9, 157.8, 137.7, 137.1, 131.3, 129.3, 128.5, 128.2, 126.0, 122.0, 114.1, 55.6, 40.8, 28.4, 28.2, 21.2, 16.2. **HRMS** (APCI-FIA-TOF) for $C_{22}H_{28}NO_2$ $[M+H]^+$: calculated: 338.2116, found: 338.2115.



***N*-(4-methoxyphenyl)-*N*-[(1*E*)-2-(*p*-tolyl)prop-1-en-1-yl]benzamide (26c).** Following the *general procedure U*, **26c** (0.04 g, 0.1 mmol) was isolated by FC (pentane/EtOAc 4:1) in 94% yield as a yellow oil starting from allenylamide **21h** (0.13 g, 0.5 mmol), B_2pin_2 (0.15 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol), MeOH (1.2 mL), $Pd(PPh_3)_4$ (0.002 g, 0.02 mmol), 1-iodo-4-methylbenzene (0.33 g, 1.5 mmol), KOH 3 *M* (1.00 mL, 3.0 mmol) and toluene (0.6 mL). **^{1}H NMR** (400 MHz, toluene) (δ, ppm): 7.56 (m, 2H, C_{arom}-H), 7.45 (d, *J* = 6.4 Hz, 1H, CH=C), 7.27 (m, 1H, C_{arom}-H), 7.12 (d, *J* = 7.7 Hz, 2H, C_{arom}-H), 7.04 (m, 2H, C_{arom}-H), 6.94 (m, 2H, C_{arom}-H), 6.91 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 6.58 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 3.24 (s, 3H, OCH_3), 2.12 (s, 3H, C_{arom}-CH_3), 1.77 (s, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, toluene) (δ, ppm): 168.8, 157.5, 138.1, 136.6, 135.9, 130.3, 128.9, 128.8, 127.4, 126.5, 125.8, 124.1, 114.2, 113.8, 54.3, 15.9, 12.2. **HRMS** (APCI-FIA-TOF) for $C_{24}H_{24}NO_2$ $[M+H]^+$: calculated: 358.1801, found: 358.1803.



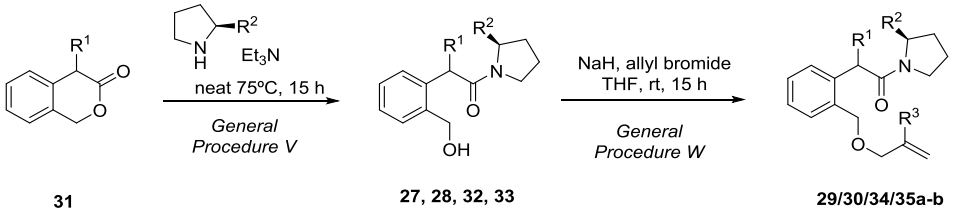
***N*-(4-methoxyphenyl)-4-methyl-*N*-[(1*E*)-2-(*p*-tolyl)prop-1-en-1-yl]benzamide (26d).** Following the *general procedure U*, **26d** (0.12 g, 0.3 mmol) was isolated by FC (pentane/EtOAc 6:1) in 65% yield as a yellow oil starting from allenylamide **21g** (0.14 g, 0.5 mmol), B_2pin_2 (0.15 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol), MeOH (1.2 mL), $Pd(PPh_3)_4$ (0.002 g, 0.02 mmol), 1-iodo-4-methylbenzene (0.33 g, 1.5 mmol), KOH 3 *M* (1.00 mL, 3.0 mmol) and toluene (0.6 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.60 (br s, 1H, CH=C), 7.37 (m, 2H, C_{arom}-H), 7.20 (m, 8H, C_{arom}-H), 6.96 (m, 2H, C_{arom}-H), 3.79 (s, 3H, OCH_3), 2.34 (d, *J* = 5.3 Hz, 6H, 2 x C_{arom}-CH_3), 1.80 (s, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 203.0, 157.5, 140.6, 137.8, 137.3, 132.9, 130.18, 129.1, 128.7, 128.4, 127.2, 125.9, 122.1, 114.4, 114.1, 55.4, 21.5, 21.1, 16.2. **HRMS** (ESI) for $C_{25}H_{26}NO_2$ $[M+H]^+$: calculated: 371.1889, found: 371.1885.



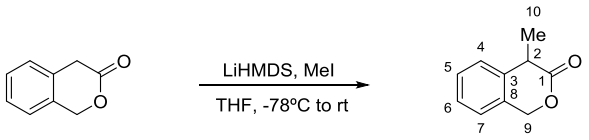
***N*-[4-(dimethylamino)phenyl]-*N*-[(1*E*)-2-(*p*-tolyl)prop-1-en-1-yl]acetamide (26e).** Following the *general procedure U*, **26e** (0.11 g, 0.4 mmol) was isolated by FC (pentane/EtOAc 1:1) in 74% yield as a yellow oil starting from allenylamide **21b** (0.11 g, 0.5 mmol), B_2pin_2 (0.15 g, 0.6 mmol), KO^{t}Bu (0.02 g, 0.2 mmol), MeOH (1.2 mL), $Pd(PPh_3)_4$ (0.002 g, 0.02 mmol), 1-iodo-4-methylbenzene (0.33 g, 1.5 mmol), KOH 3 *M* (1.00 mL, 3.0 mmol) and toluene (0.6 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.29 (d, *J* = 7.9 Hz, 1H, CH=C), 7.17 (m, 2H, C_{arom}-H), 7.10 (d, *J* = 6.3 Hz, 2H, C_{arom}-H), 6.85 (m, 2H, C_{arom}-H), 6.70 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 2.99 (s, 6H, NCH_3), 2.32 (s, 3H, C_{arom}-CH_3), 2.01 (s, 3H, CH_3C=O), 1.72 (s, 3H, CH=CCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 171.4, 149.3, 139.0, 136.6, 129.1, 128.9, 128.3, 126.4, 126.0, 112.5, 40.5, 22.8, 21.0, 16.0. **HRMS** (ESI) for $C_{20}H_{24}N_2NaO$ $[M+Na]^+$: calculated: 308.1889, found: 308.1887.

4. AMIDE ACTIVATION: SYNTHESIS OF CHIRAL ISOCHROMANONES

4.1. Synthesis of starting materials



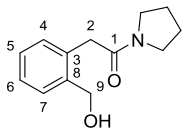
Synthesis of 4-methylisochromanone (31)



31

Into a solution of lithium hexamethyldisilazide (LiHMDS, 1*M* in THF, 8.40 mL, 8.4 mmol, 1.2 eq) at -78ºC, a cooled solution of 3-isochromanone (1.05 g, 7.0 mmol, 1.0 eq) in THF (30 mL, 0.25 *M*) was cannulated dropwise. After completion of the addition, the reaction mixture was stirred at -78ºC for 30 minutes, after which methyl iodide (1.76 mL, 4.0 mmol, 4.0 eq) was added in one portion. The resulting mixture was allowed to warm to room temperature and stirred at that temperature for 15 hours. Once the reaction was finished, excess of base was quenched by the addition of HCl 1 *M* (20 mL) and the resulting biphasic mixture was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with a saturated aqueous solution of brine (2 x 20 mL) and subsequently dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/EtOAc 7:1) to afford **31** (0.55 g, 3.4 mmol) in 48% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.42-7.37 (m, 1H, H4), 7.34-7.28 (m, 2H, H6, H7), 7.26-7.23 (m, 1H, H5), 5.36-5.26 (m, 2H, H9), 3.64 (q, *J* = 7.0 Hz, 1H, H2), 1.65 (d, *J* = 7.0 Hz, 3H, H10). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 173.6 (C1), 135.7 (C8), 132.1 (C3), 129.1 (C_{arom}-C), 127.2 (C_{arom}-C), 124.8 (C_{arom}-C), 124.9 (C_{arom}-C), 69.4 (C9), 39.5 (C2), 13.0 (C10). **FTIR** (neat), ν max cm^{-1}: 1739 (C=O st). **HRMS** (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}O_2Na$) requires m/z 185.0573, found m/z 185.0573.

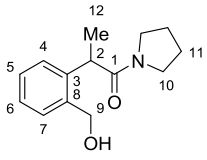
General procedure V: Corresponding isochromanone (5.0 mmol, 1.0 eq) was dissolved in a mixture of pyrrolidine (10.0 mmol, 2.0 eq) and triethylamine (15 mmol, 3.0 eq) and the resulting solution was heated to 75ºC for 15 hours. After this time, the reaction was quenched by the addition of HCl 0.5 *M* (20 mL) and the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford pure **27, 28, 32, 33**.



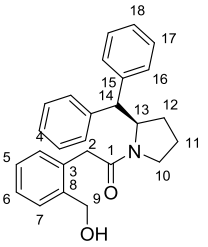
2-(2-(Hydroxymethyl)phenyl)-1-(pyrrolidin-1-yl)ethan-1-one (27).[23] Following the *general procedure V*, **27** (1.04 g, 4.7 mmol) was isolated in 95% yield as a yellow oil starting from 3-isochromanone (0.74 g, 5.0 mmol), pyrrolidine (0.82 mL, 10.0 mmol) and Et_3N (2.09 mL, 15.0 mmol), and it was used in the next step without further purification. **^{1}H NMR (**400 MHz, $CDCl_3$) (δ, ppm): 7.41 (dd,

[23] Padmanaban, M.; Carvalho, L. C. R.; Petkova, D.; Lee, J.-W.; Santos, A. S.; Marques, M. M. B.; Maulide, N. *Tetrahedron* **2015**, *71*, 5994.

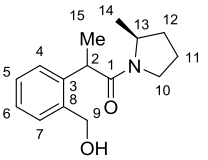
J = 7.1, 1.8 Hz, 1H, C_{arom}-H), 7.27-7.24 (m, 2H, C_{arom}-H), 7.15 (dd, *J* = 7.2, 1.6 Hz, 1H, C_{arom}-H), 4.60 (s, 2H, H9), 3.77 (s, 2H, H2), 3.65 (t, *J* = 6.9 Hz, 2H, H10), 3.47 (t, *J* = 6.8 Hz, 2H, H10), 2.04-1.85 (m, 4H, H11).



2-(2-(hydroxymethy)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (32). Following the *general procedure V*, **32** (1.14 g, 4.9 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 98% yield as a yellow oil starting from **31** (0.81 g, 5.0 mmol), pyrrolidine (0.82 mL, 10.0 mmol) and Et_3N (2.09 mL, 15.0 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.52-7.26 (m, 4H, C_{arom}-H), 7.26-7.13 (m, 4H, C_{arom}-H), 4.89 (t, *J* = 6.1 Hz, 1H, OH), 4.71 (ddd, *J* = 31.7, 12.6, 5.2 Hz, 2H, H9), 4.59 (d, *J* = 6.0 Hz, 2H, H9), 4.59 (d, *J* = 6.0 Hz, 2H, H9), 4.08 (q, *J* = 6.9 Hz, 1H, H2), 3.65 (t, *J* = 6.9 Hz, 1H, H2), 3.65 (t, *J* = 6.9 Hz, 2H, H10), 3.52 (ddd, *J* = 18.3, 11.0, 5.7 Hz, 1H, H10), 3.46 (t, *J* = 6.9 Hz, 2H, H10), 3.44-3.38 (m, 2H, H10), 3.34-3.28 (m, 1H, H10), 2.99 (t, *J* = 10.0, 6.7 Hz, 1H, H2), 2.01-1.98 (m, 2H, H11), 1.91-1.86 (m, 2H, H11), 1.85-1.64 (m, 4H, H11), 1.41 (d, *J* = 6.9 Hz, 3H, H12). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.8 (C1), 170.3 (C1), 140.4 (C8), 140.3 (C8), 137.8 (C3), 133.9 (C3), 130.7 (C_{arom}-H), 130.4 (C_{arom}-H), 128.9 (C_{arom}-H), 128.5 (C_{arom}-H), 128.2 (C_{arom}-H), 127.7 (C_{arom}-H), 127.3 (C_{arom}-H), 126.9 (C_{arom}-H), 63.7 (C9), 63.1 (C9), 47.5 (C10), 46.3 (C10), 46.2 (C10), 46.1 (C10), 40.8 (C2), 26.2 (C11), 26.1 (C11), 24.4 (C11), 24.2 (C11), 19.7 (C12). **FTIR** (neat): 3340 (O-H st), 2979 (C-H st), 1617 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{19}NO_2Na$) requires m/z 256.1416, found m/z 256.1303.



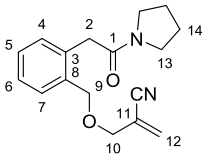
(*R*)-1-(2-benzhydrylpyrrolidin-1-yl)-2-(2-(hydroxymethyl)phenyl)ethan-1-one (28). Following the *general procedure V*, **28** (0.08 g, 0.3 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 15% yield as a yellow oil starting from 3-isochromanone (0.30 g, 4.0 mmol), (*R*)-(+)-2-(Diphenylmethyl)pyrrolidine (0.90 mL, 10.0 mmol) and Et_3N (0.84 mL, 6.0 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.51-6.99 (m, 14.3H, C_{arom}-H), 6.81-6.74 (m, 0.4H, C_{arom}-H), 5.05 (ddd, *J* = 8.0, 5.1, 3.0 Hz, 0.6H, H13), 4.83 (dd, *J* = 9.9, 6.6 Hz, 0.4H, H13), 4.64 (t, *J* = 9.0 Hz, 1H, H14), 4.42 (dt, *J* = 28.8, 14.7 Hz, 3H, H2), 3.89-3.65 (app q, *J* = 12.1 Hz, 2H, H9), 3.64-3.48 (m, 1H, H10), 3.30 (ddd, *J* = 30.3, 14.8, 9.8 Hz, 1H, H10), 2.18-1.65 (m, 4H, H11, H12). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 171.3 (C1), 170.6 (C1), 142.0 (C_{arom}), 141.8 (C_{arom}), 141.5 (C_{arom}), 140.7 (C_{arom}), 140.6 (C_{arom}), 140.5 (C_{arom}), 134.1 (C_{arom}), 134.0 (C_{arom}), 131.0 (C_{arom}), 130.8 (C_{arom}), 130.7 (C_{arom}), 130.3 (C_{arom}), 129.9 (C_{arom}), 129.3 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 128.9 (C_{arom}), 128.8 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.3 (C_{arom}), 127.2 (C_{arom}), 126.8 (C_{arom}), 126.3 (C_{arom}), 63.9 (C9), 63.6 (C9), 62.9 (C13), 60.3 (C13), 54.4 (C14), 51.4 (C14), 48.0 (C10), 45.4 (C10), 39.4 (C2), 37.5 (C2), 30.7 (C12), 27.4 (C12), 23.8 (C11), 21.3 (C11). **FTIR** (neat): 2924 (C-H st), 1745 (C=C st), 1634 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{27}NO_2Na$) requires m/z 408.2042, found m/z 408.1932.



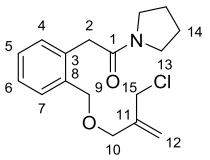
2-(2-(hydroxymethyl)phenyl)-1-((*S*)-2-methylpyrrolidin-1-yl)propan-1-one (33). Following the *general procedure V*, **33** (0.05 g, 2.0 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 49% yield as a yellow oil starting from **31** (0.30 g, 4.0 mmol), (*R*)-(+)-2-(Diphenylmethyl)pyrrolidine (0.90 mL, 10.0 mmol) and Et_3N (0.84 mL, 6.0 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.39-7.31 (m, 1.6H, C_{arom}-H), 7.31-7.15 (m, 2.4H, C_{arom}-H),

4.83-4.65 (m, 2H, H9), 4.31-3.97 (m, 2H, H12), 3.54-3.31 (m, 1H, H13), 3.07-2.91 (m, 1H, H2), 1.94-1.51 (m, 4H, H10, H11), 1.47-1.34 (m, 3H, H15), 1.24-1.17 (m, 2H, H14), 1.13 (t, *J* = 12.2 Hz, 1H, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.6 (C1), 172.5 (C1), 140.8 (C8), 140.4 (C8), 137.7 (C3), 137.4 (C3), 129.3 (C_{arom}-H), 129.1 (C_{arom}-H), 129.0 (C_{arom}-H), 128.9 (C_{arom}-H), 127.7 (C_{arom}-H), 127.5 (C_{arom}-H), 127.3 (C_{arom}-H), 127.0 (C_{arom}-H), 63.5 (C9), 63.4 (C9), 53.5 (C13), 46.2 (C10), 41.3 (C2), 41.0 (C2), 31.9 (C12), 31.7 (C12), 24.0 (C11), 23.9 (C11), 19.8 (C14), 19.7 (C14), 19.6 (C15), 18.9 (C15). **FTIR** (neat): 3385 (O-H st), 2972 (C-H st), 1619 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{21}NO_2Na$) requires m/z 270.1572, found m/z 270.1465.

General procedure W: **27-28, 32-33** (3.0 mmol, 1.0 eq) was dissolved in THF (6 mL, 0.5 *M*) and cooled to 0°C. NaH (60 wt.% in mineral oil, 6.0 mmol, 2.0 eq) was added and the resulting mixture was brought to 23°C and stirred at this temperature. After 30 minutes, the corresponding allyl bromide (6.0 mmol, 2.0 eq) was added and the reaction mixture was stirred at the same temperature for 15 hours. After this time, excess sodium hydride was carefully quenched by the addition of HCl 1 *M* (20 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL), and the organic phases were combined and subsequently dried over anhydrous Na_2SO_4. The dried solution was filtered, the filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography to afford pure **29/30/34/35a-b**.

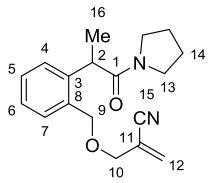


2-(((2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzyl)oxy)methyl)acrylonitrile (29a). Following the *general procedure W*, **29a** (0.02 g, 0.1 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 16% yield as a yellow oil starting from **27** (0.11 g, 0.5 mmol), NaH (0.04 g, 1.0 mmol), 2-(bromomethyl)acrylonitrile (0.15 g, 1.0 mmol) and THF (1 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.30-7.13 (m, 4H, C_{arom}-H), 5.96 (t, *J* = 4.1 Hz, 1H, H12*cis*), 5.93 (t, *J* = 1.3 Hz, 1, H12*trans*), 4.57 (s, 2H, H9), 4.02-3.99 (m, 2H, H10), 3.70 (s, 2H, H2), 3.42 (td, *J* = 6.8, 4.2 Hz, 4H, H13), 1.96- 1.86 (m, 2H, H14), 1.86-1.75 (m, 2H, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 169.2 (C1), 135.4 (C8), 134.7 (C3), 131.9 (C12), 130.5 (C_{arom}-H), 129.8 (C_{arom}-H), 128.7 (C_{arom}-H), 127.0 (C_{arom}-H), 129.5 (C11), 117.3 (C15), 71.5 (C9), 69.4 (C10), 46.9 (C13), 46.0 (C13), 39.0 (C2), 26.2 (C14), 24.5 (C14). **FTIR** (neat): 2971 (C-H st), 2872 (C-H st), 1721 (C=C st), 1630 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2O_2Na$) requires m/z 307.1325, found m/z 307.1415.

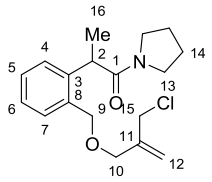


2-(2-(((2-(chloromethyl)allyl)oxy)methyl)phenyl)-1-(pyrrolidin-1-yl)ethan-1-one (29b). Following the *general procedure W*, **29b** (0.19 g, 0.6 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 40% yield as a yellow oil starting from **27** (0.31 g, 1.5 mmol), NaH (0.12 g, 3.0 mmol), 3-chloro-2-(chloromethyl)-1-propene (0.46 mL, 3.0 mmol) and THF (4 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.38-7.15 (m, 4H, C_{arom}-H), 5.30 (s, 1H, H12*cis*), 5.24 (d, *J* = 1.1 Hz, 1H, H12*trans*), 4.56 (s, 2H, H9), 4.10 (s, 2H, C10), 4.08 (s, 2H, H15), 3.75 (s, 2H, H2), 3.50 (t, *J* = 6.8 Hz, 2H, H13), 3.43 (t, *J* = 6.8 Hz, 2H, H13), 1.98-1.79 (m, 4H, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 169.5 (C1), 142.1 (C11), 136.2 (C8), 134.5 (C3), 130.1 (C_{arom}-H), 129.7 (C_{arom}-H), 128.5 (C_{arom}-H), 127.0 (C_{arom}-H), 116.9 (C12), 71.3 (C10), 70.3 (C9), 47.0 (C13), 46.1 (C13), 45.4 (C15), 39.0 (C2), 26.3 (C14), 24.5 (C14). **FTIR** (neat): 2971 (C-H st), 2873

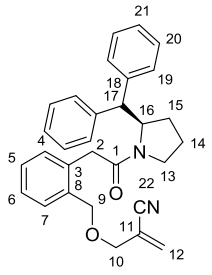
(C-H st), 1722 (C=C st), 1636 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}{}^{35}ClNO_2Na$) requires m/z 330.1339, found m/z 330.1226.



2-(((2-(1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)benzyl)oxy)methyl)acrylonitrile (34a). Following the *general procedure W*, **34a** (0.06 g, 0.2 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 10% yield as a yellow oil starting from **32** (0.43 g, 1.9 mmol), NaH (0.15 g, 3.7 mmol), 2-(bromomethyl)acrylonitrile (0.54 g, 3.7 mmol) and THF (4 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.35-7.27 (m, 3H, C_{arom} H), 7.25-7.20 (m, 1H, C_{arom}-H), 6.06 (s, 1H, H12*cis*), 6.01 (t, *J* = 1.4 Hz, 1H, H12*trans*), 4.70 (dd, *J* = 10.1, 5.6 Hz, 1H, H9), 4.57 (dd, *J* = 12.1, 3.4 Hz, 1H, H9), 4.11 (s, 2H, H10), 4.07-4.02 (m, 1H, H12), 3.58-3.47 (m, 2H, H13), 3.47-3.33 (m, 2H, H13), 1.87-1.70 (m, 4H, H14), 1.42 (d, *J* = 6.8 Hz, 3H, H16). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.4 (C1), 141.5 (C8), 133.5 (C12), 132.0 (C3), 130.3 (C_{arom}-H), 129.7 (C_{arom}-H), 127.8 (C_{arom}-H), 126.9 (C_{arom}-H), 120.5 (C11), 117.3 (C15), 71.4 (C9), 69.7 (C10), 46.3 (C13), 46.2 (C13), 40.9 (C2), 26.2 (C14), 24.3 (C14), 19.9 (C16). **FTIR** (neat): 2978 (C-H st), 1636 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2O_2Na$) requires m/z 321.1681, found m/z 321.1572.

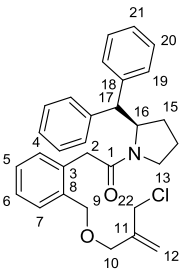


2-(2-(((2-(chloromethyl)allyl)oxy)methyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (34b). Following the *general procedure W*, **34b** (0.12 g, 0.4 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 21% yield as a yellow oil starting from **32** (0.43 g, 1.8 mmol), NaH (0.09 g, 3.7 mmol), 3-chloro-2-(chloromethyl)-1-propene (0.43 mL, 3.7 mmol) and THF (4 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.34 (dd, *J* = 7.7, 1.0 Hz, 1H, C_{arom}-H), 7.26 (ddd, *J* = 7.6, 7.0, 1.3 Hz, 2H, C_{arom}-H), 7.19 (td, *J* = 7.4, 1.3 Hz, 1H, C_{arom}-H), 5.29 (d, *J* = 0.7 Hz, 1H, H12*cis*), 5.22 (d, *J* = 1.2 Hz, 1H, H12*trans*) 4.62 (d, *J* = 11.6 Hz, 1H, H9), 4.50 (d, *J* = 11.6 Hz, 1H, H9), 4.12-4.06 (m, 4H, H10,15), 4.03 (q, *J* = 6.8 Hz, 1H, H2), 3.55-3.46 (m, 1H, H13), 3.46-3.31 (m, 2H, H13), 2.95-2.87 (m, 1H, H13), 1.84-1.63 (m, 4H, H14), 1.39 (d, *J* = 6.8 Hz, 3H, H16). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.5 (C1), 141.9 (C8), 141.2 (C3), 134.0 (C11), 130.0 (C_{arom}-H), 129.1 (C_{arom}-H), 127.3 (C_{arom}-H), 126.7 (C_{arom}-H), 116.9 (C12), 70.9 (C10), 70.4 (C9), 46.2 (C13), 46.0 (C13), 45.3 (C15), 40.7 (C2), 26.1 (C14), 24.2 (C14), 19.9 (C16). **FTIR** (neat): 2973 (C-H st), 2872 (C-H st), 1636 (C=O st), 1080 (C-Cl st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{24}{}^{35}ClNO_2$) requires m/z 344.1496, found m/z 344.1388.

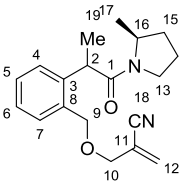


(*R*)-2-(((2-(2-(2-benzhydrylpyrrolidin-1-yl)-2-oxoethyl)benzyl)oxy)methyl)acrylonitrile (30a). Following the *general procedure W*, **30a** (0.04 g, 0.1 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 47% yield as a yellow oil starting from **28** (0.08 g, 0.2 mmol), NaH (0.02 g, 0.4 mmol), 2-(bromomethyl)acrylonitrile (0.06 g, 0.4 mmol) and THF (1 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.33-6.96 (m, 22H, C_{arom}-H), 5.94 (s, 1H, H12*cis*), 5.90 (td, *J* = 6.7, 3.4 Hz, 1H, H12*trans*), 5.01 (dt, *J* = 12.9, 3.7 Hz, 1H, H17), 4.66-4.52 (m, 1H, H16), 4.51-4-43 (m, 2H, H10), 4.42-4.26 (m, 2H, H2), 4.00-3.91 (m, 2H, H13), 3.63 (app q, *J* = 29.0, 14.3 Hz, 2H, H9), 2.02-1.62 (m, 4H, H15, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.1 (C1), 169.6 (C1), 142.3 (C_{arom}), 142.1 (C_{arom}),

141.9 (C_{arom}), 141.8 (C_{arom}), 140.9 (C_{arom}), 136.5 (C_{arom}), 135.4 (C_{arom}), 135.3 (C_{arom}), 134.8 (C_{arom}), 134.7 (C_{arom}), 131.9 (C12), 131.8 (C12), 130.8 (C_{arom}), 130.7 (C_{arom}), 130.5 (C_{arom}), 129.9 (C_{arom}), 129.9 (C_{arom}), 129.6 (C_{arom}), 129.3 (C_{arom}), 129.3 (C_{arom}), 129.1 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.8 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 128.1 (C_{arom}), 127.1 (C_{arom}), 127.1 (C_{arom}), 127.1 (C_{arom}), 126.9 (C_{arom}), 126.7 (C_{arom}), 126.3 (C_{arom}), 120.7 (C11), 117.4 (C22), 71.6 (C10), 71.3 (C10), 69.4 (C9), 69.2 (C9), 62.4 (C16), 60.1 (C16), 54.3 (C17), 52.4 (C17), 47.2 (C13), 45.1 (C13), 39.3 (C2), 37.5 (C2), 30.6 (C15), 27.8 (C15), 23.7 (C14), 21.4 (C14). **FTIR** (neat): 2924 (C-H st), 1743 (C=C st), 1638 (C=C st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{30}H_{30}N_2O_2Na$) requires m/z 473.2307, found m/z 473.2193.

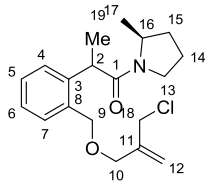


(*R*)-1-(2-benzhydrylpyrrolidin-1-yl)-2-(2-(((2-(chloromethyl)allyl)oxy)methyl)phenyl)ethan-1-one (30b). Following the *general procedure W*, **30b** (0.24 g, 0.5 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 53% yield as a yellow oil starting from **28** (0.37 g, 0.9 mmol), NaH (0.08 g, 1.9 mmol), 3-chloro-2-(chloromethyl)-1-propene (0.22 mL, 1.9 mmol) and THF (2 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.39-7.13 (m, 22H, C_{arom}-H), 7.09-7.03 (m, 1H, C_{arom}-H), 6.91-6.83 (m, 1H, C_{arom}-H), 5.32- 5.29 (m, 1H, H12*cis*), 5.24 (d, *J* = 1.4 Hz, 1H, H12*trans*), 5.11 (ddd, *J* = 8.2, 5.9, 2.8 Hz, 1H, H16), 4.58 (d, *J* = 6.0 Hz, 1H, H17), 4.52 (app q, *J* = 11.4 Hz, 2H, H9), 4.11 (s, 2H, H22), 4.06 (s, 2H, H10), 3.70 (d, *J* = 3.9 Hz, 2H, H2), 3.43 (dt, *J* = 10.2, 8.0 Hz, 1H, H13), 3.18 (ddd, *J* = 10.1, 8.8, 4.1 Hz, 1H, H13), 2.01-1.77 (m, 4H, H14, H15). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.3 (C1), 169.8 (C1), 142.3 (C_{arom}), 142.2 (C_{arom}), 142.1 (C_{arom}), 141.8 (C_{arom}), 140.9 (C_{arom}), 136.2 (C_{arom}), 136.0 (C_{arom}), 134.6 (C_{arom}), 134.5 (C_{arom}), 130.4 (C_{arom}), 130.0 (C_{arom}), 129.8 (C_{arom}), 129.6 (C_{arom}), 129.2 (C_{arom}), 129.2 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 127.1 (C_{arom}), 127.1 (C_{arom}), 127.0 (C_{arom}), 126.8 (C_{arom}), 126.7 (C_{arom}), 126.2 (C_{arom}), 116.9 (C12), 116.8 (C12), 71.2 (C10), 70.8 (C10), 70.2 (C9), 70.1 (C9), 62.4 (C16), 60.5 (C16), 54.3 (C17), 52.4 (C17), 47.6 (C13), 45.4 (C22), 45.1 (C13), 39.2 (C2), 37.4 (C2), 30.5 (C15), 27.7 (C15), 23.8 (C14), 21.4 (C14). **FTIR** (neat): 2983 (C-H st), 1638 (C=C st), 1078 (C-Cl st) cm^{-1}. **HRMS** (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{30}H_{32}{}^{35}ClNO_2Na$) requires m/z 496.2122, found m/z 496.2010.

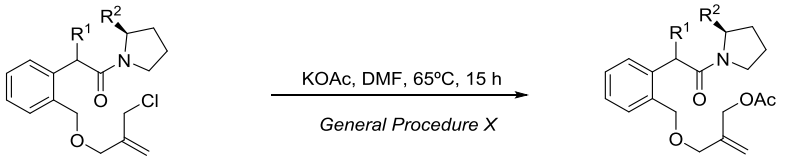


2-(((2-(1-((*S*)-2-methylpyrrolidin-1-yl)-1-oxopropan-2-yl)benzyl)oxy)methyl)acrylonitrile (35a). Following the *general procedure W*, **35a** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 26% yield as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.80-7.74 (m, 0.3H, C_{arom}-H), 7.59-7.18 (m, 4.5H, C_{arom}-H), 6.08-6.04 (m, 1H, H12*cis*), 6.03-5.98 (m, 1H, H12*trans*), 4.69 (dt, *J* = 15.8, 7.9 Hz, 1H, H9), 4.55 (dd, *J* = 11.6, 2.8 Hz, 1H, H9), 4.28-4.14 (m, 1.5H, H13), 4.13-4.20 (m, 1H, H10), 4.10-4.06 (m, 1H, H10), 3.58-3.33 (m, 1.5H, H13, H2), 3.09-2.87 (m, 1H, H16), 1.96-1.73 (m, 3H, H14, H15), 1.53-1.46 (m, 1H, H15), 1.45-1.35 (m, 3H, H19), 1.23-1.20 (m, 1.5H, H17), 1.15-1.09 (m, 1.5H, H17). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.1 (C1), 172.0 (C1), 144.4 (C8), 143.8 (C8), 142.2 (C3), 141.8 (C12), 141.7 (C3), 141.4 (C12), 135.1 (C_{arom}-H), 134.9 (C_{arom}-H), 134.5 (C_{arom}-H), 134.5 (C_{arom}-H), 133.5 (C_{arom}-H), 133.5 (C_{arom}-H), 132.0 (C_{arom}-H), 131.9 (C_{arom}-H), 130.3 (C_{arom}-H), 130.2 (C_{arom}-H), 129.6 (C_{arom}-H), 129.6 (C_{arom}-H), 128.6 (C_{arom}-H), 128.5 (C_{arom}-H), 127.6

(C_{arom}-H), 127.4 (C_{arom}-H), 127.2 (C_{arom}-H), 126.8 (C_{arom}-H), 120.4 (C11), 117.2 (C18), 117.2 (C18), 71.4 (C9), 71.3 (C9), 69.7 (C10), 69.6 (C10), 62.6 (C16), 53.4 (C13), 53.1 (C13), 46.4 (C2), 46.2 (C2), 41.1 (C15), 40.9 (C15), 24.0 (C14), 24.0 (C14), 19.9 (C17), 19.7 (C17), 18.9 (C19). **FTIR** (neat): 2970 (C-H st), 2871 (C-H st), 1692 (C=O st), 1630 (C=C st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{24}N_2O_2Na$) requires m/z 335.1838, found m/z 335.1731.

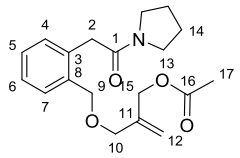


2-(2-(((2-(chloromethyl)allyl)oxy)methyl)phenyl)-1-((*S*)-2-methylpyrrolidin-1-yl)propan-1-one (35b). Following the *general procedure W*, **35b** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 26% yield as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.50-7.05 (m, 4H, C_{arom}-H), 5.37-5.18 (m, 2H, H12), 4.68-4.58 (m, 1H, H9), 4.53-4.45 (m, 1H, H9), 4.30-4.14 (m, 1H, H10), 4.14-4.06 (m, 3H, H10, H18), 4.05-3.94 (m, 0.7H, H13), 3.59-3.30 (m, 1.2H, H13), 2.98-2.84 (m, 1H, H2), 1.96-1.53 (m, 4H, H14, H15), 1.44-1.34 (m, 3H, H19), 1.23-1.18 (m, 1.6H, H17), 1.18-1.14 (m, 0.4H, H17), 1.12 (d, *J* = 6.3 Hz, 1H, H17). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.2 (C1), 172.1 (C1), 160.7 (C11), 141.9 (C8), 141.6 (C8), 134.4 (C3), 134.4 (C3), 130.0 (C_{arom}-H), 129.9 (C_{arom}-H), 129.2 (C_{arom}-H), 129.2 (C_{arom}-H), 127.2 (C_{arom}-H), 127.1 (C_{arom}-H), 126.7 (C_{arom}-H), 126.7 (C_{arom}-H), 116.9 (C12), 71.0 (C10), 70.9 (C10), 70.5 (C9), 70.4 (C9), 63.6 (C16), 63.5 (C16), 53.4 (C13), 53.1 (C13), 46.3 (C18), 46.1 (C18), 41.0 (C2), 40.8 (C2), 31.9 (C15), 31.7 (C15), 24.0 (C14), 23.9 (C14), 19.9 (C17), 19.8 (C17), 19.7 (C19), 18.9 (C19). **FTIR** (neat): 2972 (C-H st), 2872 (C-H st), 1720 (C=C st), 1618 (C=C st), 1085 (C-Cl st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{26}{}^{35}ClNO_2Na$) requires m/z 358.1652, found m/z 358.1545.

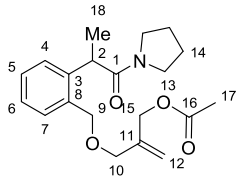


29/30/34/35b **29c/30c/34c/35c**

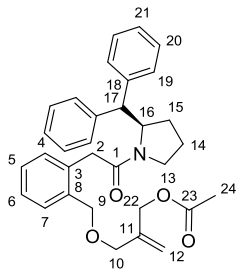
General procedure X: To a solution of **29/30/34/35b** (1.0 mmol, 1.0 eq) in DMF (2.5 mL, 0.4 *M*) KOAc (1.1 mmol, 1.1 eq) was added and the solution was stirred at 65°C for 15 hours. After that time, the reaction was quenched with H_2O (10 mL) and it was diluted with Et_2O (10 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography to afford **29c/30c/34c/35c**.



2-(((2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzyl)oxy)methyl)allyl acetate (29c). Following the *general procedure X*, **29c** (0.07 g, 0.2 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 71% yield as a yellow oil starting from **29b** (0.96 g, 0.3 mmol), KOAc (0.03 g, 0.3 mmol) and DMF (1 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.33-7.17 (m, 4H, C_{arom}-H), 5.25-5.14 (m, 2H, H12), 4.59 (s, 2H, H9), 4.53 (s, 2H, H15), 3.98 (s, 2H, H10), 3.72 (s, 2H, H2), 3.48 (t, *J* = 6.8 Hz, 2H, H13), 3.41 (t, *J* = 6.8 Hz, 2H, H13), 2.04 (s, 3H, H17), 1.98-1.76 (m, 4H, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.7 (C16), 169.4 (C1), 140.7 (C11), 136.2 (C8), 134.5 (C3), 130.0 (C_{arom}-H), 129.6 (C_{arom}-H), 128.3 (C_{arom}-H), 126.9 (C_{arom}-H), 115.2 (C12), 71.0 (C10), 70.7 (C9), 64.7 (C15), 46.9 (C13), 46.0 (C13), 38.9 (C2), 26.2 (C14), 24.5 (C14), 20.9 (C17). **FTIR** (neat): 2982 (C-H st), 1738 (C=O st), 1637 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{25}NO_4Na$) requires m/z 354.1784, found m/z 354.1680.

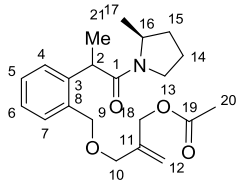


2-(((2-(1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)benzyl)oxy)methyl)allyl acetate (34c). Following the *general procedure X*, **34c** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 9% yield (over 3 steps) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.36-7.33 (m, 1H, C_{arom}-H), 7.30-7.24 (m, 2H, C_{arom}-H), 7.20 (td, *J* = 7.4, 1.2 Hz, 1H, C_{arom}-H), 5.23 (s, 2H, H12), 4.64-4.59 (m, 3H, H9, H10) 4.50 (d, *J* = 11.7 Hz, 1H, H9), 4.08-3.99 (m, 3H, H2, H10), 3.55- 3.49 (m, 1H, H13), 3.46-3.33 (m, 2H, H13), 2.94-2.88 (m, 1H, H13), 2.07 (s, 3H, H17), 1.87-1.64 (m, 4H, H14), 1.40 (d, *J* = 6.9 Hz, 3H, H18). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.5 (C1), 141.3 (C8), 140.6 (C3), 134.4 (C11), 130.1 (C_{arom}-H), 129.2 (C_{arom}-H), 127.4 (C_{arom}-H), 126.7 (C_{arom}-H), 115.4 (C12), 71.0 (C10), 70.7 (C9), 64.7 (C15), 46.2 (C13), 46.1 (C13), 40.8 (C2), 26.1 (C14), 24.2 (C14), 21.0 (C17), 19.9 (C18). **FTIR** (neat): 2974 (C-H st), 2873 (C-H st), 1748 (C=O st), 1687 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{27}NO_4Na$) requires m/z 368.1940, found m/z 368.1828.

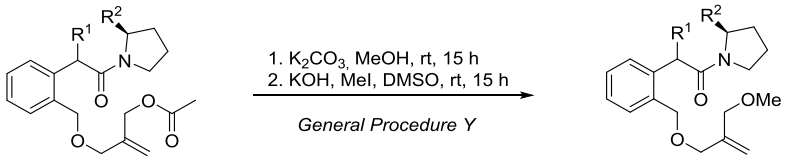


(*R*)-2-(((2-(2-(2-benzhydrylpyrrolidin-1-yl)-2-oxoethyl)benzyl)oxy)methyl)allyl acetate (30c). Following the *general procedure X*, **30c** (0.08 g, 0.2 mmol) was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 71% yield as a yellow oil starting from **30b** (0.11 g, 0.2 mmol), KOAc (0.03 g, 0.3 mmol) and DMF (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.41-7.11 (m, 22H, C_{arom}-H), 7.08-7.02 (m, 1H, C_{arom}-H), 6.92-6.81 (m, 0.6H, C_{arom}-H), 5.26-5.20 (m, 2H, H12), 5.11 (ddd, *J* = 8.2, 6.0, 2.8 Hz, 1H, H16), 4.64-4.58 (m, 2H, H22), 4.58 (d, *J* = 6.0 Hz, 1H, H17), 4.45 (app q, *J* = 12.9 Hz, 2H, H9), 3.99 (s, 2H, H10), 3.90 (d, *J* = 4.3 Hz, 2H, H2), 3.49-3.13 (m, 2H, H13), 2.06 (d, *J* = 3.2 Hz, 3H, H24), 2.04-1.83 (m, 4H, H14, H15). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 170.7 (C23), 170.3 (C23), 169.8 (C1), 169.2 (C1), 142.3 (C11), 142.2 (C11), 140.9 (C_{arom}), 140.8 (C_{arom}), 136.2 (C_{arom}), 136.0 (C_{arom}), 134.5 (C_{arom}), 134.4 (C_{arom}), 130.3 (C_{arom}), 130.3 (C_{arom}), 130.0 (C_{arom}), 129.7 (C_{arom}), 129.6 (C_{arom}), 129.2 (C_{arom}), 129.2 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 128.9 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.3 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 127.2 (C_{arom}), 127.1 (C_{arom}), 127.0 (C_{arom}), 126.9 (C_{arom}), 126.7 (C_{arom}), 126.2 (C_{arom}), 115.4 (C12), 115.3 (C12), 70.9 (C10), 70.6 (C10), 70.6 (C9), 70.5 (C9), 64.8 (C16), 62.4 (C22), 60.0 (C22), 54.3 (C17), 52.3 (C17), 47.1 (C13), 45.1 (C13), 39.2 (C2), 37.5 (C2), 30.6 (C15), 30.2 (C15), 27.7

(C14), 23.7 (C14), 21.4 (C24), 21.1 (C24. **FTIR** (neat): 2980 (C-H st), 1739 (C=O st), 1640 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{32}H_{35}NO_4Na$) requires m/z 520.2566, found m/z 520.2469.

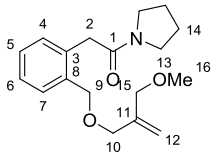


2-(((2-(1-((*S*)-2-methylpyrrolidin-1-yl)-1-oxopropan-2-yl)benzyl)oxy)methyl)allyl acetate (35c). Following the *general procedure X*, **35c** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 18% yield (over 3 steps) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.49-7.13 (m, 4H, C_{arom}-H), 5.21 (s, 2H, H12), 4.63-4.57 (m, 3H, H18, H19), 4.50-4.44 (m, 1H, H9), 4.27-4.12 (m, 1H, H10), 4.09-3.92 (m, 3H, H10, H13), 3.45-3.30 (m, 1H, H16), 2.96-2.86 (m, 1H, H2), 1.94-1.42 (m, 4H, H14, H15), 1.38 (td, *J* = 8.8, 4.4 Hz, 3H, H21), 1.20 (d, *J* = 6.4 Hz, 1.6 H, H17), 1.14 (d, *J* = 6.4 Hz, 0.4H, H17), 1.11 (d, *J* = 6.4 Hz, 1H, H17). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.1 (C1), 170.7 (C19), 141.2 (C11), 140.6 (C11), 130.2 (C_{arom}), 130.1 (C_{arom}), 130.0 (C_{arom}), 130.0 (C_{arom}), 129.2 (C_{arom}), 129.1 (C_{arom}), 129.0 (C_{arom}), 127.2 (C_{arom}), 127.1 (C_{arom}), 127.1 (C_{arom}), 126.7 (C_{arom}), 115.3 (C12), 71.0 (C10), 70.9 (C10), 70.7 (C9), 70.6 (C9), 64.7 (C18), 64.7 (C18), 53.3 (C16), 53.0 (C16), 46.3 (C13), 46.1 (C13), 41.0 (C2), 40.8 (C2), 31.9 (C15), 31.7 (C15), 24.0 (C14), 23.9 (C14), 20.9 (C20), 19.9 (C17), 19.7 (C17), 19.6 (C21), 18.8 (C21). **FTIR** (neat): 2970 (C-H st), 2871 (C-H st), 1740 (C=O st), 1637 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}NO_4Na$) requires m/z 382.2097, found m/z 382.1988.

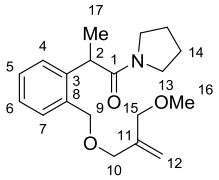


29c/34c/35b **29d/34d/35d**

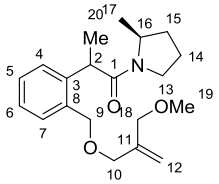
General procedure Y: To a solution of **29c/30c/34c/35c** (0.5 mmol, 1.0 eq) in MeOH (2.5 mL, 0.2 *M*) a solution of K_2CO_3 (0.5 mmol, 1.0 eq) in water (0.3 mL, 1.7 *M*) was added. The mixture was stirred at room temperature for 15 hours before being quenched by the addition of saturated aqueous NH_4Cl (10 mL). The solution was then extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was added to a stirred solution of powdered KOH (2.0 mmol, 4.0 eq) in DMSO (1 mL, 0.5 *M*), followed by iodomethane (1.0 mmol, 2.0 eq). The reaction mixture was stirred at room temperature for 15 hours before being quenched with a saturated aqueous solution of NH_4Cl (10 mL). Aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with H_2O (2 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel to afford pure **29d/34d/35d**.



2-(2-(((2-(methoxymethyl)allyl)oxy)methyl)phenyl)-1-(pyrrolidin-1-yl)ethan-1-one (29d). Following the *general procedure Y*, **29d** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 5% yield (over 5 steps) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.40-7.14 (m, 4H, C_{arom}-H), 5.23-5.16 (m, 2H, H12), 4.54 (s, 2H, H9), 3.99 (s, 2H, H15), 3.93 (s, 2H, H10), 3.75 (s, 2H, H2), 3.50 (t, *J* = 6.8 Hz, 2H, H13), 3.42 (t, *J* = 6.8 Hz, 2H, H13), 3.32 (s, 3H, H16), 1.99-1.77 (m, 4H, H14). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 169.4 (C1), 142.6 (C11), 136.3 (C8), 134.4 (C3), 129.8 (C_{arom}-H), 129.5 (C_{arom}-H), 128.3 (C_{arom}-H), 126.8 (C_{arom}-H), 114.0 (C12), 73.4 (C15), 71.0 (C10), 70.7 (C9), 58.1 (C16), 46.8 (C13), 45.9 (C13), 38.8 (C2), 26.2 (C14), 24.4 (C14). **FTIR** (neat): 2872 (C-H st), 1720 (C=O st), 1633 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NO_3Na$) requires m/z 326.1834, found m/z 326.1726.

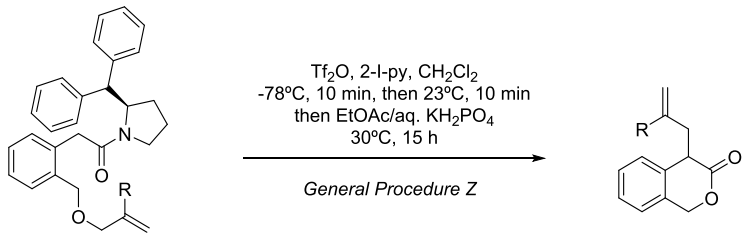


2-(2-(((2-(methoxymethyl)allyl)oxy)methyl)phenyl)-1-(pyrrolidin-1-yl)propan-1-one (34d). Following the *general procedure Y*, **34d** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 10% yield (over 5 steps) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.34 (d, *J* = 7.7 Hz, 1H, C_{arom}-H), 7.30-7.24 (m, 2H, C_{arom}-H), 7.19 (t, *J* = 7.4 Hz, 1H, C_{arom}-H), 5.19 (s, 2H, H12), 4.62 (d, *J* = 11.6 Hz, 1H, H9), 4.51 (d, *J* = 11.6 Hz, 1H, H9), 4.08-3.99 (m, 3H, H2,15), 3.93 (s, 2H, H10), 3.55-3.49 (m, 1H, H13), 3.45-3.36 (m, 2H, H13), 3.32 (s, 3H, H16), 2.91 (dt, *J* = 10.3, 6.5 Hz, 1H, H13), 1.84-1.63 (m, 4H, H14), 1.39 (d, *J* = 6.9 Hz, 3H, H17). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.6 (C1), 142.5 (C8), 141.3 (C3), 134.6 (C11), 130.0 (C_{arom}-H), 129.1 (C_{arom}-H), 127.3 (C_{arom}-H), 126.7 (C_{arom}-H), 114.3 (C12), 73.5 (C15), 71.0 (C10), 70.8 (C9), 58.2 (C16), 46.2 (C13), 46.1 (C13), 40.7 (C2), 26.1 (C14), 24.2 (C14), 19.9 (C17). **FTIR** (neat): 2973 (C-H st), 2929 (C-H st), 1635 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{27}NO_3Na$) requires m/z 340.1991, found m/z 340.1885.



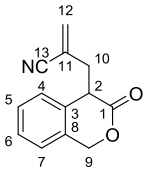
2-(2-(((2-(methoxymethyl)allyl)oxy)methyl)phenyl)-1-((*S*)-2-methylpyrrolidin-1-yl)propan-1-one (35d). Following the *general procedure Y*, **35d** was isolated by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 11% yield (over 5 steps) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.42-7.16 (m, 4H, C_{arom}-H), 5.20 (s, 2H, H12), 4.67-4.59 (m, 1H, H9), 4.51 (t, *J* = 8.4 Hz, 1H, H9), 4.31-4.16 (m, 1H, H10), 4.08-3.98 (m, 3H, H18, H10), 3.94 (s, 2H, H13), 3.48-3.38 (m, 1H, H16), 3.33 (s, 3H, H19), 2.97-2.87 (m, 1H, H2), 1.97-1.69 (m, 3H, H15, H14), 1.67-1.53 (m, 1H, H14), 1.43-1.35 (m, 3H, H20), 1.22 (d, *J* = 6.4 Hz, 1.6 H, H17), 1.17 (d, *J* = 6.4 Hz, 0.4H, H17), 1.13 (d, *J* = 6.3 Hz, 1H, H17). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.3 (C1), 172.2 (C1), 142.5 (C11), 141.7 (C8), 141.2 (C8), 134.7 (C3), 134.6 (C3), 130.0 (C_{arom}-H), 130.0 (C_{arom}-H), 129.1 (C_{arom}-H), 129.0 (C_{arom}-H), 127.1 (C_{arom}-H), 127.0 (C_{arom}-H), 126.7 (C_{arom}-H), 126.7 (C_{arom}-H), 114.3 (C12), 73.5 (C18), 71.1 (C10), 71.0 (C10), 70.8 (C9), 70.8 (C9), 58.2 (C19), 53.4 (C16), 53.0 (C16), 46.3 (C13), 46.1 (C13), 41.0 (C2), 40.8 (C2), 32.0 (C15), 31.8 (C15), 24.0 (C14), 23.9 (C14), 20.0 (C17), 19.8 (C17), 19.7 (C20), 18.9 (C20). **FTIR** (neat): 2978 (C-H st), 1639 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{29}NO_3Na$) requires m/z 354.2147, found m/z 354.2040.

4.2. Synthesis of α-chiral isochromanones

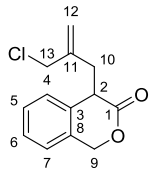


30a-c **36a-c**

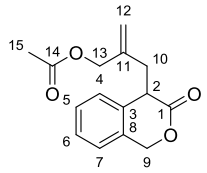
General procedure Z: A flame-dried Schlenk flask containing a solution of amide **30a-c** (0.1 mmol, 1.0 eq) and 2-iodopyridine (0.2 mmol, 2.0 eq) in CH_2Cl_2 (0.5 mL, 0.2 *M*) was cooled to -78°C. To the cooled mixture, triflic anhydride (0.105 mmol, 1.05 eq) was added dropwise and the resulting solution was subsequently stirred at the same temperature for 10 min. After this time, the flask was brought to room temperature (23°C) and kept at this temperature for another 10 min, before EtOAc was added. The resulting solution was treated with a saturated aqueous solution of NH_4Cl (3 mL), the phases were separated and the organic phase was washed once more with a saturated aqueous solution of NH_4Cl (3 mL). The washed solution was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was redissolved in a mixture of EtOAc and a saturated aqueous solution of KH_2PO_4 (3 mL/1 mL, 0.025 *M*). The biphasic resulting mixture was stirred vigorously at 30°C for 15 hours, after which the phases were separated and the organic phase was washed twice with HCl 1 *M* (2 x 5 mL). The washed solution was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford pure isochromanones **36a-c**.



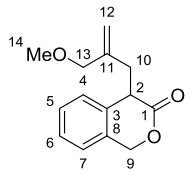
2-((3-oxoisochroman-4-yl)methyl)acrylonitrile (36a). Following the *general procedure Z*, **36a** was isolated (7.00 mg, 0.030 mmol) by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 30% yield as a yellow oil starting from **30a** (45.00 mg, 0.100 mmol), 2-iodopyridine (0.020 mL, 0.200 mmol), Tf_2O (0.02 mL, 0.100 mmol) and CH_2Cl_2 (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.43-7.32 (m, 2H, C_{arom}-H), 7.30-7.26 (m, 2H, C_{arom}-H), 6.03 (d, *J* = 1.0 Hz, 1H, H12*cis*), 5.88 (t, *J* = 1.5 Hz, 1H, H12*trans*), 5.38 (s, 2H, H9), 3.91 (t, *J* = 7.0 Hz, 1H, H2), 3.10 (ddt, *J* = 15.0, 6.7, 1.2 Hz, 1H, H10), 2.91 (ddt, *J* = 14.7, 7.2, 1.2 Hz, 1H, H10). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 171.0 (C1), 133.7 (C8), 132.6 (C3), 131.9 (C12), 129.2 (C_{arom}-H), 128.1 (C_{arom}-H), 125.7 (C_{arom}-H), 125.3 (C_{arom}-H), 119.9 (C11), 118.0 (C13), 69.7 (C9), 43.5 (C2), 33.7 (C10). **FTIR (**neat): 2921 (C-H st), 1742 (C=O st) cm^{-1}. **HRMS** (ESI^+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{11}NO_2Na$) requires m/z 236.0790, found m/z 236.0682.



4-(2-(chloromethyl)allyl)isochroman-3-one (36b). Following the *general procedure Z*, **36b** was isolated (3.00 mg g, 0.010 mmol) by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 20% yield as a yellow oil starting from **30b** (30.00 mg, 0.060 mmol), 2-iodopyridine (0.013 mL, 0.100 mmol), Tf_2O (0.011 mL, 0.060 mmol) and CH_2Cl_2 (0.3 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.34 (tdt, *J* = 17.4, 7.4, 1.6 Hz, 2H, C_{arom}-H), 7.28-7.22 (m, 2H, C_{arom}-H), 5.44 (d, *J* = 14.1 Hz, H1, H9), 5.33 (d, *J* = 14.1 Hz, H1, H9), 5.28 (s, 1H, H12*cis*), 4.98 (s, 1H, H12*trans*), 4.13 (qd, *J* = 11.9, 1.0 Hz, 2H, H13), 3.87 (t, *J* = 7.3 Hz, 1H, H2), 2.92 (ddd, *J* = 15.6, 7.1, 1.2 Hz, 1H, H10), 2.83 (ddt, *J* = 15.7, 7.7, 1.1 Hz, H10). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 171.9 (C1), 141.5 (C11), 134.1 (C8), 131.6 (C3), 129.0 (C_{arom}), 127.6 (C_{arom}), 126.6 (C_{arom}), 124.9 (C_{arom}), 117.5 (C12), 69.7 (C9), 48.3 (C13), 44.1 (C2), 33.1 (C10). **FTIR** (neat): 2925 (C-H st), 1740 (C=O st), 1646 (C=C st), 1031 (C-Cl st) cm^{-1}. **HRMS** (ESI$^+$) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{13}{}^{35}ClO_2Na$) requires m/z 259.0604, found m/z 259.0499.



2-((3-oxoisochroman-4-yl)methyl)allyl acetate (36c). Following the *general procedure Z*, **36c** was isolated (10.00 mg, 0.036 mmol) by FC (heptane/EtOAc gradient from 7:3 to 1:1) in 36% yield as a yellow oil starting from **30c** (0.050 g, 0.100 mmol), 2-iodopyridine (0.020 mL, 0.200 mmol), Tf_2O (0.018 mL, 0.1 mmol) and CH_2Cl_2 (0.5 mL). **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.38-7.28 (m, 2H, C_{arom}-H), 7.25-7.19 (m, 2H, C_{arom}-H), 5.43 (d, *J* = 14.0 Hz, 1H, H9), 5.31 (d, *J* = 14.0 Hz, 1H, H9), 5.19 (td, *J* = 1.4, 0.7 Hz, 1H, H12*cis*), 4.93 (td, *J* = 1.4, 0.7 Hz, 1H, H12*trans*), 4.59 (q, *J* = 13.2 Hz, 2H, H13), 3.85 (dd, *J* = 8.2, 6.1 Hz, 1H, H2), 2.88 (ddd, *J* = 15.7, 6.4, 1.2 Hz, 1H, H10), 2.76- 2.56 (m, 1H, H10), 2.09 (s, 3H, H15). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.1 (C14), 170.8 (C1), 140.1 (C11), 134.1 (C8), 131.6 (C3), 128.9 (C_{arom}-H), 127.6 (C_{arom}-H), 126.8 (C_{arom}-H), 124.9 (C_{arom}-H), 116.1 (C12), 69.7 (C9), 66.9 (C13), 44.2 (C2), 33.3 (C10), 21.0 (C15). **FTIR** (neat): 2926 (C-H st), 1733 (C=O st), 1654 (C=C st) cm^{-1}. **HRMS** (ESI$^+$) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}O_4Na$) requires m/z 283.1049, found m/z 283.0939.



4-(2-(methoxymethyl)allyl)isochroman-3-one (36d).[24] **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm): 7.32 (dqd, *J* = 9.0, 7.3, 1.6 Hz, 2H, C_{arom}-H), 7.26-7.20 (m, 2H, C_{arom}-H), 5.44 (d, *J* = 14.1 Hz, 1H, H9), 5.30 (d, *J* = 14.1 Hz, 1H, H9), 5.15 (dt, *J* = 1.5, 0.8 Hz, 1H, H12*cis*), 4.91 (q, *J* = 1.0 Hz, 1H, H12*trans*), 4.00-3.78 (m, 3H, H2, H13), 3.32 (s, 3H, H14), 2.93-2.75 (m, 1H, H10), 2.75-2.56 (m, 1H, H10). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm): 172.3 (C1), 142.2 (C11), 134.5 (C8), 131.6 (C3), 128.8 (C_{arom}-H), 127.4 (C_{arom}-H), 126.8 (C_{arom}-H), 124.8 (C_{arom}-H), 115.1 (C12), 75.6 (C13), 69.7 (C9), 58.2 (C14), 44.4 (C2), 33.3 (C10). **FTIR** (neat): 2922 (C-H st), 1738 (C=O st) cm^{-1}. **HRMS** (ESI$^+$) exact mass calculated for [M+Na]+ ($C_{14}H_{16}O_3Na$) requires m/z 255.1099, found m/z 255.0990.

[24] The yield of the reaction with racemic substrate was 50%.

Appendix

Abbreviations, acronyms and symbols[1]

acac$^-$	Acetylacetonate anion
Ac	Acetyl group
Ar	Aryl group
ATR	Attenuated total reflectance
BA	Brønsted acid
BB	Brønsted base
BI-DIME	(*S*)-3-(*tert*-Butyl)-4-(2,6-dimethoxyphenyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole
BINOL	1,1'-Binaphthalene-2,2'-diol
Boc	*tert*-Butyloxycarbonyl
BSA	*N*,*O*-Bis(trimethylsilyl)-acetamide
c	Concentration (measured in g/100 mL)
C_{arom}	Aromatic carbon
cat	Cathecol
Cat.	Catalyst
CBz	Benzyloxycarbonyl
COD	Cyclooctadiene
Conv.	Conversion
D-A	Donor-acceptor
dab	1,2-diaminobenzene
dan	1,8-diaminonaphtalene
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dcpe	Bis(dicyclohexylphosphino)ethane
DFT	Density functional theory
DIBAL	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMP	Dess-Martin periodinane
dppf	1,1´-bis(diphenylphosphino)ferrocene
d.r.	Diastereomeric ratio
DVCPR	Divinylcyclopropane-cycloheptadiene rearrangement

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

E	Electrophile
EDG	Electron-donating group
e.e.	Enantiomeric excess
Ent.	Enantiomer
Eq	Equivalent
EWG	Electron-withdrawing group
FC	Flash column chromatography
Fmoc	9-Fluorenylmethoxycarbonyl
gem	Geminal
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
IBX	2-Iodoxybenzoic acid
IL	Ionic liquid
IPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
J	Coupling constant
L	Ligand
LA	Lewis acid
LB	Lewis base
LDA	Lithium diisopropylamide
LNO	2,6-lutidine *N*-oxide
LUMO	Lowest Unoccupied Molecular Orbital
HDMS	Hexamethyldisilazane
hex	Hexyleneglycolato
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
M	Metal
MBH	Morita-Baylis-Hillman
***m*CPBA**	*meta*-chloroperbenzoic acid
mentimid	1-methyl-3-(+)-methylmenthoxide imidazolidene
Mes	1,3,5-trimethylbenzene
M.p.	Melting point
MS	Mass spectrometry
M.S.	Molecular sieves
nbd	Norbornadiene
***n*Bu**	*n*-butyl

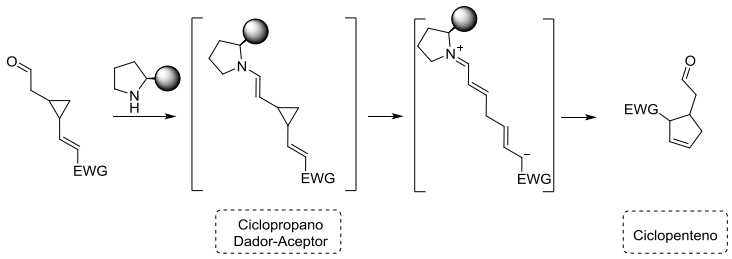
n.d.	Not determined
neop	Neopentylglycolato
NHC	*N*-heterocyclic carbene
n.r.	No reaction
Nu	Nucleophile
***o*-QMs**	*Ortho*-quinone methides
PCC	Pyridinium chlorochromate
PDIPA	Diisopropanolaminato diboron
PG	Protecting group
Pin	Pinacol
PMP	*para*-Methoxyphenyl group
***p*-TSA**	*p*-toluenesulfonic acid
py	Pyridine
QUINAP	1-(2-Diphenylphosphino-1-naphtyl)isoquinoline
pyr	Pyridine
QTOF	Quadrupole-time of flight
R	Alkyl group or substituent
r.r.	Regioisomer ratio
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TFDA	Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)-acetate
Tf	Trifluoromethanesulfonate group
TLC	Thin Layer Chromatography
TMG	1,1,4,4-Tetramethylguanidine
TMP	Tetramethylpiperidine
TMSI	Iodotrimethylsilane
TMS	Trimethylsilyl
TPFPB	Tetrakis(pentafluorophenyl)borate
Ts	Tosyl
TS	Transition state
UV	Ultraviolet

VCP-CP	Vinylcyclopropane-cyclopentene
vs	Versus
X	Halogen or heteroatom
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
δ	Chemical shift
W	Watt
WHE	Horner-Wadsworth-Emmons
τ_1	Retention time for first enantiomer
τ_2	Retention time for second enantiomer

Resumen extendido

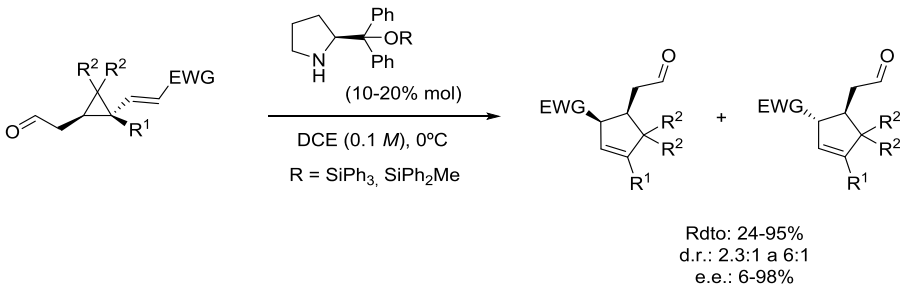
La necesidad de comercializar compuestos enantioméricamente puros por parte de las industrias farmacéuticas ha hecho que el número de metodologías para llevar a cabo transformaciones enantioselectivas haya ido en aumento en los últimos años. De entre todas las metodologías para la obtención de moléculas enantiopuras, entre las que se incluyen la resolución de mezclas racémicas y la estrategia del *Chiral Pool*, la síntesis asimétrica constituye uno de los mayores avances de este campo. En concreto, la organocatálisis asimétrica, que mediante el uso de pequeñas moléculas orgánicas quirales que no incorporan metales en estructura permite llevar a cabo un gran número de transformaciones de manera enantioselectiva, se ha convirtido en una herramienta de gran utilidad en el campo de la síntesis de moléculas enantiopuras. Los organocatalizadores pueden clasificarse en ácidos y bases de Brønsted y ácidos y bases de Lewis. En el trabajo de investigación recogido en la presente memoria se han desarrollado nuevas transformaciones en el ámbito de la catálisis por bases de Lewis.

El principal proyecto de la tesis doctoral consiste en el estudio de la versión organocatalítica enantioselectiva del reagrupamiento viniciclopropano-ciclopenteno. En vista de la ausencia de versiones organocatalíticas enantioselectivas de dicha transformación y dada la experiencia del grupo en el ámbito de la aminocatálisis y en el empleo de moléculas cíclicas altamente tensionadas, se decidió estudiar dicho reagrupamiento empleando como sustratos ciclopropilacetaldehidos sustituidos por un grupo vinilo aceptor de electrones. Estos ciclopropanos pueden activarse mediante el empleo de aminas secundarias quirales a través de la formación de una enamina, tal y como está descrito en trabajos anteriores realizados independientemente por el Prof. Jørgensen y el Prof. Vicario. La formación de la enamina, transformará al ciclopropano inicial en un ciclopropano dador-aceptor contribuyendo a la polarización del enlace C-C entre los sustituyentes dador y aceptor, y por lo tanto a la ruptura del enlace y consiguiente apertura de ciclo. La apertura del ciclopropano dará lugar a la formación de un intermedio zwitteriónico, en el que la carga negativa estará estabilizada por el sustituyente aceptor del ciclopropano. Dicho intermedio experimentará una reacción de cierre de anillo a través de un proceso 5-exo-trig dando lugar a la formación enantioselectiva de ciclopentenos (Esquema 1).



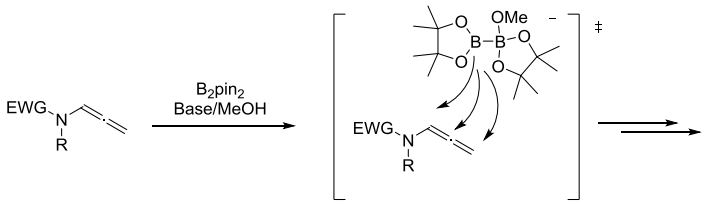
Esquema 1. Reagrupamiento vinilciclopropano-ciclopenteno catalizado por aminas secundarias quirales

Una vez probada la viabilidad de la reacción, y tras un proceso de optimización de las condiciones experimentales para conseguir la formación de los aductos ciclopenténicos *cis* y *trans* con el mayor rendimiento y enantiocontrol posible, se pudo llevar a cabo la extensión de la metodología, la cual permitió la síntesis de ciclopentenos con diferente patrón de sustitución. La metodología permitió la incorporación de cetonas α,β-insaturadas como grupo aceptor, dando lugar a los correspondientes ciclopentenos con buenos rendimientos y excelentes enantioselectividades. Otros grupos aceptores como esteres y nitrilos dieron lugar a los productos deseados con rendimientos moderados y bajo control enantiomérico. La metodología también permitió introducir sustituyentes en la estructura ciclopropánica, obteniendose los ciclopentenos correspondientes con rendimientos de buenos a moderados (Esquema 2). Por último, mediante estudios experimentales, se concluyó que la reacción de reagrupamiento vinilciclopropano-ciclopenteno llevada a cabo en el presente trabajo tenía lugar a través de un mecanismo por pasos y no de una manera concertada.



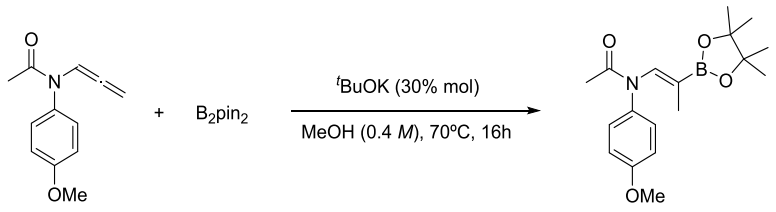
Esquema 2. Reagrupamiento vinilciclopropano-ciclopenteno desarollado

Por otro lado, en el tercer capítulo de la presente tesis doctoral se recoge el trabajo llevado a cabo en colaboración con el grupo de la Prof. Elena Fernández de la Universidad Rovira i Virgili en Tarragona. En dicho trabajo se ha llevado a cabo el estudio de la activación del bis(pinacolato)diboro en ausencia de metales, y su reactividad frente a alenilamidas, sustratos inexplorados en este campo, estudiando la regio- y la diastereoselctividad del proceso. Mediante la activación del B_2pin_2 a través de la formación de un alcóxido, se genera una especie nucleófila de boro que es capar de reaccionar con las posiciones electrófilas de las alenilamidas (Esquema 3).



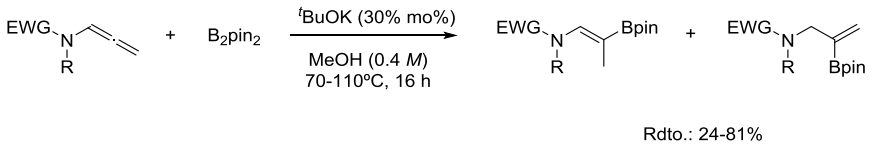
Esquema 3. Activación del B_2pin_2 y su reactividad frente a alenilamidas

Inicialmente se probó como sustrato modelo una alenilamida con un grupo acetilo como sustituyente aceptor y un sustituyente *para*-metoxifenilo. Tras la reacción con B_2pin_2, ^{t}BuOK y MeOH, como condiciones estándar para la activación organocatalítica del bis(pinacolato)diboro, se observó la formación de un único producto de reacción con un alto rendimiento. Este producto presentaba la unidad Bpin en la posición central de la alenilamida, con el consiguiente proceso de hidroboración a lo largo del enlace terminal, observándose una disposición *trans* entre la amina y el grupo Bpin (Esquema 4).



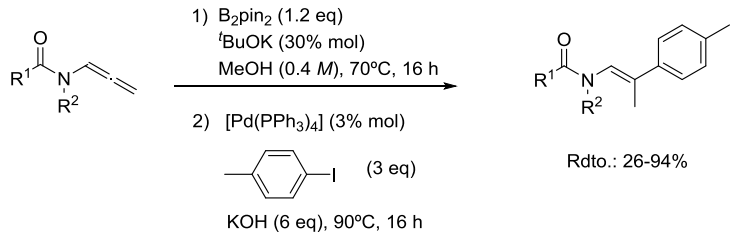
Esquema 4. Estudios preliminares de la reacción

Tras comprobar la viabilidad de la reacción y tras un proceso de optimización de las condiciones experimentales, se extendió la metodología a otras alenilamidas. En primer lugar, se modificó el grupo arilo y se incorporaron sustituyentes en el grupo acetilo de las alenilamidas obteniéndose en todos los casos un único producto de reacción. Sin embargo, al introducir otros grupos aceptores como los grupos *p*-toluenosulfonilo y *terc*-butiloxicarbonilo se observó la formación de dos productos borilados. En ambos productos el grupo Bpin se localizaba en la posición central de la alenilamida, dándose el proceso de hidroboración a lo largo de los enlaces distal y proximal, obteniéndose en una relación 2:1 a favor de la hidroboración en el enlace distal (Esquema 5).



Esquema 5. Borilación de alenilamidas diferentemente sustituidas

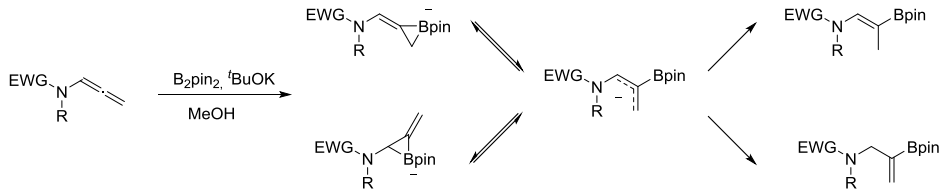
Además, se demostró la utilidad sintética de estos aductos mediante el desarrollo de una secuencia *one-pot* de borilación de alenilamidas/reacción de acoplamiento cruzado de Suzuki, que permitía la formación de olefinas trisustituidas de una manera rápida y eficaz (Esquema 6).



Esquema 6. Reaccion *one-pot* borilación de alenilamidas/reacción de acoplamiento de Suzuki

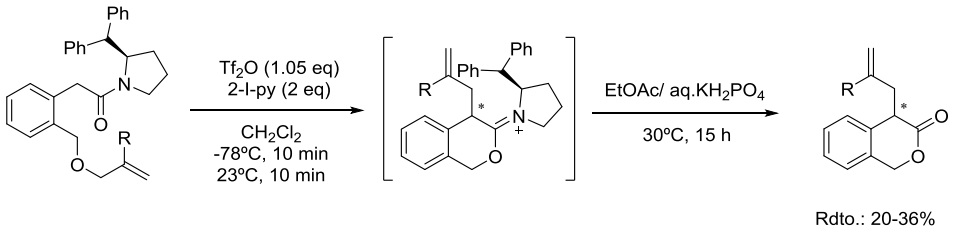
Finalmente, mediante estudios computacionales se comprobó que la reacción de borilación de alenilamidas desarrollada constituía un proceso *umpolung* de la reactividad típica de las alenilamidas. Así, en vez de producirse una activación electrófila, tal y como está descrito en la bibliografía, en nuestro sistema tenía lugar una activación nucleófila, generándose dos intermedios boracíclicos que daban lugar a un intermedio alílico aniónico que, a través de un

proceso de protonación en las posiciones α y γ, daba lugar a los productos observados (Esquema 7).



Esquema 7. Activación nucleófila de las alenilamidas

Finalmente, en un último capítulo, se recogen los resultados más relevantes obtenidos durante la estancia predoctoral de tres meses de duración llevada a cabo en la Universidad de Viena (Austria) bajo la supervisión del Prof. Nuno Maulide. El trabajo de investigación desarrollado ha estado enfocado en la activación de amidas mediante el empleo de anhídrido tríflico. El objetivo de dicho trabajo constituía la continuación del estudio del alcance de la versión enantioselectiva de una reacción de agrupamiento sigmatrópico [3,3] previamente desarrollada por el grupo. La inducción de quiralidad se realizó a través del empleo de auxiliares quirales, en concreto mediante pirrolidinas quirales sustituidas en posición dos. A pesar de los esfuerzos realizados, no se consiguieron buenos resultados en cuanto a los rendimientos de reacción y los excesos enantioméricos no pudieron determinarse (Esquema 8).



Esquema 8. Estudio de la versión asimétrica de la activación de amidas/reacción de reagrupamiento [3,3]