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Novel Asymmetric Transformations under Covalent Organocatalysis

MEMORIA PRESENTADA POR

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“Izena duen guztia omen da”

(Basque mythology)

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Summary

Aminocatalysis has become a field of great interest, especially for the development of stereocontrolled chemical transformations. This methodology implies the condensation of chiral primary or secondary amines with aldehydes or ketones, generating substoichiometric amounts of activated azomethine intermediates (an enamine or iminium ion). Simultaneously, the use of nucleophilic phosphines as organocatalysts has been gaining importance during the last years, explained by their ability to satisfactorily promote enantioselective transformations involving electron-deficient alkynes, alkenes and allenes, that could not have been promoted by other nucleophilic catalysts. The present manuscript complies the study and development of enantioselective organocatalytic reactions under both aminocatalysis and phosphine catalysis. In this sense, alternative reagents to the commonly reported ones have been selected with the aim of developing novel transformations using covalent organocatalysts.

In this context, investigations were directed to the use of *meso*-formylcyclopropanes in nucleophile promoted ring-opening reactions under iminium ion activation using a chiral secondary amine as catayst. Carboxylic acids were found to satisfactorily participate in the transformation as nucleophiles leading to γ-acyloxy aldehydes in high yields and excellent diastereo- and enantiocontrol. In addition, the applicability of the methodology could be demonstrated, as it was used as key step on the first described total synthesis of natural product speciosin H. The target compound could be prepared in an overall yield of 9% after 10 steps, starting from commercially available reagents.

Finally, the ability of chiral nucleophilic phosphines to generate a 1,3-dipolo upon addition to electron-poor allenes was employed to achieve a formal

enantioselective high-order [8+4] cycloaddition, in the presence of azaheptafulvenes that played the role of 8π-components. Reaction between methyl-2,3-butadienoate and *N*-nosylazaheptafulvene rendered the final cycloadduct as a mixture of regioisomers with excellent enantiocontrol.

Resumen

La aminocatalisis se ha convertido en un área de gran interés especialmente para el desarrollo de reacciones químicas estereocontroladas. Esta metodología implica la condensación de aminas primarias o secundarias quirales con aldehídos o cetonas, generando cantidades subestequiométricas de intermedios tipo azometino activados (enamina o ion iminio). Simultáneamente, el empleo de fosfinas nucleófilas como organocatalizadores ha ido ganando importancia durante los últimos años debido a su habilidad para promover satisfactoriamente transformaciones enantioselectivas en las que participan alquinos, alquenos y alenos pobres en electrones, las cuales no han podido ser promovidas previamente por otros catalizadores nucleófilos. Esta memoria recoge el estudio y desarrollo de reacciones organocatalíticas enantioselectivas usando tanto aminas secundarias quirales como fosfinas quirales como catalalizadores. En este sentido, se han seleccionado reactivos alternativos a los comúnmente descritos con la intención de desarrollar transformaciones nuevas empleando organocatalizadores covalentes.

En primer lugar, se presenta la investigación dirigida al empleo de *meso*-formilciclopropanos en reacciones de apertura de anillo promovidas por nucleófilos externos, catalizadas mediante aminas secundarias *via* ion iminio. Se comprobó que los ácidos carboxílicos participaban satisfactoriamente en la reacción como nucleófilos dando lugar a aldehídos γ-aciloxi sustituidos como producto final, con altos rendimientos y diastereo- y enantioselectividad excelentes. Adicionalmente, se pudo demostrar la utilidad de la metodología empleándola como paso clave en la primera síntesis total descrita del producto natural speciosin H. El objetivo sintético pudo ser preparado en un rendimiento global del 9% en 10 pasos, empezando por substratos comercialmente disponibles.

Finalmente, la capacidad de fosfinas nucleófilas quirales para generar 1,3-dipolos después de la adición a alenos pobres en electrones fue empleada para desarrollar una cicloadición [8+4] de alto orden enantioselectiva, en presencia de azaheptafulvenos los cuales actuaron como componentes-8π. La reacción entre 2,3-butadienoate de metilo y *N*-nosilazaheptafulveno dieron el cicloaducto final como mezcla de regioisomeros, mostrando enantioselectividad excelente.

Laburpena

Aminokatalisia interes handiko esparrua bilakatu da erreakzio kimiko estereokontrolatuak garatzerako unean. Metodologia hau amina primario edo sekundario eta konposatu karbonilikoen arteko kondentsazioan oinarritzen da, konposatu azometinikoak (enamina edo iminio ioia) sortuz bitartekari aktibatu bezala, kantitate katalitikoetan. Era berean, azken urteotan fosfina nukleozaleen erabilera organokatalizatzaile bezala gero eta nabariagoa izan da, bereziki beste katalizatzaile nukleozaleek sustatu ezin izan duten erreakzio enantioselektiboetan non elektroi-ahulak diren alkino, alkeno eta alenoak parte hartzen dute. Eskuizkribu honetan erreakzio organokatalitiko enantioselektiboen garapena bilatzen da amina sekundario kiralak eta fosfina kiralak erabiliz katalizatzaile bezala. Horren inguruan, normalean erabiltzen diren konposatuen ordez erreaktibo alternatiboak aukeratu dira transformazio berriak garatzeko aukera izateko, organokatalizatzaile kobalenteak erabiliz.

Lehenik eta behin, *meso*-formilziklopropanoen inguruan garatutako irekiera aurkezten da, amina sekundario batetik eratutako iminio ioi bat bitartekari izanez. Erreakzio honetan azido karboxilikoak irekiera sustatzen duen nukleozale bezala jokatzen dute, adizioaren ondoren γ-aziloxi aldehidoak eratuz etekin, diastereo- eta enantioselektibitate altuekin. Gainera, metodologiaren erabilgarritasuna frogatua izan zen, speciosin H productu naturalaren lehen sintesi totalean oinarrizko urrats giza erabiliz. Helburu sintetikoa %9-ko etekin globalean prestatu zen 10 urratseko prozesu bat jarraituz, komertzialki eskuragarri dauden substratuetatik hasita.

Azkenik, fosfina nukleozaleen trebetasuna 1,3-dipoloak eratzeko elektroi-ahulak diren alenoen gaineko adizioaren ondoren erabili zen maila altuko [8+4] zikloadizio enantioselektiboa garatzeko, 8π-konposatu bezala jokatzen duten

azaheptafulbenoen presentzian. Metil 2,3-butadienoato eta *N*-nosilazaheptafulbenoaren arteko erreakzioan eratutako produktua leku-isomeroen arteko nahasketa moduan lortu zen enantioselektibitate altuan.

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Chapter 1

1

Asymmetric Organocatalysis

1. INTRODUCTION

As it has been observed through the last decades, many of the most important properties of organic compounds might be influenced by their stereochemistry. For example, enantiomers of the same molecule can have completely different biological effects,[1] and macroscopic physical characteristics of polymers can be affected by changing the stereochemistry of their backbones.[2] Thus, asymmetric synthesis has become a major concern across many sectors of modern synthetic chemistry. In this sense, asymmetric catalysis is one of the most effective tools for the synthesis of enantioenriched compounds through a broad range of transformations, where a chiral catalyst provides the stereocontrol for the reaction. Although the field has been dominated for decades by enzymatic transformations[3] and metal catalysis,[4] reactions catalysed by metal-free small compounds have gathered importance over the past two decades. This activation method, known today as *organocatalysis*,[5] has shown high efficiency and selectivity in a wide variety

1 Testa, B.; Trager, W. F. *Chirality* **1990**, *2*, 129.

2 Odian, G. *Principles of Polymerization*; 4th ed.; John Wiley & Sons, Inc.: New Jersey, 2004.

3 For enzymatic catalysis examples, see: (a) Callender, R.; Dyer, B. *Acc. Chem. Res.* **2015**, *48*, 407. (b) Drauz, K.; Gröger, H.; May, O. *Enzyme Catalysis in Organic Chemistry*; 3rd ed.; Wiley-VCH: Weinheim, 2012. (c) Moniruzzaman, M.; Kamiya, N.; Goto, M. *Org. Biomol. Chem.* **2010**, *8*, 2887. (d) Tao, J.; Zhao, L.; Ran, N. *Org. Process Res. Dev.* **2007**, *11*, 259.

4 For metal catalysis examples, see: (a) Dixneuf, P. H.; Cadierno, V. *Metal Catalyzed Reactions in Water*; Wiley-VCH: Weinheim, 2013. (b) Duka, G. *Homogeneus Catalysis with Metal Complexes*; Springer: Berlin, 2012. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; 2nd ed.; Wiley-VCH: New York, 2010. (d) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; 3rd ed.; Wiley-VCH: Weinheim, 2004.

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

of organic transformations and the relevance gathered nowadays is clear by the large amount of contributions made to the field.[6]

Organocatalysts usually have quite robust structures that sometimes can be obtained from natural sources and when they have to be hand-made, they are easy to design and to synthesize. Moreover, due to their inertness towards moisture and/or oxygen, there is usually no need for inert atmosphere nor dry solvents when performing the reactions. Although they were only used sporadically throughout the previous century, some of the very first examples of nonenzymatic asymmetric catalytic reactions occurred *via* organocatalysis and were described more than a century ago. For instance, in 1904 Marckwald presented the enantioselective decarboxylation of 2-ethyl-2-methylmalonic acid by heating up the reaction in the presence of brucine, obtaining α-methylbutyric acid with a small excess of the levorotatory form (Scheme 1.1).[7]

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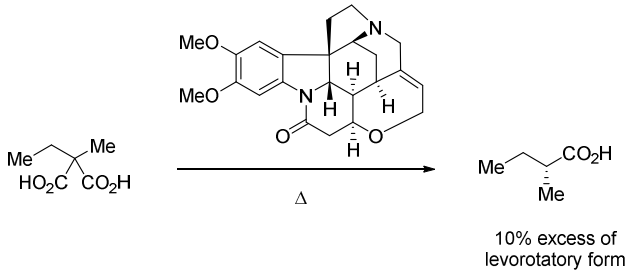
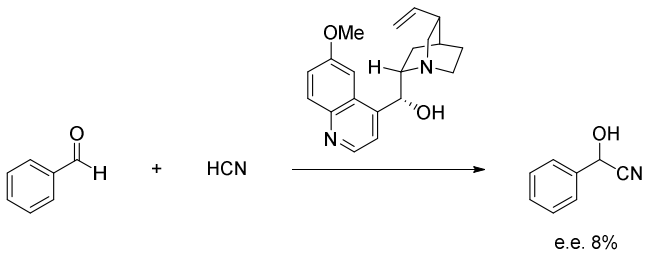
6 For general reviews on organocatalysis, see: (a) Chanda, T.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2018**, *360*, 2. (b) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (c) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (d) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (e) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712. (f) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618. (g) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138. (h) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (i) Special issue on organocatalysis: List, B. *Chem. Rev.* **2007**, *107*, 5413. (j) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. For books about organocatalysis, see: (k) Rios-Torres, R. *Stereoselective Organocatalysis. Bond Formation and Activation Modes*; Wiley-VCH: Weinheim, 2013. (l) Waser, M. *Asymmetric Organocatalysis in Natural Products Synthesis*; Springer: Heidelberg, 2012. (m) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; RSC Publishing: Cambridge, 2010.

7 (a) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349. (b) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1368.



Scheme 1.1. Organocatalytic decarboxylation of 2-ethyl-2-methylmalonic acid.

Few years later, the first enantioselective C-C bond formation reaction was presented by Bredig and Fiske.[8] They obtained a cyanohydrin with a slight enantiomeric excess when hydrogen cyanide was added to benzaldehyde in presence of quinine (shown in the scheme below) or quinidine, obtaining compounds with opposite chirality depending on the organocatalyst employed (Scheme 1.2).

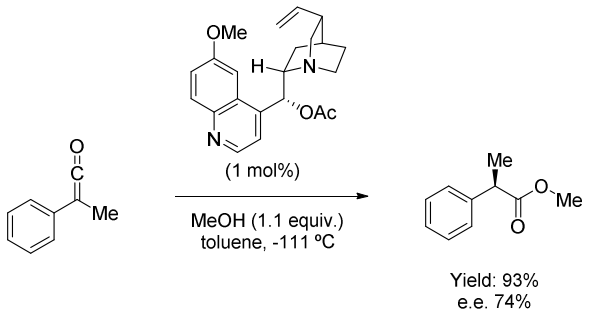


Scheme 1.2. Organocatalytic reaction between benzaldehyde and hydrogen cyanide.

Despite these early examples, it was not until 1960 that the first reaction providing high level of enantiocontrol was published. Pracejus studied the addition of methanol to methyl phenyl ketene in the presence of a quinine derivative,

8 Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7.

obtaining the final product with an enantiomeric excess of 74%. In this particular case 1 mol% of *O*-acetylquinine served as catalyst (Scheme 1.3).[9]



Scheme 1.3. Enantioselective addition of methanol to methyl phenyl ketene.

Probably the most famous example from that time is the Hajos-Parrish-Eder-Sauer-Wiechert reaction, named after the discoverers.[10,11] They independently developed a highly enantioselective intramolecular aldol reaction catalysed by L-proline, used for the preparation of chiral intermediates in the synthesis of steroids (Scheme 1.4).

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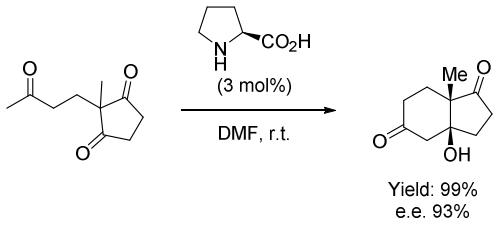
9 Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.

10 (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Hajos, Z. G.; Parrish, D. R. *Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds.* German Patent DE 2102623, **1971**.

11 (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496. (b) Eder, U.; Sauer, G.; Wiechert, R. *Optically Active 1,5-Indanone and 1,6-Naphthalenedione.* German Patent DE 2014757, **1971**.



Scheme 1.4. Hajos-Parrish-Eder-Sauer-Wiechert reaction.

Things began to change around the 1990s when various organocatalytic activation manifolds were reported (Figure 1.1). Chiral Brønsted acids were found to direct the enantiocontrol trough hydrogen-bonding interactions when Inoue[12] presented the first example of an asymmetric hydrocyanation of aldehydes, which was further expanded by Jacobsen[13] and Corey[14] to the asymmetric Strecker reaction. In addition, the enantioselective alkylation of enolates employing quaternary ammonium salts based on cinchona alkaloids, under phase-transfer-catalysis was described around the same time.[15] However, organocatalysis was not considered an important tool for carrying out asymmetric reactions until 2000, when two key publications appeared almost simultaneously. On one hand List, Lerner and Barbas III applied the enamine activation concept to the aldol reaction[16] and on the other hand, MacMillan introduced the iminium activation approach to the Diels-Alder reaction.[17]

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12 Oku, J.-I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229.
13 Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
14 Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
15 (a) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710. (b) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
16 List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
17 Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

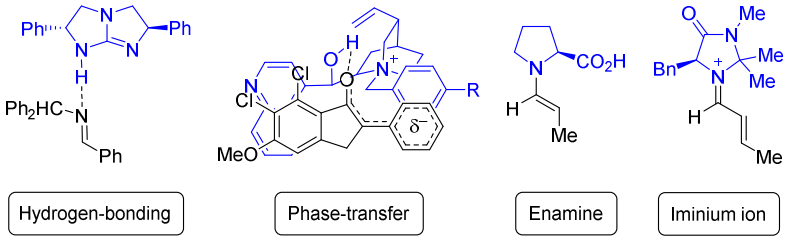
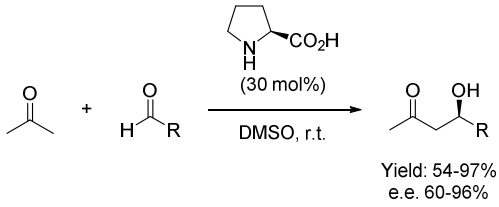


Figure 1.1. Organocatalytic activation manifolds discovered at the end of the 20th century.

Concerning the work of List, Lerner and Barbas III, they published the first enantioselective intermolecular aldol reaction catalysed by L-proline between acetone and several aldehydes (Scheme 1.5). Experimental and mechanistic insights suggested that after condensation of the aminocatalyst with acetone, and enamine intermediate was formed, which participated as the nucleophile of the reaction.[18] By this study, it was confirmed that a small amino acid could mimic the role of aldolase antibodies and furthermore, it showed that the activation manifold employed in the pioneering Hajos-Parrish-Eder-Sauer-Wiechert reaction could be extended to different related transformations.

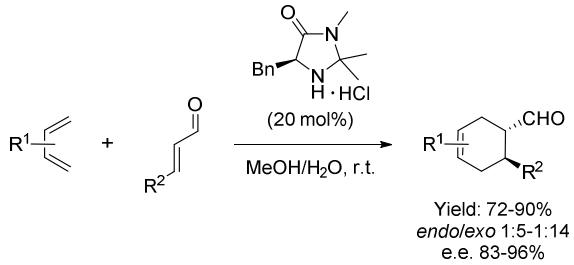


Scheme 1.5. L-Proline catalysed aldol reaction between acetone and different aldehydes.

On the other hand, MacMillan presented the enantioselective Diels-Alder cycloaddition between enals and dienes, which was catalysed in this case by a chiral imidazolidium salt (Scheme 1.6). He described that secondary amines can condense

[18] Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

with α,β-unsaturated aldehydes leading to the reversible formation of an iminium ion, which activates the substrate lowering the energy of its LUMO orbital, as a Lewis acid does, and therefore turning it more susceptible towards the [4+2] process in the presence of a diene.



Scheme 1.6. Organocatalytic Diels-Alder cycloaddition between α,β-unsaturated aldehydes and electron-rich dienes.

Once it was demostrated that excellent enantiocontrol could be achieved *via* organocatalysis and that the different activation manifolds could be applied to several reaction types, the field grew quickly. The interest generated by this methodology is based on the important advantages of this approach in terms of cost and simplicity of experimental procedures.[6i,19] As organocatalysts are available from chiral natural products they are relatively inexpensive and usually easier to prepare when compared with other chiral catalysts. It should be pointed out that usually both enantiomeric forms of the organocatalysts or their precursors are also commercially available, making them suitable for the synthesis of both enantiomers of the projected products. Furthermore, as organocatalysis provides the transformation in a metal-free context, it has become an important methodology especially in pharmaceutical industry for the screening of biologically active compounds. In this phase of the process, when the substrates are synthesised in

[19] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8.

low amounts, the use of organocatalysts guarantees that there will not be metal impurities in the final products that could interfere on the results obtained when testing their biological activity.

Despite the aforementioned advantages, there are still several issues that need to be improved. The high amount of catalyst typically necessary for the reactions to occur and the long reaction times normally required are the most relevant problems that this methodology presents. Due to these drawbacks, scaling up some of these transformations is not possible in many cases, making its utility in the chemical industry limited. However, great efforts are being made to overcome these negative aspects like, for example, through the application of flow chemistry, which appears as a possible solution.[20]

[20] For selected examples on organocatalytic transformation in flow, see: (a) Kasaplar, P.; Ozkal, E.; Rodríguez-Escrich, C.; Pericàs, M. A. *Green Chem.* **2015**, *17*, 3122. (b) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 2367. (c) Bortolini, O.; Caciolli, L.; Cavazzini, A.; Costa, V.; Greco, R.; Massi, A.; Pasti, L. *Green Chem.* **2012**, *14*, 992. (d) Alza, E.; Rodríguez-Escrich, C.; Satalero, S.; Bastero, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, *15*, 10167.

2. ORGANOCATALYTIC ACTIVATION MANIFOLDS

Organocatalytic activation manifolds can be classified into two main groups based on the interactions between the catalyst and the substrate in the transition state. The first group would be the *covalent organocatalysis*, where covalent interactions are formed between the catalyst and the substrate along the catalytic cycle, and the second one would be the *non-covalent organocatalysis*, in which the catalyst activates the substrate by other weaker interactions, such as hydrogen-bonding, ion pair and Van der Waals interactions. In many cases these generic modes of reactivity are executed by very different types of catalyst scaffolds. In this sense, Figure 2.1 shows some representative examples of organocatalysts classified as the abovementioned manner.

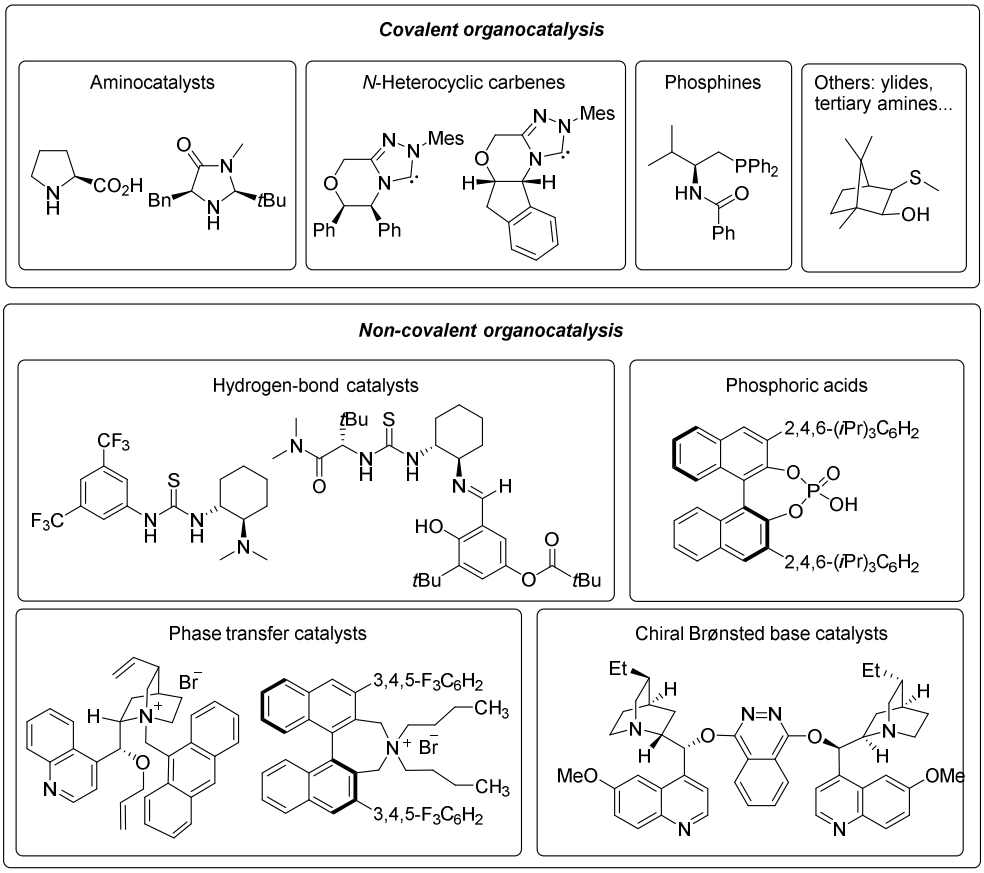


Figure 2.1. Examples of organocatalysts classified according the activation manifold.

Among organocatalytic reactions proceeding through covalent interactions between the catalyst and the substrate, aminocatalysis has been the most studied activation method up to date. Primary or secondary amines condense with the carbonyl group present in the substrate leading to its functionalization trough iminium ion, enamine or radical cation (SOMO catalysis) intermediates.[21] *N*-

[21] A section of this chapter is dedicated to discuss aminocatalysis, see: Chapter 1. Section 3. Aminocatalysis.

Heterocyclic carbenes (NHCs) also create a covalent bond with aldehydes, obtaining a neutral enaminol (known as Breslow intermediate) as activated species.[22] In addition to these main activation manifolds, chiral phosphines have also gathered some importance, catalysing transformations with alkenes, alkynes or allenes trough nucleophilic addition.[23]

On the other hand, non-covalent catalysis despite presenting weaker interactions between the catalyst and the substrate has also accomplish excellent results. One of the most studied ones has been the hydrogen-bond catalysis;[24] where ureas, thioureas[25] and squaramides[26] are able to form hydrogen-bonds with several functional groups promoting C-C and C-heteroatom bond-formations. These catalysts might be classified as mild Brønsted acids in contrast with phosphoric acids that would be strong Brønsted acids. For these last acids, the transition state of the hydrogen-bond catalysis could be either a hydrogen-bonded complex or a protonated ion pair. In this regard, chiral BINOL-derived phosphates

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22 For selected reviews on *N*-heterocyclic carbenes, see: (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (b) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686. (c) Bugaut, X.; Glorious, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (d) Grossman, A.; Enders, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 2. (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

23 A section of this chapter is dedicated to discuss chiral phosphines as catalysts, see: Chapter 1. Section 4. Chiral nucleophilic phosphine catalysis.

24 For general reviews on hydrogen-bond catalysis, see: (a) Akiyama, S.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (b) Siau, W. Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298. (c) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, 2009. (d) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (g) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

25 For a selected review on ureas and thioureas as catalysts, see: Zhang, Z.; Schreiner, P. R.; *Chem. Soc. Rev.* **2009**, *38*, 1187.

26 For a selected review on squaramides as catalysts, see: Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

have been the most successful.[27] Finally, phase-transfer catalysis (PTC)[28] and Brønsted bases,[29] which activate nucleophiles by the formation of chiral ion pairs after abstraction of a proton from the nucleophile, are also part of the non-covalent catalysis.

In the following sections aminocatalytic methodologies and the use of nucleophilic phosphines as catalysts will be briefly presented due to their direct relation with the research presented in this manuscript.

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[27] For selected reviews on phosphoric acids as catalysts, see: (a) Li, X.; Song, Q. *Chin. Chem. Lett.* **2018**, *29*, 1181. Parmar, D.; Sugiomo, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (c) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (d) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227.

[28] For selected reviews on chiral phase-transfer catalysis, see: (a) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367. (b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (c) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090. (d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

[29] For selected reviews on Brønsted base catalysis, see: (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (b) Papageorqiou, C. D.; Cubillo de Dios, L. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641.

3. AMINOCATALYSIS

The use of chiral primary or secondary amines for the activation of aldehydes and ketones towards stereocontrolled reactions has been one of the most studied organocatalytic activation manifolds.[30] The success of aminocatalysts lies in their ability to condense effectively but also reversibly with the carbonyl group, forming stereodefined intermediates that lead to stereoselective transformations. Regarding the activated azometine intermediate two main activation modes can be differentiated: *enamine*[31] and *iminion ion*[32] catalysis. Moreover, the application of the vinylogy principle[33] to these two activation modes has broaden the synthetic strategies trough *dienamine*, *trienamine* and *vinylogous iminium ion* activation.[34] These activated species together with the *SOMO* catalysis[35] allow the α-, β-, γ-, δ-

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30 For selected reviews on aminocatalysis, see: (a) Pawar, T. J.; Jiang, H.; Vázquez, M. A.; Villegas, C.; Cruz, D. *Eur. J. Org. Chem.* **2018**, 1835. (b) Lv, J.; Zhang, Q.; Cai, M.; Han, Y.; Luo, S. *Chem. Asian J.* **2018**, *13*, 740. (c) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (e) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (f) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (g) List, B. *Chem. Commun.* **2006**, 819. (h) List, B. *Tetrahedron* **2002**, *58*, 5573.

31 For selected reviews on enamine catalysis, see: (a) List, B.; Liao, S. H. *Org. Chem.* **2012**, 367. (b) MacMillan, D. W. C.; Watson, A. J. B. In *Science of Synthesis: Stereoselective Synthesis 3*; de Vries, J. G.; Evans, P. A.; Molander, G. A., Eds.; Thieme: Stuggart, Germany, 2011; pp 675-745. (c) Rios, R.; Moyano, A. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 191-218. (d) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, *43*, 5465. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

32 For selected reviews on iminium ion catalysis, see: (a) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 219-294. (b) Brazier, J. B.; Tomkinson, N. C. *Top. Curr. Chem.* **2010**, *291*, 281. (c) Erkkilä, A.; Majander, L.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

33 Vinilogy principle: Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.

34 For selected reviews on vinylogous aminocatalysis, see: (a) Jiang, H. J.; Albrech, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (b) Juberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869. (c) Li, J. L.; Liu, T. Y.; Chen, Y. C. *Acc. Chem. Res.* **2012**, *45*, 1491.

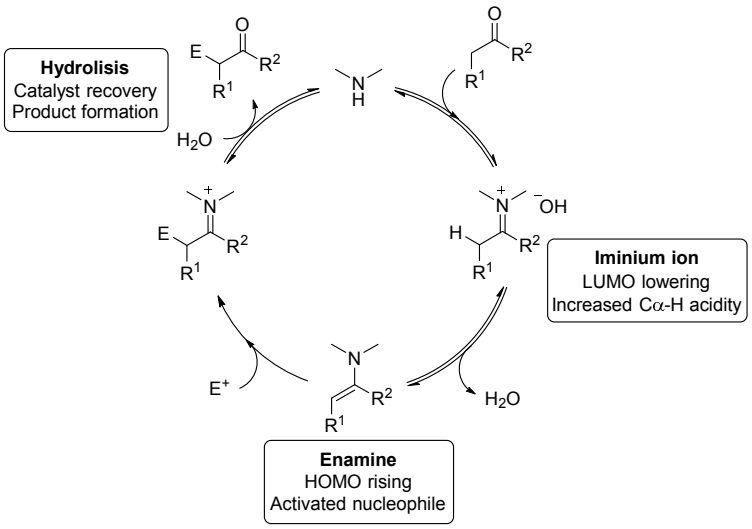
35 For some selected examples on SOMO catalysis, see: (a) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Jang, H.-Y.; Hong, J.-B.; MacMillan,

and/or ε-functionalization of carbonyl compounds in a selective and efficient manner.

3.1. Enamine and Iminium ion catalysis

Raising the HOMO energy for making the aldehyde or ketone more reactive towards reaction with an electrophile is the underlying principle of the enamine catalysis. The catalytic cycle starts with the condensation of the amine catalyst with an enolizable aldehyde or ketone obtaining the corresponding iminium ion. This catalytic species has a lower LUMO energy than its parent carbonyl derivative and therefore the acidity of the Cα-H is increased, hence, deprotonation is more prone to occur, allowing the formation of an enamine intermediate. The enamine shows a HOMO-raised energy and in consequence, this nucleophilic enolate equivalent, can react with electrophilic reagents quite easily. Finally, a hydrolysis step releases the aminocatalyst, which can re-enter the catalytic cycle, and delivers the α-functionalized aldehyde or ketone (Scheme 3.1).

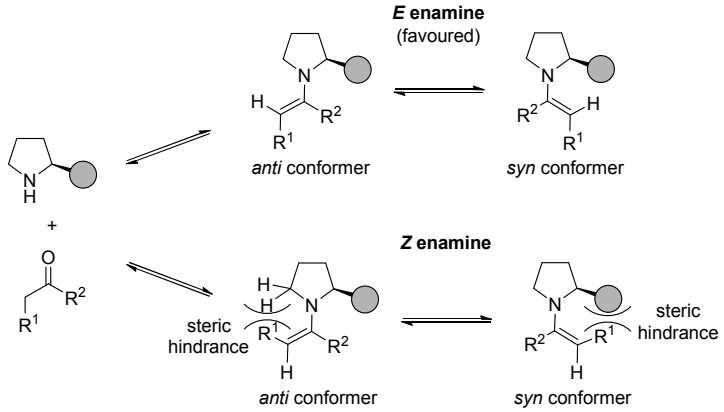
D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. For a highlight, see: (d) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356.



Scheme 3.1. Catalytic cycle of the enamine catalysis.

When using chiral aminocatalysts derived from proline in order to induce stereocontrol in the addition of the electrophilic reagent, one important issue of the catalytic cycle relies on the formation of the corresponding enamine, as the stereoinduction observed in the subsequent reaction will be directly related to the structure adopted by this intermediate. The catalyst should be able to control the *Z*/*E* geometry of the double bond at the enamine, as well as the conformational orientation of this moiety (*syn* or *anti*) relative to the substituent at C-2 in the pyrrolidine moiety (Scheme 3.2), thus, the enantiomeric excess of the synthetic transformation would be conditioned by the capacity of the catalyst to accelerate the reaction of one of the isomers/conformers over the other. Mechanistically, it has been proven that *E* enamine is favoured over *Z* enamine due to the steric repulsion interactions observed in the *Z* enamine, and as far as it is known, the *anti*

conformer of the *E* enamine is considered to be the preferred intermediate regardless the nature of the 2-substituent of the pyrrolidine based catalyst.[36]

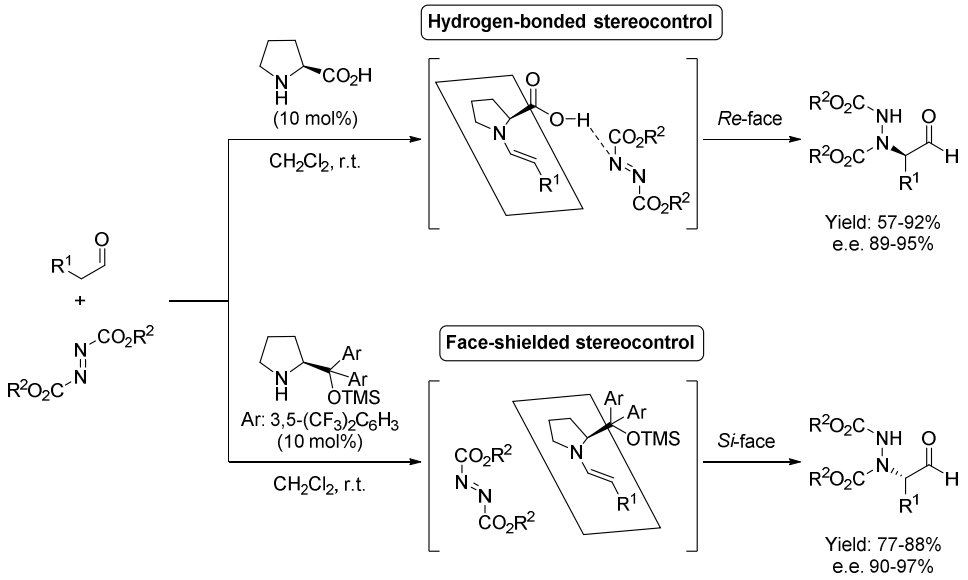


Scheme 3.2. Possible enamine structures.

Aside from choosing an aminocatalyst that is able to favour one enamine structure over the others, the trajectory of the incoming electrophile also has to be controlled, as the addition on a different face (*Re*-face or *Si*-face) would lead to opposite enantiomers. In this sense and depending on the nature of the catalyst, two different approaches can be considered: whether if a stereodirecting substituent is present in the structure or by placing a bulky substituent that would hinder one of the diastereotopic faces of the enamine. These two type of catalysts would lead to opposite enantiomers, despite having the same absolute configuration, as they promote the electrophilic addition from opposite faces of the enamine. As an example of this behavior (see Scheme 3.3), when catalysing the reaction between aldehydes and diazene-1,2-dicarboxylates under enamine activation, opposite enantiomers where obtained depending on the nature of the

[36] (a) Houk, K. N.; Cheong, P. H.-Y. *Nature* **2008**, *455*, 309. (b) Dinér, P.; Kjærsgaard, A.; Lie, M. A.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 122.

substituent placed in the pyrrolidine-derived catalyst. L-Proline interacted with the electrophile forming hydrogen-bonds, hence, directing the attack on the face where the substituent sticks out (in this case the *Re*-face). [37] On the contrary, (*S*)-diarylprolinol trimethylsilyl ether shielded the *Re*-face with its bulky arm, forcing the addition to happen on the *Si*-face.[38]



Scheme 3.3. Two different approaches for the incoming electrophile under enamine catalysis.

However, there are some transformations where the stereochemical outcome cannot be predicted by the steric shielding, nor by hydrogen-bond directing approaches. In this sense, mechanistic studies have been carried out on various

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[37] (a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. For mechanistic insights, see: (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

[38] Fanzén, J.; Marigo, M.; Fielencah, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

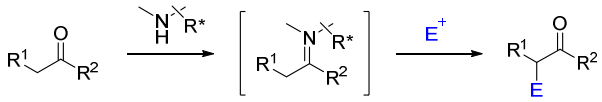
reactions catalysed by diarylprolinol ethers, such as the conjugate addition of aldehydes to nitroolefins and the α-chlorination of aldehydes.[39] The obtained results suggested that the stereochemistry of the final adduct is not defined by the transition state of the step in which the stereocenter is formed from the attack of the enamine to the incoming electrophile, but instead is derived from the relative stability and reactivity of diastereomeric intermediates downstream in the catalytic cycle. Hence, as in a Curtin-Hammett scenario, the different diastereomeric pathways would lead to opposite enantiomers and the enantiomeric excess would be defined by the relative concentration as well as the different reactivity of the diastereomeric intermediates prior to the irreversible step.

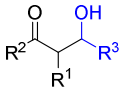
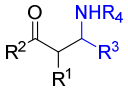
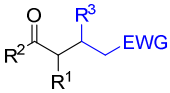
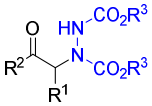
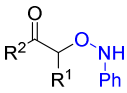
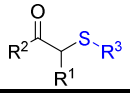
The usefulness of the enamine catalysis has been demonstrated by the wide range of asymmetric reactions developed under this catalytic method, such as aldol reaction, Mannich reaction, Michael reaction and α-functionalization (Table 3.1). Moreover, as highly enantioenriched final products are obtained, various of the transformations have been used in total synthesis of natural products.[40]

[39] (a) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741. (b) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 14264.

[40] Dibello, E.; Gamenara, D.; Seoane, G. *Curr. Org.* **2015**, *2*, 124.

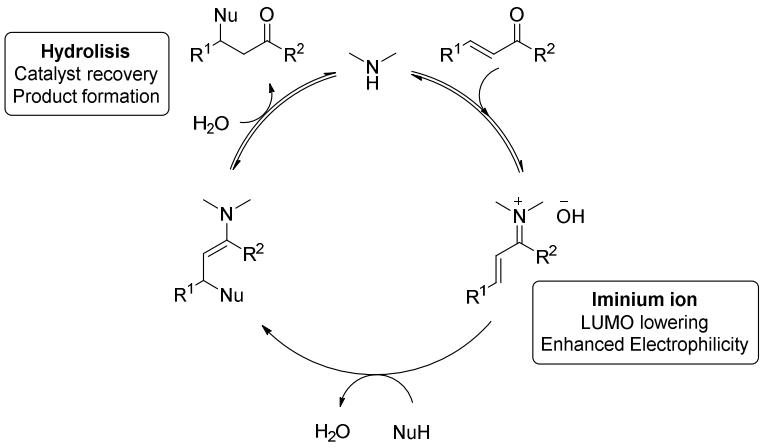
Table 3.1. Some asymmetric reactions under enamine catalysis.



Reaction type	Electrophile	Product	Pioneering example
Aldol	Aldehyde		*JACS* 2000, *122*, 2395
Mannich	Imine		*JACS* 2000, *122*, 9336
Michael	α,β-Unsaturated carbonyl comp., Nitroolefin		*ACIE* 2004, *43*, 3958
α-Amination	Azodicarboxylate		*ACIE* 2002, *41*, 1790 *JACS* 2002, *124*, 5656
α-Oxygenation	Nitrosobenzene		*ACIE* 2003, *42*, 4247 *JACS* 2003, *125*, 10808
α-Fluorination	Electrophilic fluorine source		*ACIE* 2005, *44*, 3703 *ACIE* 2005, *44*, 3706 *JACS* 2005, *127*, 8826
α-Chlorination	Electrophilic chlorine source		*JACS* 2004, *126*, 4108 *JACS* 2004, *126*, 4790
α-Sulfenylation	Electrophilic sulfur source		*ACIE* 2005, *44*, 794

The other main activation manifold in aminocatalysis is the iminium ion based catalysis. When α,β-unsaturated aldehydes or ketones condense with primary or secondary amines, the formation of the corresponding α,β-unsaturated iminium ion leads to a Michael acceptor with an enhanced electrophilicity, thus, it shows a mayor reactivity towards nucleophiles, in comparison with the starting enal or

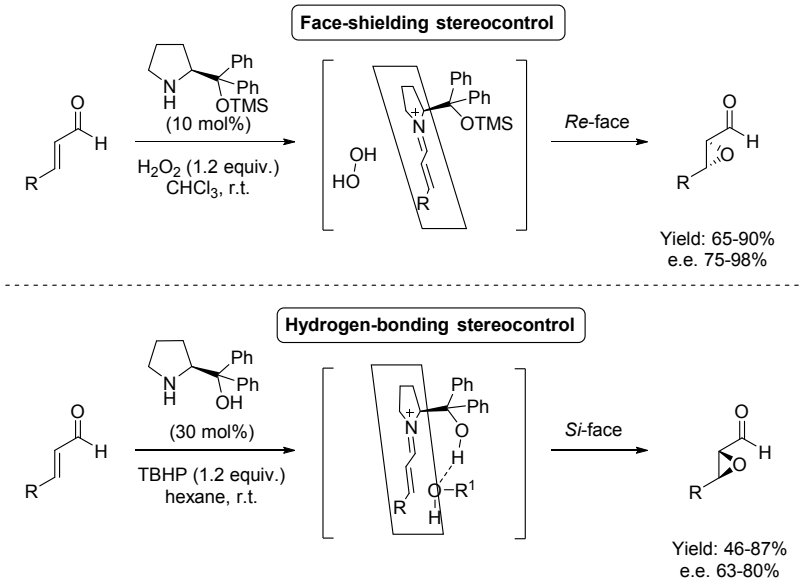
enone. In this case, the catalytic cycle starts with the condensation of the carbonyl group with the aminocatalyst forming the corresponding iminium ion. This activated intermediate shows a lower LUMO energy compared to the original enal or enone, which leads to the aforementioned enhanced reactivity, allowing the β-addition to happen. The final hydrolysis step releases the catalyst and the β-substituted carbonyl compound (Scheme 3.4).



Scheme 3.4. Catalytic cycle of the iminium catalysis.

In the asymmetric version, the stereoinduction provided by the catalyst follows the same principles as the one previously described for enamine catalysis. The chiral catalyst should be able to produce an iminium ion with a well defined geometry (*Z*/*E*) and furthermore, the trajectory of the nucleophile should be favoured towards one of the diastereotopic faces of the Michael acceptor during the 1,4-addition. Two ways of inducing stereo-differentiation between the diastereotopic faces might be considered as it can be seen in the example shown in Scheme 3.5 that corresponds to the enantioselective epoxidation of enals. The nucleophilic addition of the oxidant took place though *Re*-face when catalysts with

bulky substituents were employed, as the *Si*-face was shielded by them.[41] On the other hand, when stereodirecting substituents placed in the catalyst pointed out the *Si*-face, the nucleophilic addition occurred through that face as an interaction between the catalyst and the oxidant directed the attack, in this case through hydrogen-bonding.[42]



Scheme 3.5. Two different approaches for the incoming nucleophile under iminium ion catalysis.

Iminium ion catalysis has been applied to the conjugate addition of many different nucleophiles. In this sense, the enantioselctive formation of C-C, C-O and

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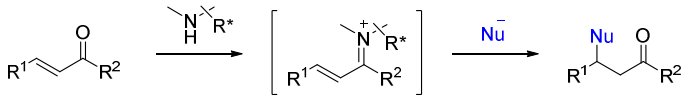
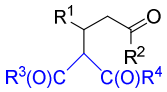
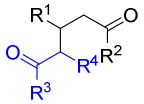
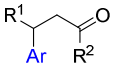
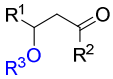
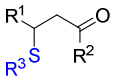
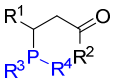
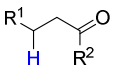
41 (a) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. For more recent studies on mechanistic aspects, see: (b) Izzo, J. A.; Poulsen, P. H.; Intrator, J. A.; Jørgensen, K. A.; Vetticatt, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 8396. (c) Davis, R. L.; Jensen, K. L.; Gschwend, B.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 64.

42 Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579.

C-N bonds has been possible, as well as the asymmetric reduction of the C-C double bond present in the enals or enones by conjugate hydride addition (Table 3.2).

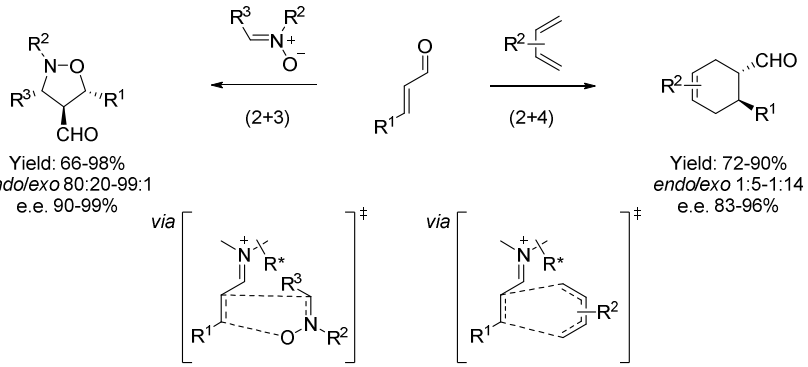
Table 3.2. Some asymmetric conjugate reactions under iminium ion catalysis.



Reaction type	Nucleophile	Product	Pioneering example
Michael	1,3-Dicarbonyl compound		*ACIE* 1993, *32*, 1176
Mukaiyama-Michael	Silyl enol ether		*JACS* 2003, *125*, 1192
Conjugated Henry	Nitroalkane		*Tetrahedron Lett.* 1994, *35*, 8233
Conjugated Friedel-Crafts	Aromatic compound		*JACS* 2001, *123*, 4370
Oxa-Michael	*O*-Nucleophile		*JACS* 2007, *129*, 1536
Aza-Michael	*N*-Nucleophile		*JACS* 2006, *128*, 9328
Sulfa-Michael	*S*-Nucleophile		*JACS* 2005, *127*, 15710
Phospha-Michael	*P*-Nucleophile		*ACIE* 2007, *46*, 4504
Conjugated hydride reduction	Hantzsch ester		*ACIE*, 2004, *44*, 108

Furthermore, both the β- and α-position of the enals and enones can be functionalised in the same process through cycloaddition reactions. As an example of this behaviour, MacMillan showed the possibility of carrying out enantioselective

Diels-Alder reactions between enals and dienes,[17] or 1,3-dipolar cycloadditions with nitrones (Scheme 3.7).[43]



Scheme 3.6. Cycloaddition reactions of enals *via* iminium ion activation.

On the other hand, since the conjugate addition to an α,β-unsaturated iminium ion generates a reactive enamine intermediate, cascade processes can be developed when an additional electrophile is present in the reaction media (see an example in Scheme 3.7).[44]

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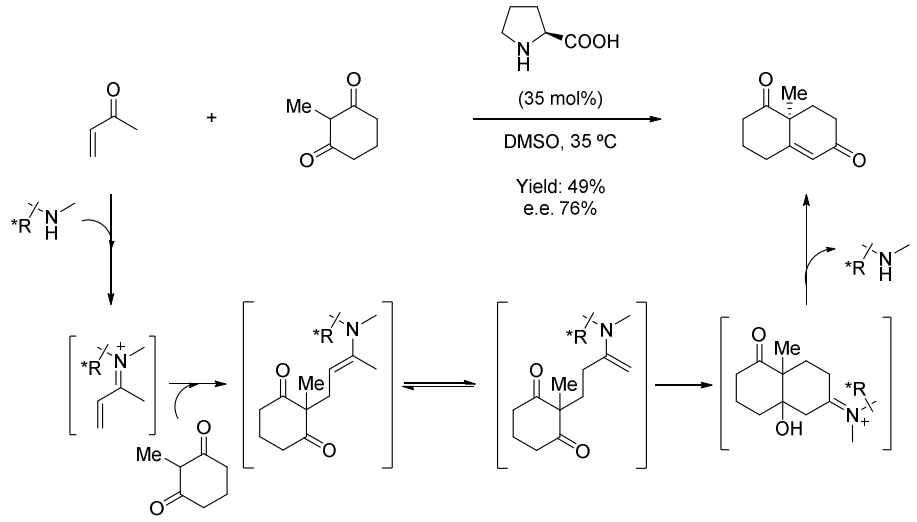
[43] For an enantioselective early example, see: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

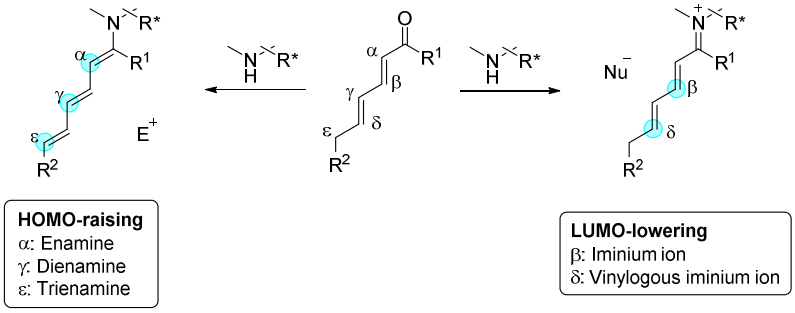
[44] (a) Bui, T.; Barbas III, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951. For a selected review, see: (b) Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.



Scheme 3.7. Cascade process *via* iminium ion/enamine activation.

3.2. Vinylogous Enamine and Iminium ion catalysis

Fuson described the principle of vinylogy in 1935 stating that "*in a molecule containing a system of conjugated double bounds, the influence of the functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule*".[33] This principle could be applied to the aminocatalysis with the aim of propagating the HOMO-raising and the LUMO-lowering activating effects along the π-system of poly-unsaturated carbonyl compounds, as well as the stereochemical information of the catalyst. This way, apart from the common enantioselective α- and β- substitutions, enantioselective γ-, δ- and ε- substitutions could be also achieved by employing chiral primary or secondary amines as catalysts (Scheme 3.8).



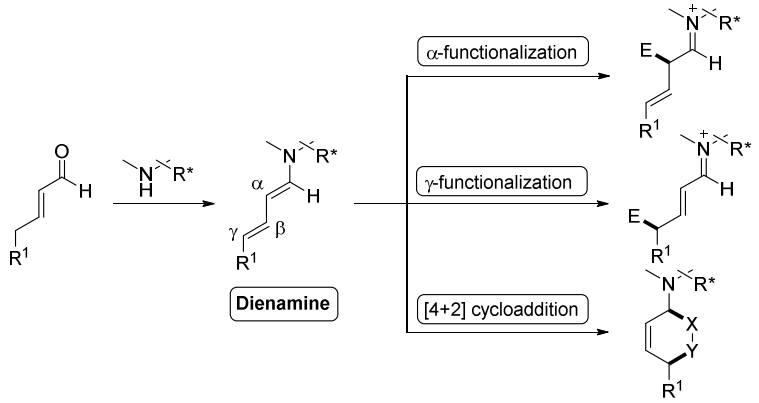
Scheme 3.8. Application of the vinylogous principle in aminocatalysis.

The dienamine activation is considered quite a new concept in the field of aminocatalysis, however non-catalytic examples have been known since the beginning of last century. Richardson and co-workers presented in 1939 the first Diels-Alder reaction that performed through a stechiometrically generated dienamine intermediate,[45] the dienamine formed after the condensation between aniline and 2-ethyl-2-hexenal was then subjected to a cycloaddition process with maleic anhydride. This work set a precedent for the use of catalytic dienamine species in different transformations when γ-enolizable α,β-unsaturated carbonyl compounds were employed in combination with primary or secondary amine catalysts; the condensation of the carbonyl group with the aminocatalyst led to the corresponding iminium ion, which rendered the dienamine species after γ-deprotonation.[46]

It should be mentioned that, due to the extended conjugation of the electron-rich system in dienamines, regioselectivity could be an issue, since more than one nucleophilic points are present in the structure. The activated species can show simple enamine reactivity functionalizing the α-position, or the further γ-carbon

[45] Snyder, H. R.; Hasbrouck, R. B.; Richardson, J. F. *J. Am. Chem. Soc.* **1939**, *61*, 3558.
[46] For a selected review, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

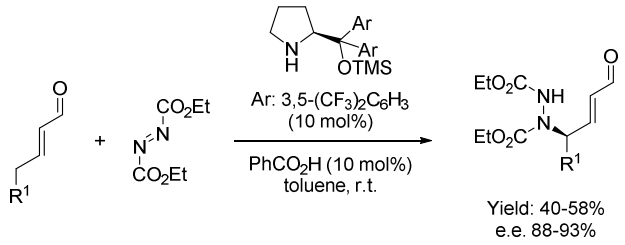
can be the one reacting with the external electrophile. Furthermore, the dienamine could be considered as an electron-rich diene capable of reacting with dienophiles in a [4+2] cycloaddition process although in this transformation the recovery of the catalyst is more difficult as it has to proceed through an elimination-type process (Scheme 3.9). On the other hand and with respect to the enantiocontrol, the catalyst should be able to favour the formation of one dienamine conformer over the others, apart from the (*E*,*Z*) or (*E*,*E*) possible configurations of the C-C double bonds, the conformational orientation of the second double bond relative to the substituent at C-2 of the catalyst (s-*trans*, s-*cis*) has to be controlled as well. In addition, when the reaction pathway occurs *via* the γ-terminus, as the catalyst is located in a remote position in the carbon chain in comparison with the enamine catalysis, the face discrimination for the addition of the incoming electrophile becomes more challenging.



Scheme 3.9. Possible reactivity of the dienamine activated specie.

Jørgensen and co-workers presented the first γ-functionalization of γ-enolizable α,β-unsaturated aldehydes with diethyl azodicarboxylate under dienamine catalysis, employing a secondary chiral amine; the final product was

obtained in a moderate yield and an excellent enantiocontrol.[47] Later studies about the transformation suggested that the preferred dienamine conformer would be the *E*,s-*trans*,*Z* and that the trajectory of the electrophile would be directed by steric shielding exerted by the bulky substituent of the aminocatalyst (Scheme 3.10).[48]



Scheme 3.10. Asymmetric γ-functionalization of enals *via* dienamine.

Although, steric shielding is the most studied strategy for achieving facial stereodiscrimination,[49] H-bonding directing approaches have also been reported with successful results. As the γ-position is further in the chain from the catalyst moiety than the α-position, an aminocatalyst with a longer arm was necessary in order to direct the addition regioselectively; in this sense, the squaramide-based pyrrolidine catalyst proved to be able to simultaneously generate the dienamine intermediate and direct the approach of the electrophile through hydrogen-bonding interactions, isolating the final product with a remarkable diastereo- and enantiocontrol (Scheme 3.11).[50]

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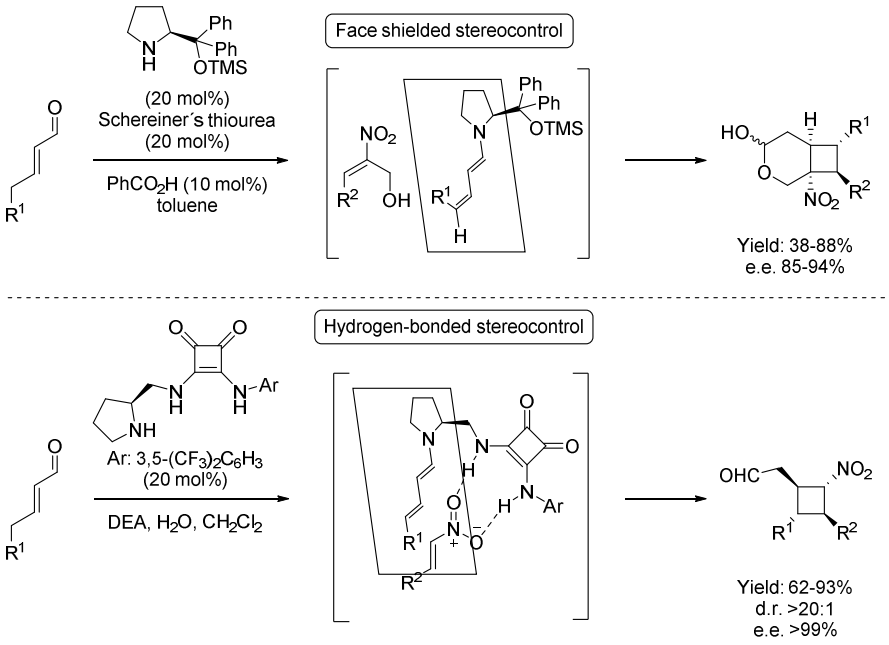
47 Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

48 Seegerer, A.; Hioe, J.; Hammer, M. M.; Morana, F.; Fuchs, P. J. W.; Gswchwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 9864.

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

50 Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.



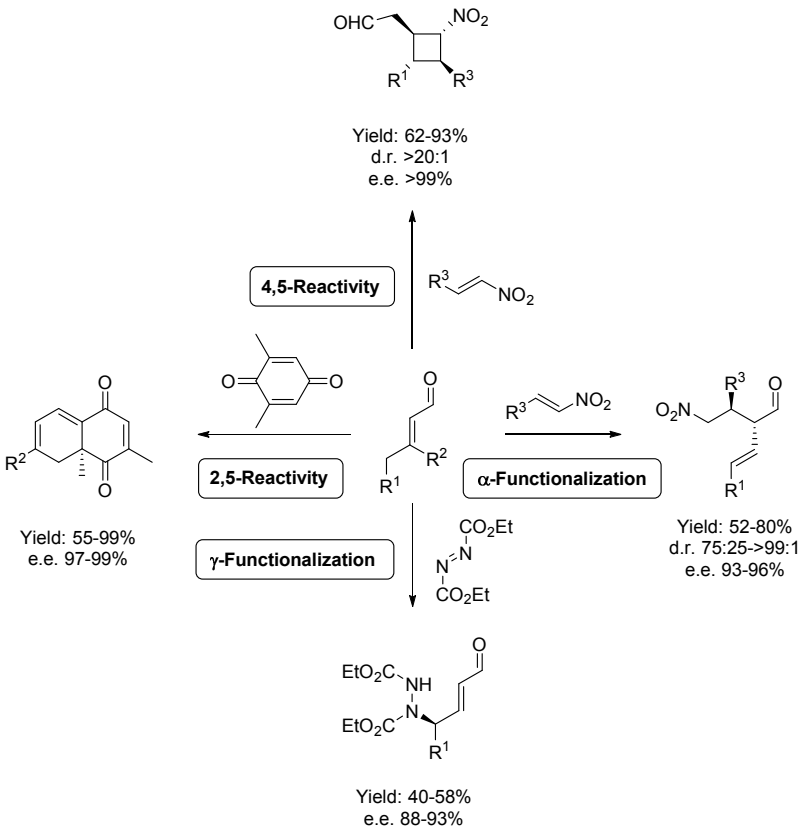
Scheme 3.11. Two different approaches for the incoming electrophile under dienamine catalysis.

The dienamine activation method has been applied to the aforementioned reactivity patterns that extended conjugation presents. Both α-[51] and γ-functionalizations[48] have been developed obtaining highly enantioenriched products. Besides, the dienamine intermediate can also promote 2,5-[52] and 4,5-reactivity[50] through various tandem processes and cycloadditions, since the enamine or iminium ion generated after the first step can further react promoting

[51] Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660.

[52] Johansen, T. K.; Gómez, C. V.; Bak, J. R.; Davis, R. L.; Jørgensen, K. A. *Chem. Eur. J.* **2013**, *19*, 16518.

a second addition in the β- or α-position respectively or the active species can act as an olefin or a diene in cycloaddition reactions (Scheme 3.12).[53]



Scheme 3.12. Various asymmetric transformations under dienamine catalysis.

More recently, the possibility of further propagating the HOMO-raising electronic effect, along the poly-unsaturated carbonyl compound has been

[53] For a selected review on dienamine catalysis, see: Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812.

demonstrated trough trienamine[54] and tetraenamine[55] activated intermediates. Trienamines usually participate in Diels-Alder type reactions with electron-deficient dienophiles, due to the HOMO-rising effect and their poly-unsaturated structure. Indeed, the first transformation *via* trienamine catalysis was a Diels-Alder reaction between 2,4-dienals and 3-olefinic oxindoles, obtaining the final product with excellent stereocontrol.[54a] Since then, the robustness of the reaction has been tested with various dienophiles such as nitroalkenes[56] and olefinic cianoacetates[54a] among others. Moreover, polyunsaturated ketones are also adequate to undergo trienamine formation, typically requiring the use of primary amines and acid additives in order to facilitate the more difficult condensation between the ketone and the aminocatalyst (Scheme 3.13).[57]

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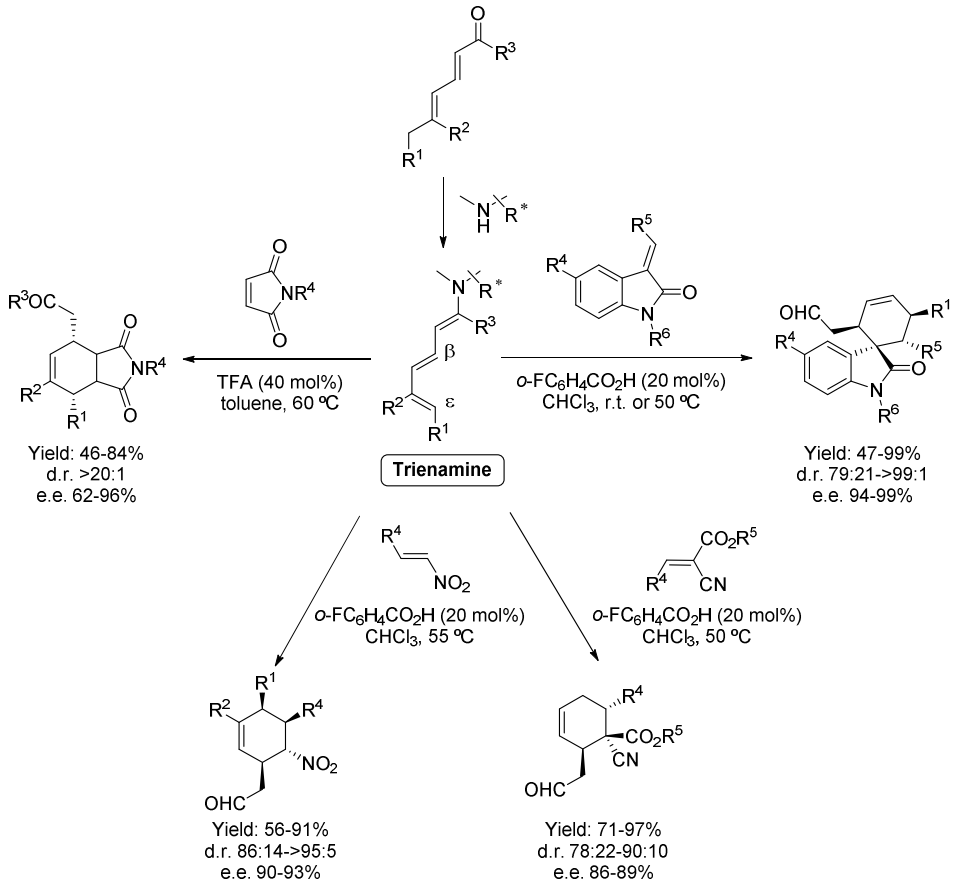
54 For pionering work in trienamine catalysis, see: (a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. For selected reviews, see: (b) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709. (c) Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5290.

55 For selected examples on tetraenamine catalysis, see: (a) Stiller, J.; Poulsen, P. H.; Cruz, D. C.; Dourado, J.; Davis, R. L.; Jørgensen, K. A. *Chem. Sci.* **2014**, *5*, 2052. (b) Zhou, Q.-Q.; Xiao, Y.-C.; Yuang, X.; Chen, Y.-C. *Asian J. Org. Chem.* **2014**, *3*, 545.

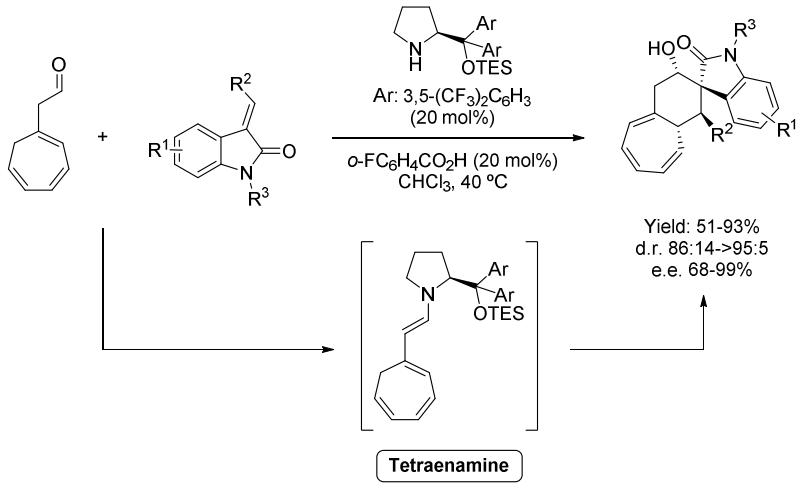
56 Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638.

57 Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2012**, *51*, 4401.



Scheme 3.13. Asymmetric Diels-Alder reaction *via* trienamine catalysis.

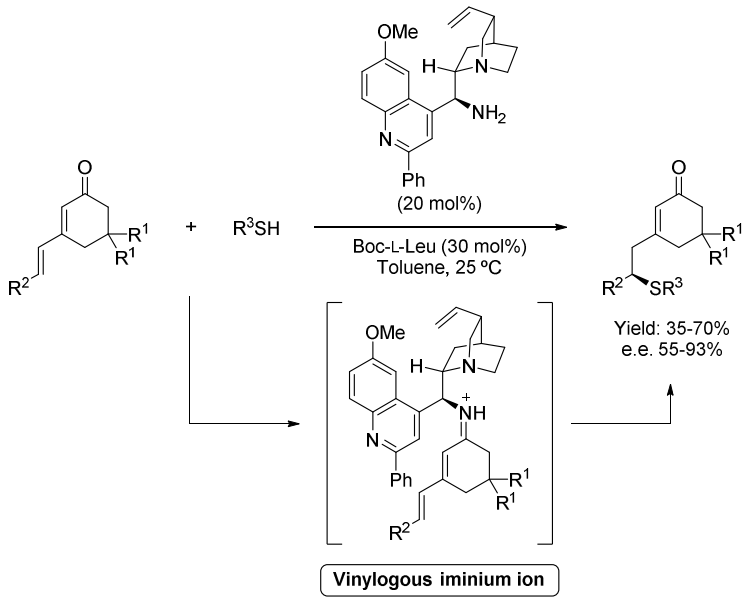
Very configurationally rigid carbonyl systems are necessary for the formation of the tetraenamine species. Hence, only a limited number of reports about this activation mode have been published. Tetraenamines, as poly-unsaturated highly energetic HOMO species, can take part in formal (4+2) cycloadditions with electron-poor olefins in a stereocontroled fashion (Scheme 3.14).



Scheme 3.14. Formal (4+2) cycloaddition *via* tetraenamine catalysis.

Finally, not only the HOMO-raising, but also the LUMO-lowering activating effect has been spread along the π-system of poly-unsaturated carbonylic chains. However, due to the reduced reactivity of the vinylogous iminium ion, this activation method has been less studied than its analogues di- and trienamine.[58] This approach allows the direct and selective functionalization of unmodified carbonyl compounds at the remote δ-position by using nucleophiles, in a sterocontrolled way (Scheme 3.15).

[58] For selected examples on vinylogous iminium ion catalysis, see: (a) Silvi, M.; Chatterjee, I.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10780. (b) Halskov, K. S.; Naicker, T.; Jensen, M. E.; Jørgensen, K. A. *Chem. Commun.* **2013**, *49*, 6382. (c) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 6439.

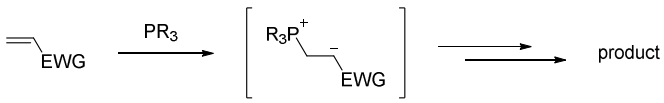


Scheme 3.15. δ-functionalization of a polyunsaturated carbonyl compound *via* vinylogous iminium ion catalysis.

It can be concluded that aminocatalysis has satisfactorily been applied in different transformations involving aldehydes and ketones with various ranges of unsaturation, providing the final adducts in high yields and excellent stereocontrol, regardless the position of the carbonyl chain that has taken part in the reaction.

4. CHIRAL NUCLEOPHILIC PHOSPHINE CATALYSIS

Trivalent phosphines and their derivatives have been widely used in organic transformations. Traditionally they were added as stoichiometric reagents in various processes, such as Wittig, Staudinger and Mitsunobu reactions;[59] and lately, they have been mainly used as ligands for transition-metal catalysed reactions in modern organic chemistry.[60] However, their nucleophilicity also makes them powerful organocatalysts; the nucleophilic attack of the phosphine catalyst to an electron-poor nuclei (normally carbon atoms) leads to a Lewis adduct, namely enolate zwitterion, as reaction intermediate, which by further reaction steps participates in the formation of new bonds (Scheme 4.1).



Scheme 4.1. General example of nucleophilic phosphines as organocatalysts.

The non-bonded lone pair of electrons presence in phosphines makes them able to form new bonds between the phosphorous atom and the electrophilic substrate to be activated. Phosphines are generally less basic and more nucleophilic than similarly substituted amines. For instance, trimethylphosphine is about 100-fold more nucleophilic than trimethylamine, yet the last is 100-fold more basic than trimethylphosphine. Polarizability of phosphines might be the reason for this non-

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[59] For a selected review on the mayor stoichiometric uses of tertiary phosphines, see: Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, *3*, 317.

[60] For selected reviews on phosphines as ligands, see: (a) Tic, W. J.; Zoltanski, A. *Current Catalysis* **2015**, *4*, 155. (b) Tschan, M. J.-L.; Diebolt, O.; van Leeuwen, P. W. N. M. *Top. Catal.* **2014**, *57*, 1054. (c) Oestreich, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 2282. (d) García-Álvarez, J.; García-Garrido, S. E.; Cadierno, V. *J. Organomet. Chem.* **2014**, *751*, 792. (e) Wong, S. M.; So, C. M.; Kwong, F. Y. *Synlett* **2012**, *23*, 1132. For a selected chapter about phosphines as ligands, see: (f) Stradiotto, M.; Lundgren, R. J. In *Ligand Design in Metal Chemistry: Reactivity and Catalysis*; Stradiotto, M.; Lundgren, R. J., Eds.; John Wiley & Sons: Chichester, UK, 2016; pp 104-133.

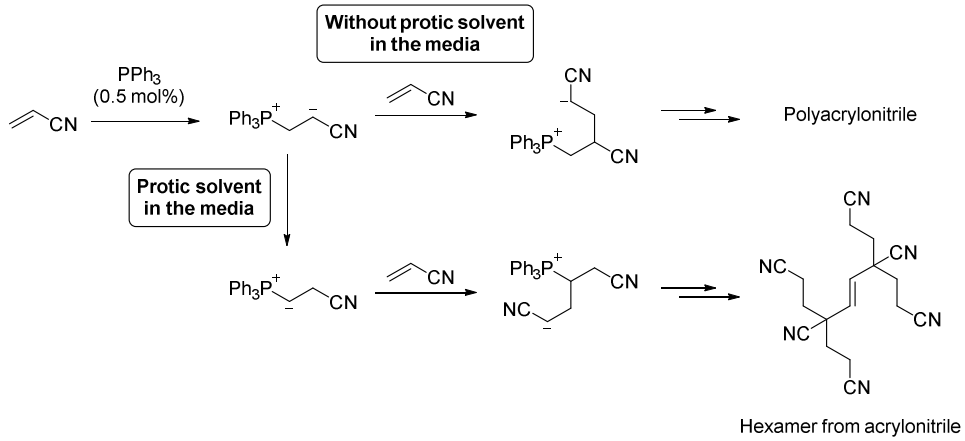
linear relationship.[61] On the other hand, the substituents placed in the phosphorous atom affect the reactivity of the molecule. In this sense, nucleophilicity is stronger in trialkylphosphines and decreases with aryl substitution (Table 4.1).

Table 4.1. Nucleophilicity and basicity properties of some nucleophiles.[62]

Nucleophile	n_{MeI}	pK_a (H_2O)	Nucleophile	n_{MeI}	pK_a (H_2O)
PhS^-	9.9	2.9	PhSH	5.7	-
PEt_3	**8.7**	**8.7**	NH_3	5.5	9.3
PBu_3	**8.7**	**8.4**	SEt_2	5.3	-5.3
I^-	7.4	-10.7	**$P(OMe)_3$**	**5.2**	**2.6**
$AsEt_3$	6.9	<2.6	$AsPh_3$	4.8	-
NEt_3	6.7	10.7	**PPh_3**	**1.3**	**2.7**

It was not until the 1960s that the first phosphine-catalysed reactions appeared in the literature. Price reported in 1962 several polymerization processes of acrylonitrile involving a phosphorus ylide intermediate (Scheme 4.2).[63]

[61] Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.
[62] Pearson, R. G.; Sobel, H. R.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.
[63] Takashina, N.; Price, C. C. *J. Am. Chem. Soc.* **1962**, *84*, 489.



Scheme 4.2. Polymerization of acrylonitrile through phosphorous ylide intermediates.

Since then, a wide variety of organocatalytic transformations have been developed and the significant growth of the field could be attributed to various factors: (a) the unique properties of trivalent phosphines gave the opportunity to develop novel transformations involving electron-deficient alkynes, alkenes and allenes, that could not have been promoted by other nucleophilic catalysts; (2) usually by-products are not formed during the reaction and the processes are highly atom-economical; (3) the reaction topology can be influenced by the choice of the phosphine catalyst.[64]

By using chiral phosphines, the stereochemical outcome of the transformation can be controlled in many cases. In this sense, a handful of chiral phosphines have been found to be effective in a variety of reactions (Figure 4.1). Chiral phosphines

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[64] For selected reviews on nucleophilic chiral phosphine catalysis, see: (a) Gao, Y.-N.; Shi, M. *Chinese Chemical Lett.* **2017**, *28*, 493. (b) Sun, Y.-L.; Wei, Y.; Shi, M. *Chem. Cat. Chem.* **2017**, *9*, 718. (c) Li, H.; Lu, Y. *Asian J. Org. Chem.* **2017**, *6*, 1130. (d) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, *49*, 1369. (e) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (f) Wei, Y.; Shi, M. *Chem. Asian J.* **2014**, *9*, 2720. (g) Marinetti, A.; Voituriez, A. *Synlett* **2010**, *2*, 174. (h) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102.

without additional functionalities usually had been previously designed as ligands for metal-catalysed reactions and they have been only effective in a few organocatalytic transformations. On the other hand, multifunctional chiral phosphines that have been synthesised installing a nucleophilic phosphine and a hydrogen-bonding moiety on a chiral backbone, in many cases derived from amino acid and thiourea systems, have provided excellent catalytic activities and enantioselectivities.

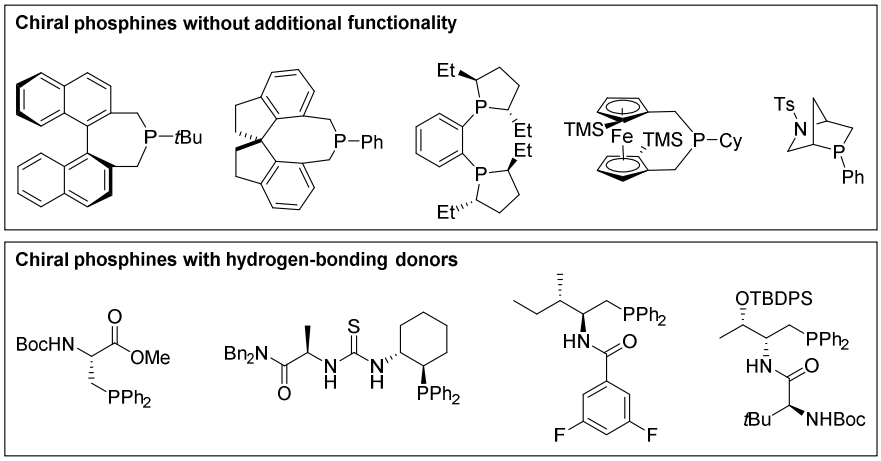


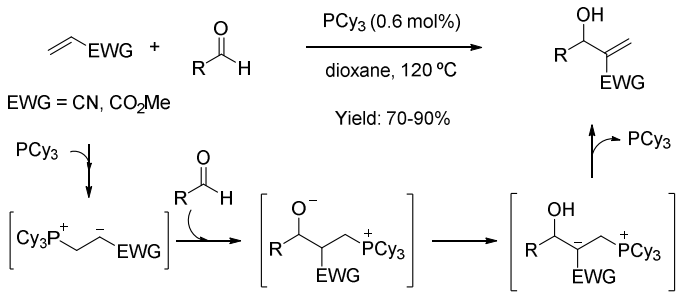
Figure 4.1. Typical chiral phosphines used in nucleophilic phosphine catalysis.

The ability of nucleophilic phosphines to activate olefins, alkynes and allenes has been extended to various reactions, achieving high stereocontrol in many cases. Hence, this covalent activation mode has gained importance inside the organocatalysis.

4.1. Morita-Baylis-Hillman reaction

Probably the most notable example from the time were the field of organophosphines was starting to grow would be the reaction of an activated olefin

and an aldehyde catalysed by a phosphine, described by Morita (Scheme 4.3).[65] This transformation, together with the similar amine-catalysed reaction discovered by Baylis and Hillman,[66] is nowadays known as the Morita-Baylis-Hillman reaction and it has become a very useful methodology in organic chemistry for the formation of C-C bonds. The transformation could be defined as the formation of α-methylene-β-hydroxycarbonyl compounds by addition of α,β-unsaturated carbonyl compounds to aldehydes in the presence of a nucleophilic catalyst. Suitably activated imines can also participate in the reaction, naming it aza-Morita-Baylis-Hillman reaction.[67]



Scheme 4.3. Phosphine-catalysed reaction between activated olefins and aldehydes.

The most significant advancements on the asymmetric Morita-Baylis-Hillman reaction have been achieved by the employment of chiral amine catalysts, although chiral phosphines have also proved to be useful, providing remarkable stereocontrol on the transformation. A good example of this behaviour is shown in Scheme 4.4, with the ability of amino acid derived phosphinothioureas to catalyse

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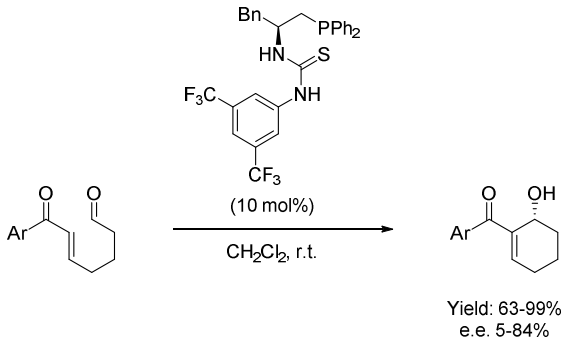
65 Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

66 (a) Baylis, A. B.; Hillman, M. E. D. *Offenlegungsschrift 2144113*; US Patent 3 743 669, **1972**. (b) Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 34174q.

67 For selected reviews on Morita-Baylis-Hillman reaction, see: (a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659. (b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1.

satisfactorily the intramolecular Morita-Baylis-Hillman reaction between aldehydes and aromatic enones, obtaining the final products in high yields and up to 84% enantiomeric excess.[68]



Scheme 4.4. Phosphine catalysed asymmetric intramolecular MBH reaction.

Intermolecular versions of the Morita-Baylis-Hillman reaction have been also developed under nucleophilic phosphine catalysis. An example of a highly efficient approach to this reaction is shown in Scheme 4.5, where activated acrylates reacted with electron rich and poor aromatic aldehydes with high stereocontrol.[69] Moreover, the scope of the transformation could be broaden to the aza counterpart obtaining excellent results.[70]

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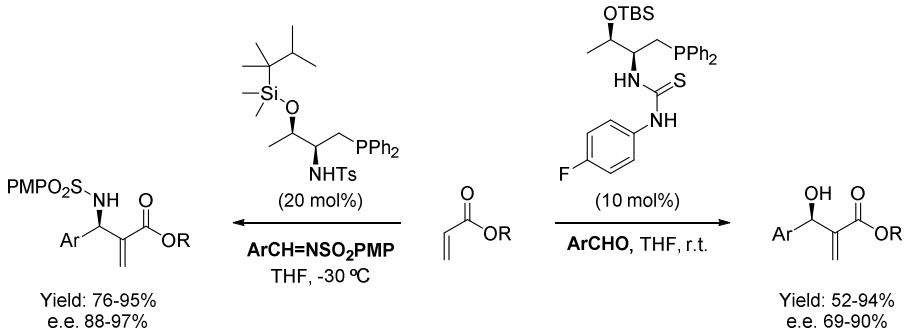
68 Gong, J.-J.; Yuan, K.; Song, H.-L.; Wu, X.-Y. *Tetrahedron* **2010**, *66*, 2439.

69 (a) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *Org. Biomol. Chem.* **2011**, *9*, 6734. (b) Gong, J.-J.; Yuan, K.; Wu, X.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2117.

70 Zhong, F.; Wang, Y.; Han, X.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 1310.

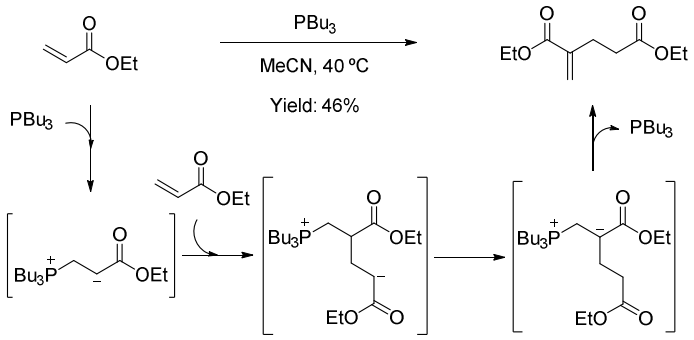


Scheme 4.5. Phosphine catalysed asymmetric intermolecular MBH and aza-MBH reactions.

4.2. Rauhut-Currier reaction

Previous to the Morita-Baylis-Hillman reaction, in 1963 Rauhut and Currier reported the dimerization of ethyl acrylate by tributylphosphine. One molecule of ethyl acrylate would suffer the nucleophilic attack of the phosphine catalyst leading to the formation of the active ylide, which would add to the second molecule of ethyl acrylate in a Michael type addition. A final prototropic shift followed by an elimination process formed the dimer, releasing the organocatalyst at the same time (Scheme 4.6).[71]

[71] (a) Rauhut, M. M.; Currier, H. *Dialkyl 2-Methyleneglutarates*, U.S. Patent 3 074 999, **1963**. (b) Rauhut, M. M.; Currier, H. *Chem. Abstr.* **1963**, *58*, 66109.



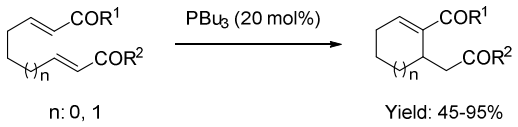
Scheme 4.6. Rauhut-Currier reaction, dimerization of ethyl acrylate.

The Rauhut-Currier reaction, also known as the vinylogous Morita-Baylis-Hillman reaction, has been proved to be a useful strategy for the α-functionalization of α,β-unsaturated systems.[72] However, when the transformation involves two different types of Michael acceptors the control of the chemo- and stereoselectivity presents mayor challenges, as both alkenes could either serve as the nucleophilic or electrophilic partner for either homodimerization or cross-coupling, however these side reactions could be minimized through the intramolecular version of the transformation. In this sense, in 2002 Krische[73] and Roush[74] independently developed a phosphine-catalysed intramolecular reaction of enones for the efficient synthesis of five- and six-membered rings with excellent chemoselectivity (Scheme 4.7).

[72] For selected reviews on Rauhut-Currier reaction, see: (a) Bharadwaj, K. C. *RSC Adv.* **2015**, *5*, 75923. (b) Xie, P.; Huang, Y. *Eur. J. Org. Chem.* **2013**, 6213.

[73] Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402.

[74] Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.



Scheme 4.7. Intramolecular cross Rauhut-Currier reaction between enones.

Few years later, the first enantioselective examples were reported employing a chiral thiolate[75] and enamine catalysis,[76] as well as a rhenium phosphine complex that provided low enantiocontrol.[77] It was not until 2011 that a highly enantioselective intramolecular Rauhut-Currier reaction between dienones catalysed by chiral phosphines derived from amino acids was developed (Scheme 4.8).[78] Moreover, the same strategy could be applied to the desymmetrization of prochiral dienones, obtaining the final cycloaduct as a single diastereoisomer and with high stereocontrol.[79]

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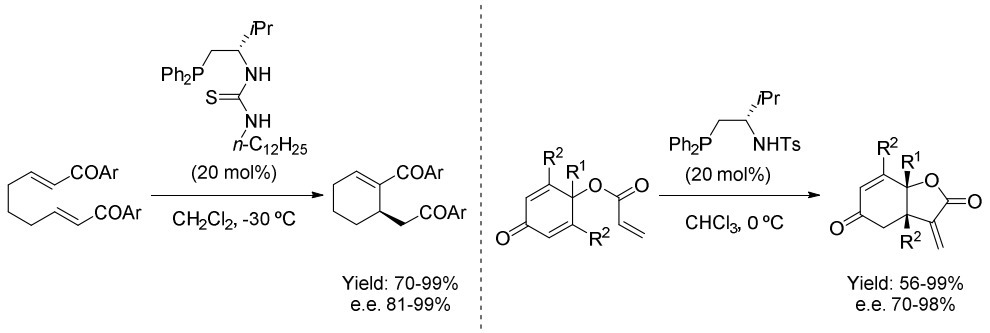
75 Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256.

76 Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11*, 4116.

77 Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986.

78 (a) Gong, J.-J; Li, T.-Z.; Pan, K.; Wu, X.-Y. *Chem. Commun.* **2011**, *47*, 1491. (b) Zhang, X.-N.; Shi, M. *Eur. J. Org. Chem.* **2012**, 6271.

79 (a) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5423. (b) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Suzuki, M.; Enders, D.; Sasai, H. *Tetrahedron* **2013**, *69*, 1202.



Scheme 4.8. Phosphine catalysed intramolecular asymmetric Rauhut-Currier reactions.

Recently, the more challenging asymmetric intermolecular Rauhut-Currier reaction has been also developed under nucleophilic phosphine catalysis. Huang´s group first reported a cross Rauhut-Currier reaction of 3-acyl acrylates with methyl vinyl ketones, obtaining the addition product in high yields and excellent stereocontrol.[80] The scope of the transformation could be satisfactorily broaden to the less reactive 2-ene-1,4-diones, as well as to different vinyl ketones[81], acrolein[82] and 2-vinylpyridines.[83] Moreover, perfluoroalkyl-substituted compounds have been obtained from the reaction between β-perfluoroalkyl enones and vinyl ketones with high e.e. values.[84] Other examples in the literature include the use of α,β-unsaturated imines in cross aza-Rauhut-Currier reactions followed by a second step leading to cycloadducts in high yields and excellent diastereo- and enantiocontrol (Scheme 4.9).[85]

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80 Dong, X.; Liang, L.; Li, E.; Huang, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 1621.

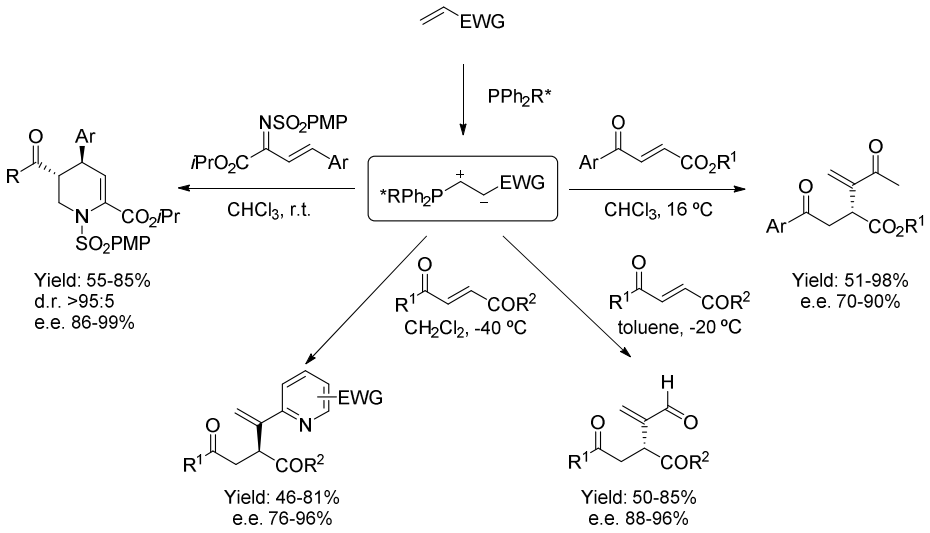
81 Zhou, W.; Su, X.; Tao, M.; Zhu, C.; Zhao, Q.; Zhang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14853.

82 Zhou, W.; Chen, P.; Tao, M.; Su, X.; Zhao, Q.; Zhang, J. *Chem. Commun.* **2016**, *52*, 7612.

83 Qin, C.; Liu, Y.; Yu, Y.; Fu, Y.; Li, H.; Wang, W. *Org. Lett.* **2018**, *20*, 1304.

84 Tao, M.; Zhou, W.; Zhang, J. *Adv. Synth. Catal.* **2017**, *359*, 3347.

85 (a) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7825. For other examples, see: (b) Zhang, X.-N.; Dong, X.; Wei, Y.; Shi, M. *Tetrahedron* **2014**, *70*, 7158. (c) Zhang, X.-N.; Chen, G.-Q.; Dong, X.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2013**, *355*, 3351. (d) Jin, Z.; Yang, R.; Du, Y.; Tiwari, B.; Ganguly, R.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 3226.



Scheme 4.9. Phosphine catalysed intermolecular asymmetric Rauhut-Currier reactions.

Finally, the vinylogous Rauhut-currier reaction was developed by performing the addition of the activated olefin over *para*-quinone methides, which is considered a vinylogous Michael acceptor. Both the intra-[86] and intermolecular[87] processes rendered satisfactorily, observing a remarkable stereocontrol (Scheme 4.10).

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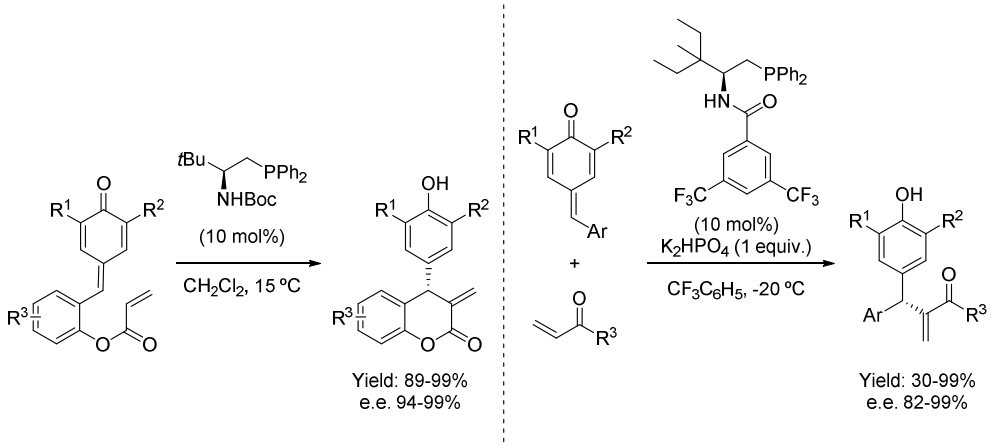
86 Zhang, X.-Z.; Gan, K.-J.; Liu, X.-X.; Deng, Y.-H.; Wang, F.-X.; Yu, K.-Y.; Zhang, J.; Fan, C.-A. *Org. Lett.* **2017**, *19*, 3207.

87 Li, S.; Liu, Y.; Huang, B.; Zhou, T.; Tao, H.; Xiao, Y.; Liu, L.; Zhang, J. *ACS Catal.* **2017**, *7*, 2805.



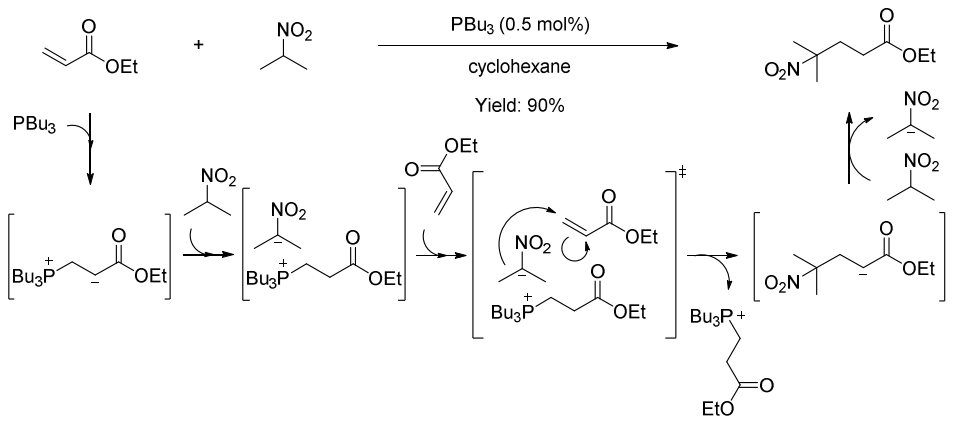
Scheme 4.10. Phosphine catalysed vinylogous asymmetric Rauhut-Currier reactions.

4.3. Michael reaction

Michael reactions catalysed by nucleophilic phosphines were not developed until 1973, when White and Baizer presented the addition of 2-nitropropane to ethyl acrylate in the presence of tributylphosphine rendering the addition product in high yield (Scheme 4.11).[88] The weak basicity of the phosphine suggests that in this case, the mechanism of the Michael addition does not proceed directly through the deprotonation of the nucleophile, but rather an addition to the acrylate occurs as the initial step. The formed zwitterionic species is the one behaving as the base of the reaction, deprotonating the nucleophile which then undergoes Michael addition to an alkene that has not suffered the addition of the phosphine. Similar

[88] White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597.

reactions were reported with other nucleophiles such as malonates and alcohols, as well as to various Michael acceptors.[89]



Scheme 4.11. Phosphine catalysed Michael addition between 2-nitropropane and ethyl acrylate.

In view of the accepted mechanism, the key for developing the enantioselective version would be to control the addition of the ion pair formed by the deprotonated nucleophile and the phosphonium intermediate to the Michael acceptor. In this sense, Lu and co-workers reported the first asymmetric Michael addition catalysed by chiral phosphines. 3-substituted oxindoles reacted with vinyl ketones in the presence of valine-based phosphine amide catalysts in high yields and excellent stereocontrol.[90] They proposed that a hydrogen-bonding interaction between the amide NH and the enolate oxygen atom of the nucleophile facilitates the formation of the nucleophile-phosphonium ion pair, also making the latter

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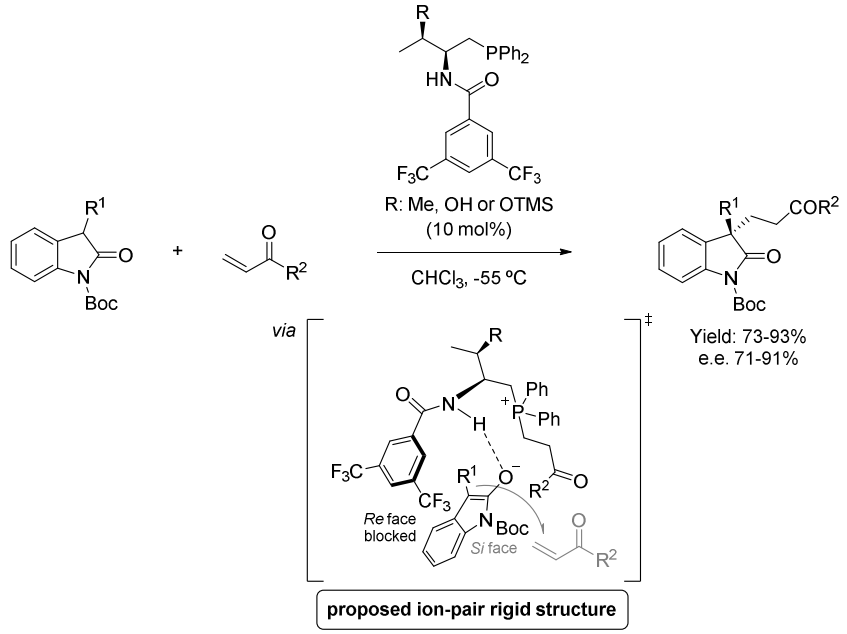
[89] (a) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598. (b) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

[90] (a) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 943. For a similar example expanding the scope of Michael acceptor, see: Huang, B.; Li, C.; Wang, H.; Wang, C.; Liu, L.; Zhang, J. *Org. Lett.* **2017**, *19*, 5102.

conformationally rigid. The aryl group present in the catalyst would block the *Re*-face making the approach of the incoming electrophile more favourable from the *Si*-face, therefore controlling the stereochemical outcome of the reaction (Scheme 4.12).

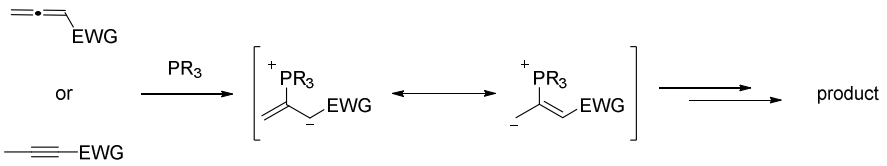


Scheme 4.12. Phosphine catalysed asymmetric Michael addition between 3-substituted oxindoles and vinyl ketones.

4.4. Umpoled nucleophilic addition to activated alkynes and allenes

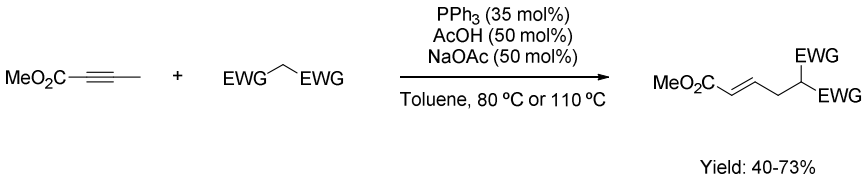
The addition of nucleophilic phosphines to activated alkynes and allenes generates a common zwitterionic intermediate that can further react with nucleophiles leading to the formation of a new bond (Scheme 4.13). As the resonance form of the generated intermediate with the terminal double bond is the one reacting with the nucleophile an umpoled reactivity can be considered for

both alkynes and the allenes. In the case of activated alkynes, under common reaction conditions the γ-carbon is considered a nucleophilic position, as it can be quite easily deprotonated, however, when catalysing the reaction with a phosphine it might also function as an electrophilic position. On the other hand, phosphines make possible the addition of nucleophiles to the relatively electron-rich β,γ-double bond of activated allenes.



Scheme 4.13. Addition of nucleophilic phosphines to activated alkynes and allenes.

The first reported example of this type of reactivity is the umpoled addition to acetylenic acceptors presented by Trost (Scheme 4.14).[91] The γ-nucleophilic addition of several carbon nucleophiles to methyl but-2-ynoate was promoted by tributylphosphine, obtaining the final adducts in good to high yields. It should be mentioned that the scope of the reaction could be expanded to nitrogen pronucleophiles satisfactorily.[92]



Scheme 4.14. Umpoled reactivity of methyl but-2-ynoate catalysed by trihenylphosphine.

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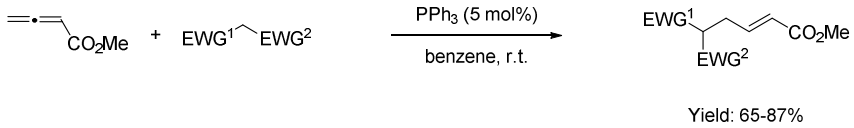
91 Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167.
92 Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670.

One year later, Lu extended this chemistry to electron poor allenes.[93] In this sense, he presented the addition of carbon nuleophiles to methyl 2,3-butadienoate in high yields and excellent diastereocontrol towards the *E* product in the presence of 5 mol% of triphenylphiosphine (Scheme 4.15).



Scheme 4.15. Umpoled reactivity of methyl 2,3-butadienoate catalysed by triphenylphosphine.

Some years after the discovery of the umpolung effect promoted by phosphines when reacting with alkynes and allenes, the asymmetric γ-addition of alcohols[94] and amines[95] to alkynes was developed using a chiral spirocyclic phosphine in both inter- and intramolecular fashion. The chiral organocatalyst provided the final product in high yields and an excellent enantiocontrol in all cases (Scheme 4.16).

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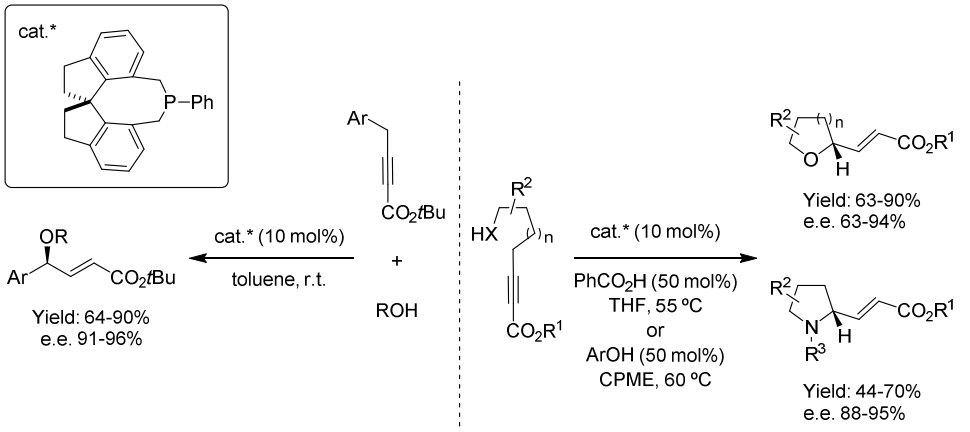
93 Zhang, C.; Lu, X. *Synlett* **1995**, *6*, 645.

94 For the intramolecular example, see: (a) Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225. For the intermolecular example, see: (b) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 2525.

95 Ziegler, D. T.; Fu, G. C. *J. Am. Chem. Soc.* **2016**, *138*, 12069.



Scheme 4.16. Phosphine catalysed asymmetric γ-addition to alkynoates.

On the other hand, structurally very different chiral phosphines have been employed for the γ-addition of several nucleophiles to allenes. Allenoates and allenamides could be functionalised with thiols[96] and carbon nucleophiles such as nitrometane,[97] malonates[98] and 3-alkyl-substituted oxindoles.[99] As with the previous substrate, the phosphine catalysts were capable of activating the allenes, obtaining high yields, and they could perfectly control the stereochemical outcome of the reaction (Scheme 4.17).

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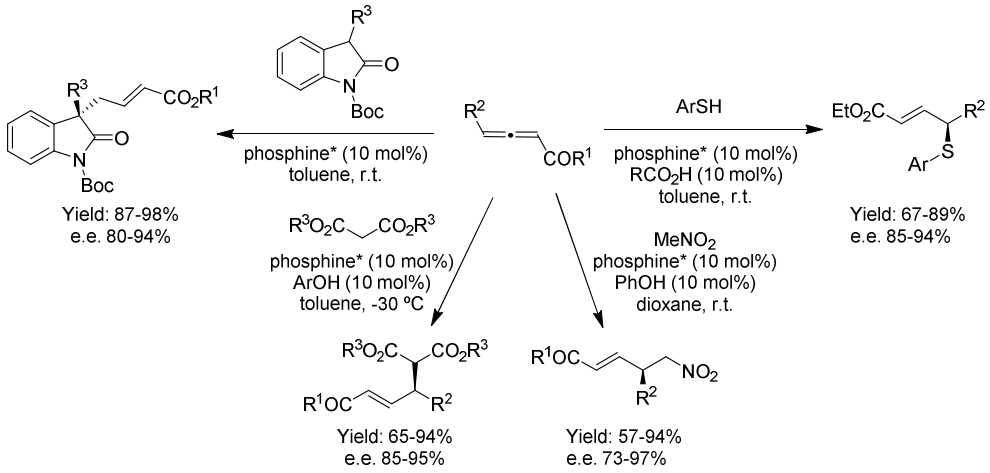
96 (a) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568. (b) Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196.

97 Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.

98 Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20652.

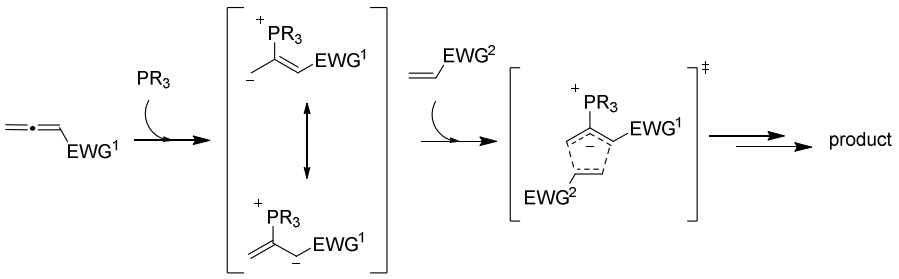
99 Wang, T.; Yao, W.; Zhong, F.; Pang, G. H.; Lu, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 2964.



Scheme 4.17. Phosphine catalysed asymmetric γ-addition to allenes.

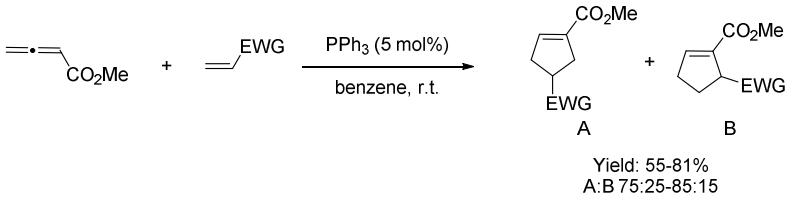
4.5. Cycloaddition reactions

The addition of a nucleophilic phosphine to an electron poor allene generates a conjugated 1,3-dipole, which apart from the abovementioned Michael addition, can also participate in cycloaddition reactions in the presence of dipolarophiles, such as electron poor olefins (Scheme 4.18).



Scheme 4.18. General example of cycloaddition reactions between activated allenes and electron poor olefins catalysed by nucleophilic phosphines.

In this sense, Lu and co-workers presented the first (3+2) annulation between allenoates and electron-deficient olefins in the presence of triphenylphosphine, rendering cyclopentenes in high yields and good regiocontrol. In all cases the α-addition product (A) was obtained in higher amount than the γ-addition product (B) (Scheme 4.19).[100]



Scheme 4.19. (3+2) annulation between allenoates and olefins promoted by triphenylphosphine.

With the aim of developing an asymmetric version of the previously described transformation, Zhang and co-workers synthesized chiral phosphines containing a rigid phosphorabicyclic structure in order to avoid the conformational flexibility. With this family of catalysts, they managed to carry out the first asymmetric (3+2) annulation between allenoates and electron-poor olefins.[101] The first reaction step occurred mainly through the α-addition, thus, obtaining the α-addition product (A) as the mayor or unique product; moreover excellent yields and enantiocontrol could be observed (Scheme 4.20). The scope of the enantioselective transformation could be further expanded to various electron-poor olefins, such as enones[102], and less activated α-substituted acrylates,[103] acrylamides[104] and maleimides.[105]

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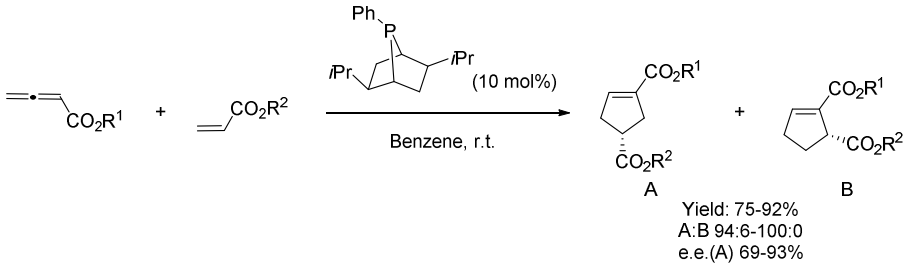
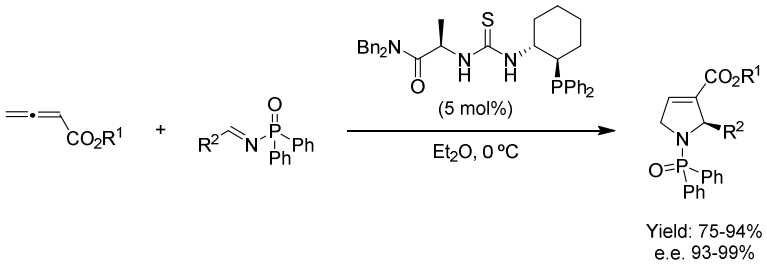
100 Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.
101 Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.
102 Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988.
103 Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726.
104 Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *Synthesis* **2011**, 1859.
105 Zhao, Q.; Han, X.; Wei, Y.; Shi, M.; Lu, Y. *Chem. Commun.* **2012**, *48*, 970.



Scheme 4.20. Phosphine catalysed asymmetric (3+2) annulation between allenoates and electron-poor olefins.

All the C_2 synthons of the (3+2) cycloaddition discussed so far are activated olefins, leading to substituted cyclopentenes. Five-membered structures containing a heteroatom could be furnished by reacting allenoates with imines, ketones and aldehydes.[106] In this sense, the cycloaddition between allenes and imines catalysed by chiral bifunctional phosphines provided dihydropyrrole adducts with excellent regio- and enantiocontrol (Scheme 4.21).[107]



Scheme 4.21. Phosphine catalysed enantioselective (3+2) annulation between allenoates and imines.

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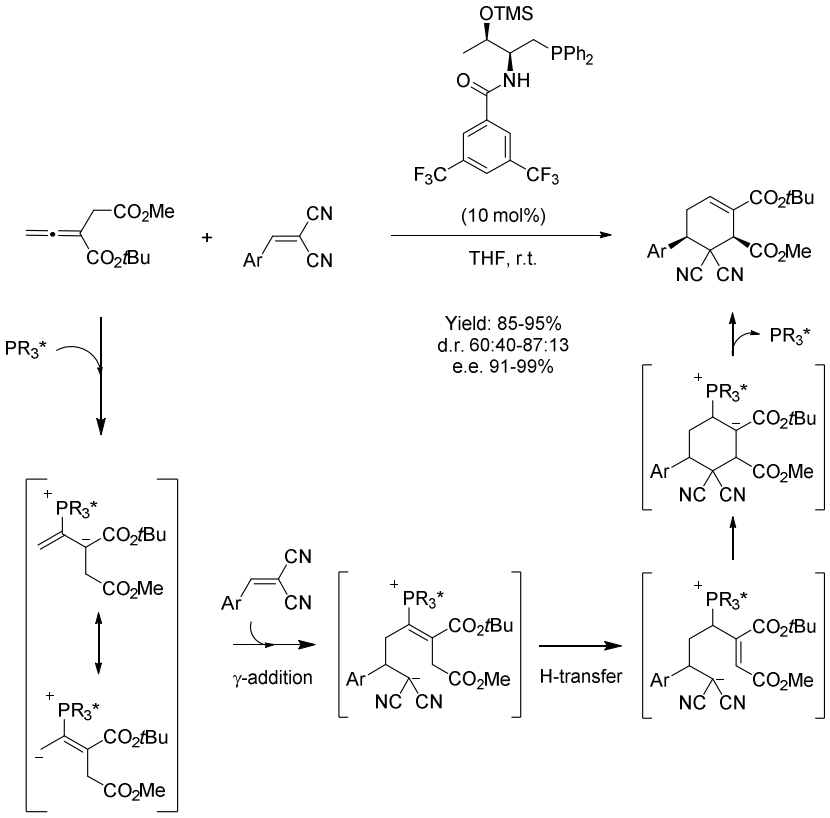
[106] For a selected review on phosphine catalysed cycloadditions between allenes and dipolarophiles, see: Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

[107] (a) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 767. (b) Fang, Y.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

On the other hand, α-substituted allenoates can also perform as C_4 synthons generating cyclohexenes upon reaction with an activated alkene. The phosphonium dienolate intermediate generated after the addition of the nucleophilic phosphine to the allenoate reacts with the electron-poor olefin through a γ-addition. The following hydrogen transfer leads to a phosphonium intermediate that delivers the six-membered ring after ring-closure.[108] As an example of this behaviour, aminoacid derived aminophosphines catalysed the reaction between 1-(*tert*-butyl) 4 methyl 2-vinylidenesuccinate and several substituted 2-methylenemalononitriles, obtaining the final cycloadducts in high yields, good diastereocontrol and excellent enantiocontrol (Scheme 4.22).[109]

[108] For a mechanistic study, see: Zhao, L.; Wen, M.; Wang, Z.-X. *Eur. J. Org. Chem.* **2012**, 3587.
[109] Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231.



Scheme 4.22. Phosphine catalysed asymmetric (4+2) cycloaddition of allenoates and electron poor olefins.

As it has been described, although the development of chiral nucleophilic phosphines started late in comparison with other asymmetric catalysts, they have gathered great interest as they are able to catalyse important reactions providing high yields and good control of the stereochemical outcome. Moreover, it has been proved that they can be used as an alternative to tertiary amines, especially in reactions where the first ones were not completely efficient.

5. PRECEDENTS OF THE GROUP

Historically, our research group has focused on developing new asymmetric transformations and at the beginning, the stereocontrol of the reactions was achieved by employing chiral auxiliaries. In this sense, very good results were obtained by using β-aminoalcohol (*S*,*S*)-(+)-pseudoephedrine as auxiliary in enolate chemistry[110] and several conjugate additions.[111]

More recently we moved to the organocatalysis field, studying asymmetric reactions promoted by various types of catalysts such as aminocatalysts, and in the past few years *N*-heterocyclic carbenes and chiral Brønsted acids. In this regard, aminocatalysis has been the most studied activation mode and the first example reported by the group consisted in a Michael reaction between α-enolizable aldehydes and β-nitroacroleine dimethyl acetal *via* enamine catalysis, obtaining the final adducts in high yield and excellent diastereo- and enantiocontrol (Scheme 5.1).[112]

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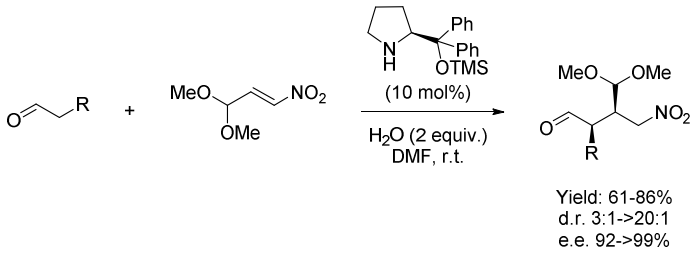
[110] Most recent aldol reaction: (a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460. (b) Most recent Mannich reaction: (b) Iza, A.; Vicario, J. L.; Badía, D.; Varrillo, L. *Synthesis* **2006**, 4065. Most recent electrophilic amination reaction: (c)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

[111] Conjugate addition reactions: (a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404. (b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. Aza-Michael reactions: (c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790. (d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Chem.* **2004**, *69*, 2588. Tandem reaction: (e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535.

[112] (a) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135. (b) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357.



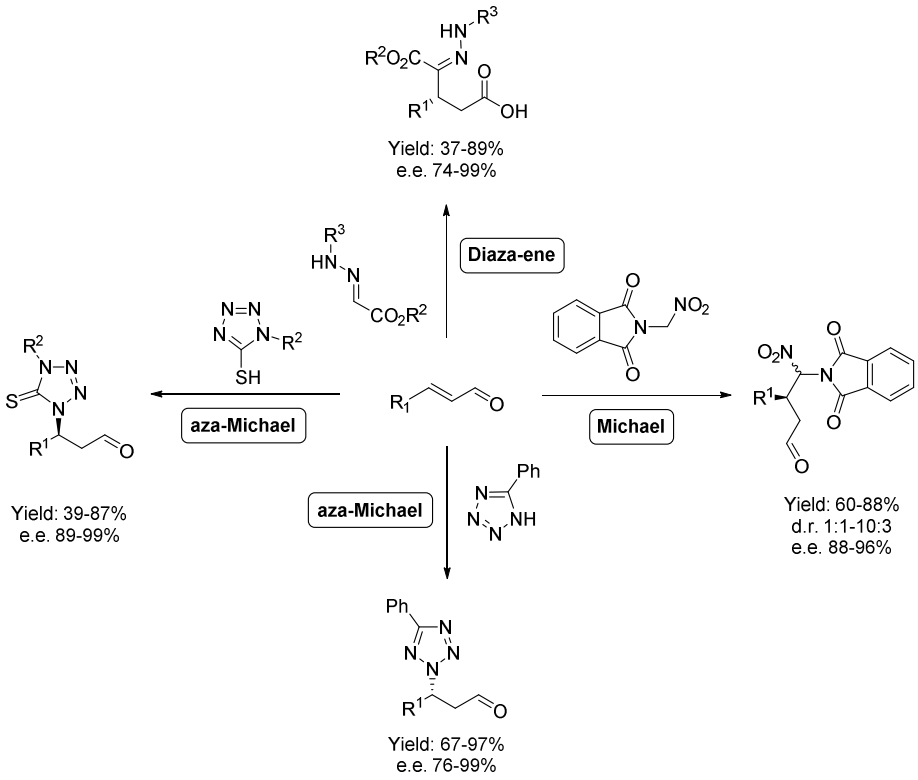
Scheme 5.1. Michael reaction between α-enolizable aldehydes and β-nitroacroleine dimethyl acetal *via* enamine catalysis.

Iminium ion catalysis was also studied in Michael[113], aza-Michael[114] and diaza-ene[115] processes, employing imizadolidinone type and diarylprolinol derived secondary amines satisfactorily (Scheme 5.2). In the case of the diaza-ene reaction, hydrazones were employed as glyoxyl anion equivalents in the enantioselective conjugate addition to α,β-unsaturated aldehydes for the synthesis of γ-hydrazonocarboxylic acids after oxidation of the aldehyde moiety and [1,3]-hydride shift process.

[113] Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.

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

[115] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872.

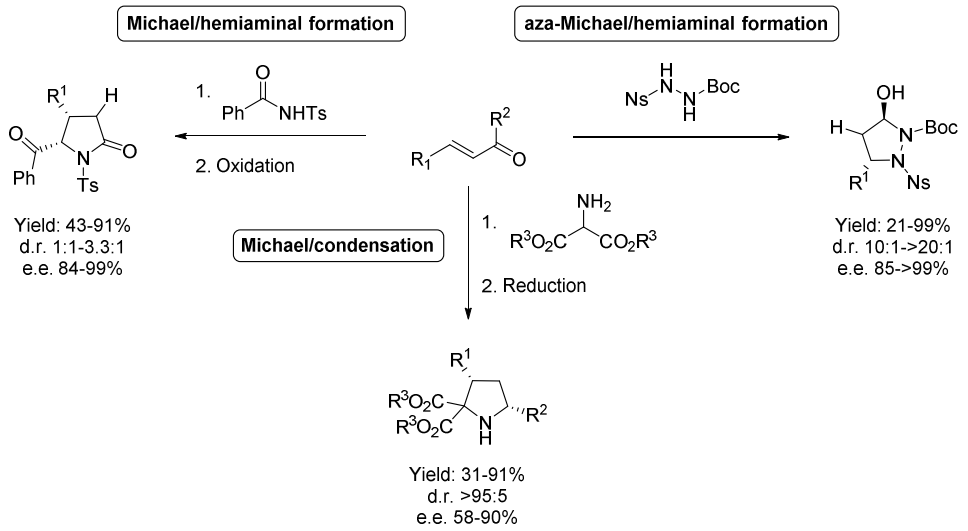


Scheme 5.2. Various transformations promoted by iminium ion catalysis.

Furthermore, Michael reactions followed by condensation or hemiaminal formation right after removal of the catalyst, led to cyclic products with an excellent stereocontrol. In this sense, pyrazolidines could be accessed through an enantioselective aza-Michael/hemiaminal cascade process from α,β-unsaturated aldehydes and *N*,*N*´-disubstituted hydrazines, employing a diarylprolinol silylated catalyst.[116] The just mentioned hemiaminal formation as a second step proved to be also useful after the Michael addition of *N*-monosubstituted α-aminoacetophenones to enals, furnishing highly enantioenriched γ-lactams after

[116] Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371.

oxidation.[117] With a similar strategy pyrrolidines could be also prepared through a cascade process between α,β-unsaturated ketones and dialkylaminomalonate, activating the Michael acceptor with a cinchona alkaloid based primary amine. An intramolecular condensation occurred after the nucleophilic addition and an additional diastereoselective reduction rendered the final products satisfactorily (Scheme 5.3).[118]



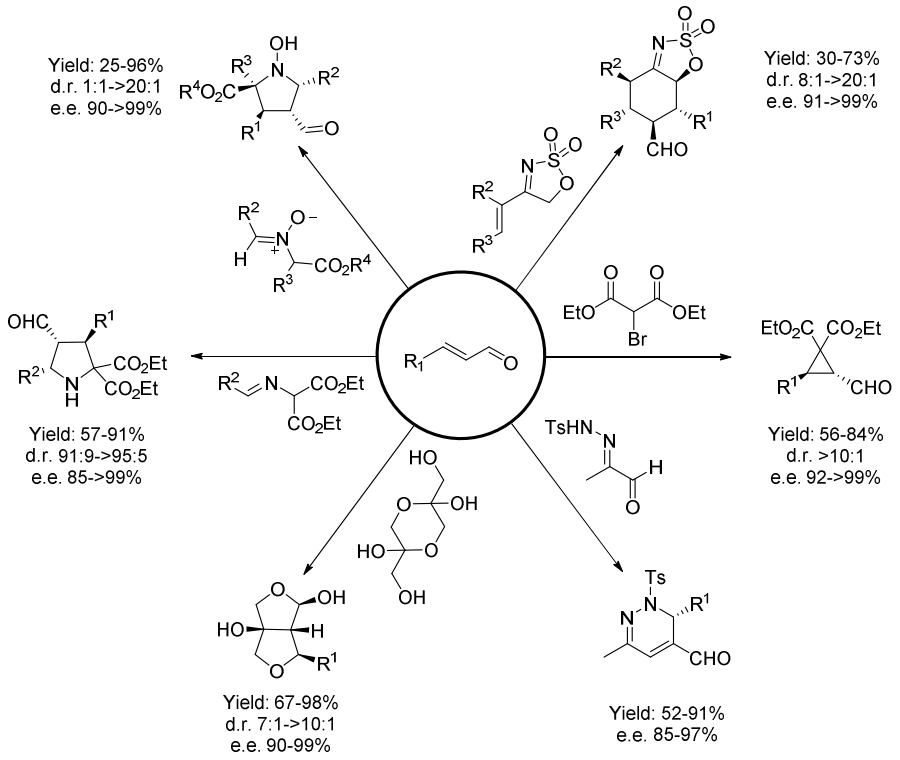
Scheme 5.3. Asymmetric cascade processes initiated by an iminium catalysed Michael-type addition.

Having studied both the enamine and iminium ion activation, as well as iminium ion initiated cascade processes, the group was encouraged to develop transformations where the enamine formed after the nucleophilic addition to the iminium ion would take part in a second step. The strategy could be applied for the synthesis of highly functionalised cyclopropanes by the conjugate addition of

[117] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653.
[118] Riaño, I.; Díaz, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330.

bromomalonates to enals followed by α-alkilation of the resulting enamine intermediate,[119] as well as in an aza-Michael/aldol condensation process for the formation of pyridazines.[120] A more complex oxa-Michael/aldol/hemiacetalization reaction could be also carried out rendering furofuranes in good yields and high stereocontrol starting from dihydroxyacetone and α,β-unsaturated aldehydes.[121] Moreover, the participation of azomethine ylides led to a formal (3+2) cycloaddition obtaining highly functionalised pyrrolidines in one single step,[122] and also *N*-(alkoxycarbonylmethyl)nitrones proved to promote the (3+2) annulation participating as 1,3-C-C dipoles in the presence of a thiourea.[123] Finally, densely functionalized cyclohexanes were synthesised trough a formal (4+2) cycloaddition with remarkable diastereo- and enantiocontrol (Scheme 5.4).[124]

[119] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701.
[120] Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092.
[121] Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701.
[122] (a) Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313. (b) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307. (c) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.
[123] Prieto, L.; Juste-Navarro, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764.
[124] Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.* **2015**, *2*, 206.

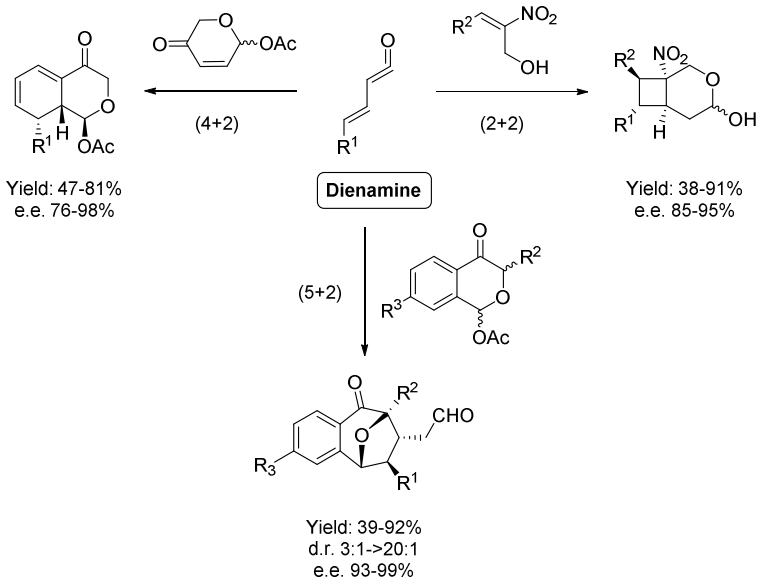


Scheme 5.4. Various cascade processes applying the iminium/enamine manifold.

On the other hand, carbonyl compounds have been functionalized in further positions applying the vinylogy principle. Dienamine activation approach has been used in a formal (2+2) cycloaddition between enals and α-hydroxyethylnitrostyrenes to afford enantioenriched cyclobutenes, through a Micahel/Michael process followed by a intrameculecular hemiacetalization.[125] The same β,γ-reactivity could be observed in a (5+2) cycloaddition with *in situ* generated oxidopyrylium ylides, providing direct access to compounds with the 8-oxabicyclo-[3.2.1]octane framework with a high stereocontrol.[126] Moreover, α,γ-

[125] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.
[126] Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3043.

reactivity could be applied to 5-acyloxydihydropyranones, preparing 1-*H*-isochromanes through a Diels-Alder/elimination cascade reaction (Scheme 5.5).[127]



Scheme 5.5. Various formal cycloadditions *via* dienamine catalysis.

Finally, the trienamine activating manifold has also been studied in our group. In this case, unconjugated 2,5-dienals satisfactorily furnished the trienamine activated specie, further reacting with nitrostyrene in a Diels-Alder reaction. Despite the challenge that implies the functionalization in a position that is so far from the catalyst, final cyclohexenes were rendered in excellent yields and stereocontrol (Scheme 5.6).[128]

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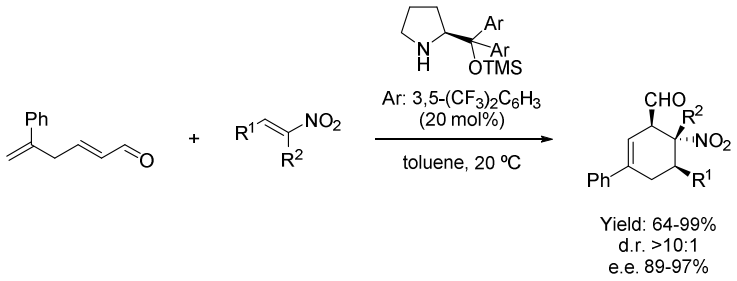
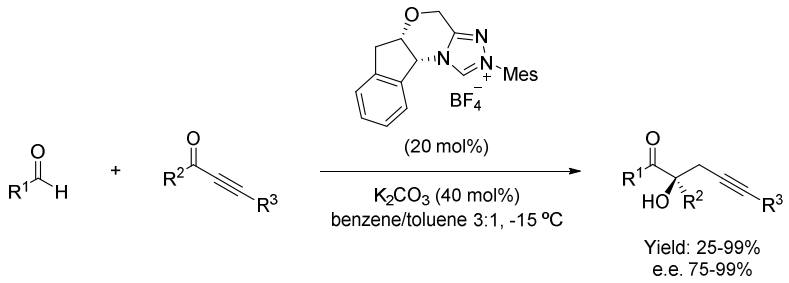
[127] Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uxue, U. *Org. Lett.* **2012**, *14*, 3740.
[128] Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.



Scheme 5.6. Trienamine catalysis in a Diels-Alder reaction.

Moving to a different type of covalent organocatalysis, *N*-heterocyclic carbenes have been successfully used in asymmetric transformations, such as the cross-benzoin reaction between aldehydes and alkynones, yielding tertiary alkynyl carbinols as highly enantioenriched materials (Scheme 5.7).[129]

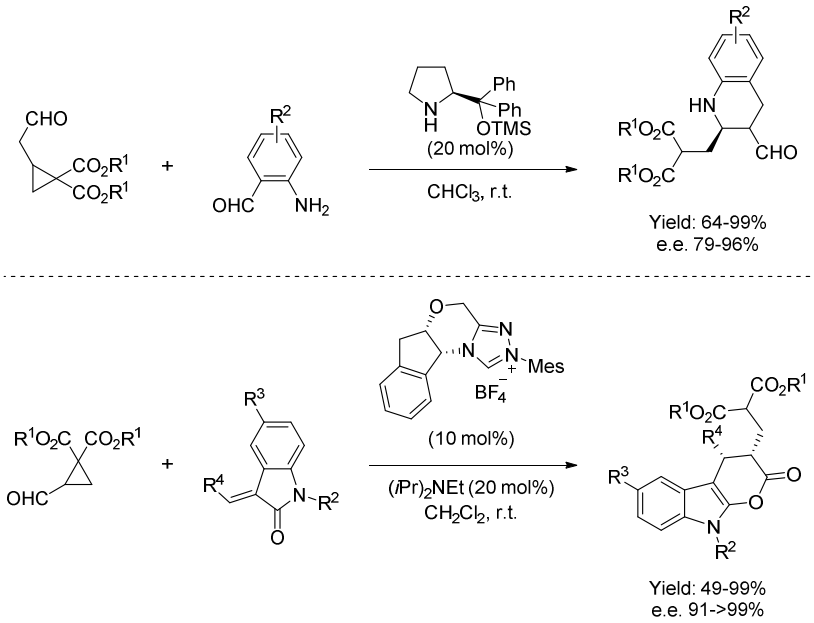


Scheme 5.7. Asymmetric cross-benzoin reaction employing a chiral NHC as catalyst.

Recently, transformations based on ring-strain release of substituted cyclopropanes have been developed. For that, the aforementioned organocatalysts, amynocatalysts and *N*-heterocyclic carbenes, were employed for conveniently functionalizing formylcyclopropanes and cyclopropaneacetaldehydes and therefore, enabling the catalytic generation of donor-acceptor cyclopropanes.

[129] Sánchez-Díez, E.; Fernández, M.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Eur. J.* **2015**, *21*, 8384.

These intermediates have the potential to undergo ring-opening, followed by already known asymmetric organocatalytic transformations (Scheme 5.8).[130]

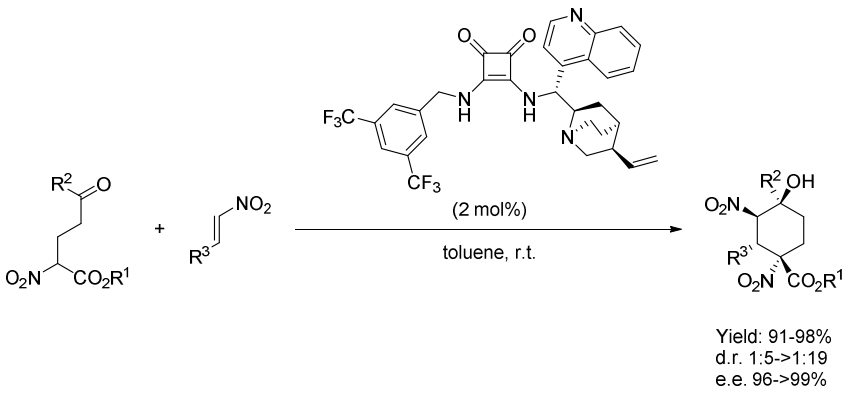


Scheme 5.8. Various transformations promoted by the *in situ* generation of donor-acceptor cyclopropanes *via* aminocatalysis or NHC based catalysis.

It should be mentioned that not only covalent organocatalysis has been surveyed in the group, but also hydrogen-bonding base organocatalysis. Highly enantioenriched cyclohexenes containing four stereocenters were synthesised through a Michael/Henry cascade reaction employing a bifunctional squaramide as catalyst. In this case, mechanistic studies showed that the catalyst was able to

[130] (a) Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270. (b) Prieto, L.; Sánchez-Díez, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Adv. Synth. Catal.* **2017**, *359*, 1678.

coordinate to both reactants by hydrogen-bond interactions, bringing them closer, as well as directing the trajectory of the addition (Scheme 5.9).[131]



Scheme 5.9. Asymmetric Michael/Henry cascade reaction employing a bifunctional squiaramide as catalyst.

Brønsted acid catalysis has also been studied in the group by using chiral phosphoric acids as catalysts. In this sense, an enantioselective oxidative (4+3) cycloaddition between allenamides and furans,[132] an enantioselective Cloke-Wilson rearrangement[133] and the asymmetric addition of hydrazones to *N*-acyldihydropyrrole derivatives have been reported,[134] obtaining high stereocontrol in all cases (Scheme 5.10).

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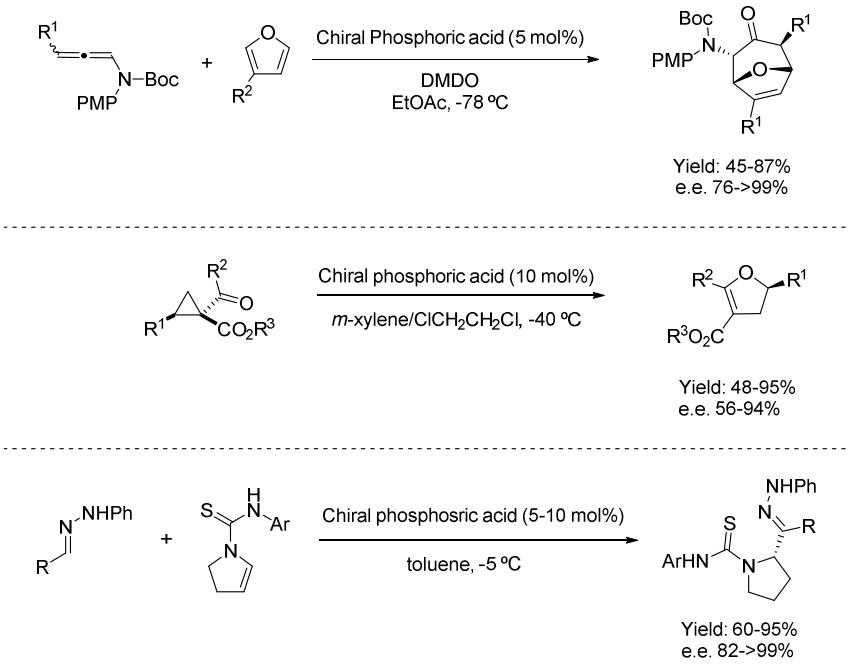
131 (a) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627. See also: (b) Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beilstein J. Org. Chem.* **2015**, *11*, 2577.

132 Villar, L.; Uria, U.; Martínez, J. I.; Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10535.

133 Ortega, A.; Manzano, R.; Uria, M.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8225.

134 Zabaleta, N.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2018**, *54*,8905.



Scheme 5.10. Asymmetric organocatalytic transformations promoted by chiral phosphoric acids.

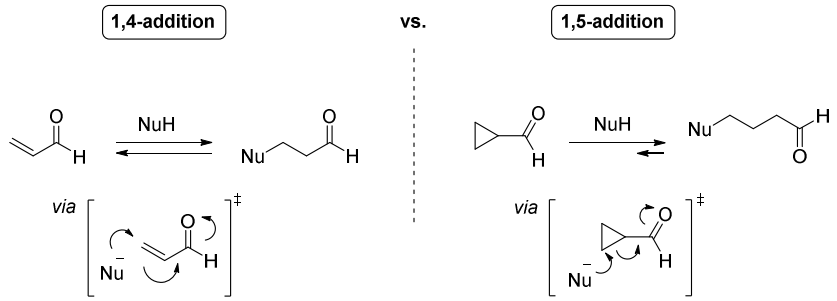
6. GENERAL OBJECTIVES OF THE PRESENT WORK

The work summarized in this thesis has been carried out in the line with the recent research of the group. Hence, it has been focused on developing asymmetric organocatalytic transformations and further proving their synthetic applicability.

Aminocatalysis has played an important role in the development of new strategies for the synthesis of enantioenriched compounds, through a wide variety of chemical transformations. However, as this activation manifold is based on the formation of azometine intermediates by condensation of a primary or secondary amines with the carbonyl group present in one of the reagents, the methodology is limited to the activation of aldehydes and ketones. In this sense, enals and enones have been typically used substrates obtaining several different final products, in this case, mainly under iminium ion and enamine catalysis. Hence, the possibility of activating alternatives substrates different from the well-known (poly)unsaturated carbonyl chains, presents the opportunity to look for novel reactivity patterns that could lead to final adducts hard to synthesise through typical strategies.

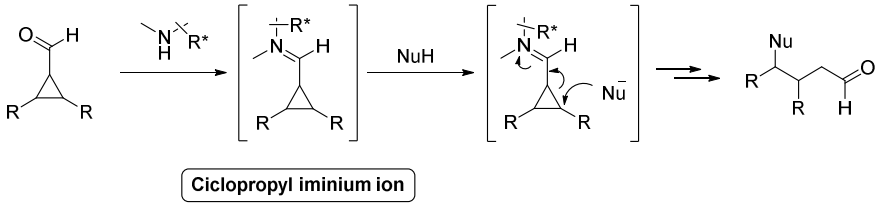
Cyclopropanes appear as interesting alternative substrates as they are prone to promote the ring-opening reaction due to the ring-strain release that occurs after the cleavage of the C-C bond. In this sense, and thinking of taking advantage of both aminocatalysis and the just mentioned ring-strain of the three-membered cycle, **we will survey the use of formylcyclopropanes as potential substrates to develop ring-opening reactions under iminium ion catalysis**. The formation of the cyclopropyliminium ion after condensation with the aminocatalyst, will lead to a more polarised C-C bond and therefore, the ring-opening reaction promoted by the addition of a nucleophile will be more favoured than in the case of the original aldehyde. Moreover, the transformation will lead to a formal 1,5-addition product

in contrast with the commonly obtained 1,4-addition product when activating enals *via* iminium ion catalysis; hence, an umpoled reactivity will be observed as in the final adduct the typically nucleophilic σ-position of a carbonyl chain, will be functionalized with a nucleophile instead of with an expected electrophile (Scheme 6.1).



Scheme 6.1. Nucleophilic addition to enals and formylcyclopropanes.

For developing the asymmetric version of the ring-opening of formylcyclopropanes under iminium ion activation, chiral secondary amines will be initially used as they have previously provided excellent results when activating aldehydes. Once the aminocatalyst condenses with the carbonyl moiety and the active intermediate is generated, the incoming nucleophile will be able to differentiate between the two carbons that can suffer the addition, due to the chiral environment provided by the catalyst, and a final enantioenriched product will be obtained. Thus, for the stereochemistry of the reaction to be controlled by the catalyst, and not by the cyclopropane itself, *meso*-formylcyclopropanes will be employed making both activated carbons equally reactive (Scheme 6.2).



Scheme 6.2. Proposal for a *meso*-formylcyclopropane ring-opening reaction under iminium ion activation.

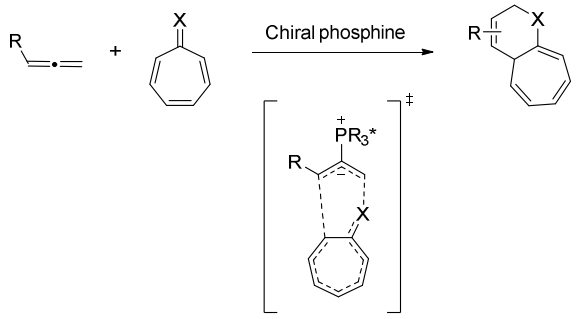
In a completely different context and as previously shown, the field of cycloaddition reactions catalysed by nucleophilic phosphines has been limited to the formal [4+2] cycloaddition obtaining five- or six-membered rings, depending on the substitution pattern of the employed allene. Both the non-asymmetric and asymmetric versions of the transformation have been developed, proving that electron poor olefins are excellent dipolarophiles and that chiral phosphines are capable of providing enantioenriched final cycloadducts. Thinking of expanding the scope of the employed dipolarophile from activated alkenes to systems with a higher amount of π-bonds, it has been envisioned the possibility of developing high-order cycloaddition reactions.

Heptafulvene derivatives have been described as useful 8π-components and a wide range of non-asymmetric [8+2] cycloaddition reactions have been reported in the literature employing them as eight-membered synthons. However, the enantioselective versions remain scarce and up to date only three examples have been published, based on different activation approaches. Jørgensen´s group reacted cyanoesterheptafulvene and dicyanoheptafulvene with 2-hexenone and 2-heptenone *via* enamine catalysis.[135] A chiral *N*-*N´*-dioxide nickel(II) complex as catalyst was employed by Feng and co-workes for the [8+2] cycloaddition between

[135] Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E. H.; Jørgensen, K. A. *Nat. Chem.* **2017**, *9*, 487.

azaheptafulvenes and electron poor alkenes,[136] and finally, Pericàs and co-workers also employed azaheptafulvenes as 8π-components, in this case in the presence of a solid-supported benzotetramisole catalyst and using chiral ammonium enolates, derived from activated carboxylic acids as 8π-dipolarophiles.[137]

With this in mind, **the ability of heptafulvene derivatives to act as 8π-compounds in the presence of allenes, promoting a high-order [8+4] cycloaddition will be studied**. For the formation of the 1,3-dipole derived from the addition of the catalyst to the allene, nucleophile phosphines will be tested, assuming that the enantiomeric version of the transformation will be possible when using chiral phosphines (Scheme 6.3).



Scheme 6.3. Proposal of a high-order [8+4] cycloaddition catalysed by a chiral phosphine.

[136] Xie, M.; Liu, X.; Wu, X.; Cai, Y.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 5604.
[137] Wang, S.; Rodríguez-Escrich, C.; Pericàs, M. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 15068.

Chapter 2

2

Desymmetrization of *meso*-Formylcyclopropanes under Iminium Ion Activation

1. CYCLOPROPANE RING-OPENIG REACTIONS

In 1882 Freund reported that by treating 1,3-dibromopropane with sodium at reflux temperature, the sodium dissolved, while sodium bromide precipitated and a gas from the reaction was collected. The unknown gas went back to 1,3-dibromopropane when treating it with bromine and it was transformed into 1-iodopropane in the presence of hydrogen iodide. After these experiments, Freund concluded that the gas was cyclopropane and assigned it the correct C3H6 formula and structure.1 As it is well known, cyclopropanes are highly strained systems with a ring strain of about 115 kJ/mol.2 The ring strain is derived from two main contributions: the angular strain due to the bond angle of 60o instead of the inherent sp3 angle of 109.5o and the torsion strain due to the disfavoured, but only possible, eclipsed conformation of its hydrogen atoms. On the other hand, the C-C and C-H bonds in cyclopropane are shorter than in ethane (Figure 1.1), despite the fact that the C-C bonds in cyclopropane are considered to be weaker than in an unstrained alkane.3

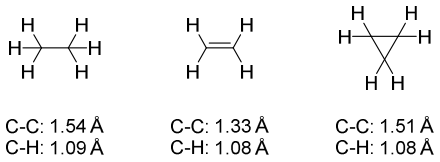


Figure 1.1. Bond lengths in ethane, ethylene and cyclopropane.

Bonding between the carbon centres can be described mainly by two different models, considering the fact that electron density has been found to lie outside the internuclear axis of the cyclopropane structure, as well as in the centre of the ring.[1]

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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 Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin. Trans. II* **1987**, *12*, S1.

The Coulson and Moffit model describes cyclopropane as having three sp^3 hybridized carbons but with a greater *p* character, which is required for the orbitals to angle one towards another and not to meet head to tail, hence forming a curve that makes the angle between them of 104°, which is closer to the ideal angle of the sp^3 hybridization.[4] As the overlap of the orbitals is reduced and it is neither end-on or lateral, but in between, it can be considered as an intermediate between σ- and π-bonding. Alternatively, the Walsh model considers that the cyclopropane consists of three methylene sp^2 units.[5] The two C-H bonds of each carbon are formed by two sp^2 orbitals of the carbons, which increases the *s* character of the bonds; the remaining sp^2 orbitals of each carbon and the three *p* orbitals participate in the formation of the C-C bonds (Figure 1.2).

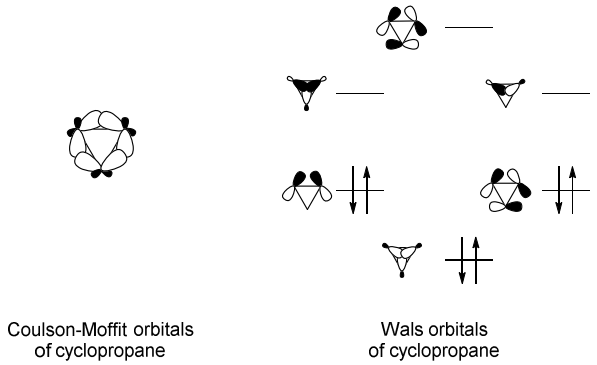
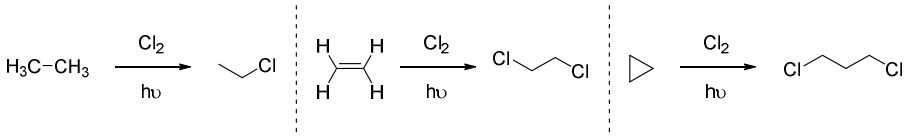


Figure 1.2. Coulson-Moffit and Walsh theoretical models for explaining bonding in cyclopropane.

Despite the high strain, the C-C bonds present in the cyclopropane are rather kinetically inert and their cleavage only happens under particular conditions. For instance, they tend to rearrange to more stable olefins catalysed by a strong acidic

4 Coulson, C. A.; Moffit, W. E. *Philos. Mag.* **1949**, *40*, 1.
5 (a) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179. (b) Walsh, A. D. *Nature* **1947**, *159*, 508.

media[6] or thermally at high enough temperatures[7]. They also show a greater similarity in reactivity with olefins rather than with alkanes. An example of it would be the chlorination reaction where a C-C bond cleavage occurs in the cyclopropane instead of a substitution of a hydrogen by a chlorine, as it happens in alkanes (Scheme 1.1).[8]



Scheme 1.1. Chlorination reaction of ethane, ethylene and cyclopropane.

Despite the inertness showed by the cyclopropane scaffold, the ring strain can be increased to higher values by strategically placing substituents in the structure, favouring the ring-opening process and allowing it to occur under mild conditions. These activated cyclopropanes show unusual reactivity, which makes them powerful building blocks in organic chemistry for the synthesis of architectures that are hard to obtain through conventional methodologies.[9] In this way, the cyclopropane can be activated placing a donor substituent, an acceptor substituent or both donor and acceptor substituents in different carbons. By varying the nature of the substituents, the cyclopropane can show different reactivity patterns, where

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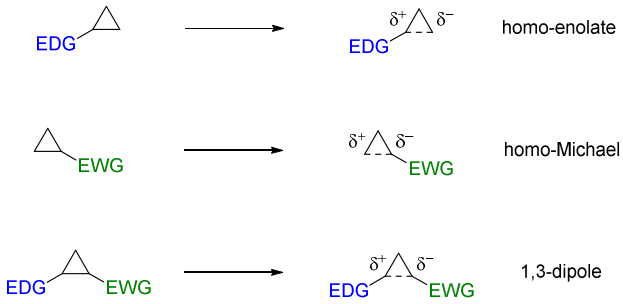
6 (a) LaLonde, R. T.; Forney, L. S. *J. Org. Chem.* **1964**, *29*, 2911. (b) Wiberg, K. B.; de Meijere, A. *Tetrahedron Lett.* **1969**, 519.

7 (a) Schlag, E. W.; Rabinovitch, B. S. *J. Am. Chem. Soc.* **1960**, *82*, 5996. (b) Frey, H. M.; Walsh, R. *Chem. Rev.* **1969**, *69*, 103.

8 Lambert, J. B.; Chelius, E.; Schulz, W. J.; Carpenter, N. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156.

9 For selected reviews on cyclopropane reactivity, see: (a) Ganesh, V.; Chandrasekaran, S. *Synthesis* **2016**, *48*, 4347. (b) Green, J. R.; Snieckus, V. *Synlett* **2014**, *25*, 2258. (c) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (g) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (h) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

the positive charge is stabilized by the donor group while the negative charge is stabilized by the acceptor group. When electron-donating groups are placed a homo-enolate reactivity is observed, whereas when the cyclopropane is substituted with electron-withdrawing groups it acts as a homo-Michael acceptor, in a similar way to electron deficient alkenes. Alternatively, when electron-withdrawing and electron-acceptor groups are installed vicinally at the three membered ring, it can be considered as a source of 1,3 zwiterionic reactive specie (Scheme 1.2).



Scheme 1.2. Donor, acceptor and donor-acceptor substituted cyclopropanes.

As it has just been mentioned, the ring opening mostly relies on activation of the cyclopropane with additional functional groups and, in this sense, the activation can be categorised in three main classes. The first class includes the reactivity of donor cyclopropanes, the second one features the ring-opening of acceptor cyclopropanes and donor-acceptor cyclopropanes are categorised as the third class.

1.1. Donor cyclopropanes

Cyclopropanes bearing an electron-donating substituent can undergo addition to an electrophile with concomitant cleavage of one C-C bond present in the ring,

and the electrophilic addition usually follows Markovnikov´s rule for substituted cyclopropanes.[10] Structures with electron-donating heteroatom substituents show a higher reactivity as they can more easily promote the ring-opening resembling the enolate reactivity. In this sense, the greater electron-donating ability of the substituent, the easier the transformation to occur (Figure 1.3).

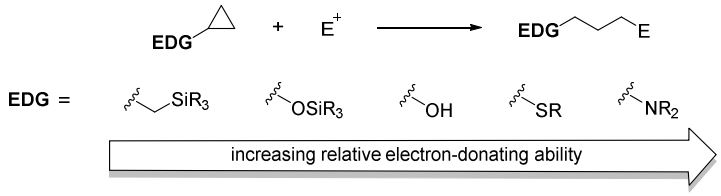


Figure 1.3. Substituents generally employed in donor cyclopropanes.

The first ring-opening reactions of donor cyclopropanes were developed employing hydroxy and amine groups as substituents. Deprotonation of hydrogen containing heteroatoms favoured the ring-opening process especially in protic media, obtaining the corresponding carbonyl compound as the final product. Secondary amines, where the deprotonation activating step cannot take place, also proved to be suitable substrates, as the ring-opening could occur in high temperatures through the formation of an iminium ion as the intermediate of the reaction.[11]

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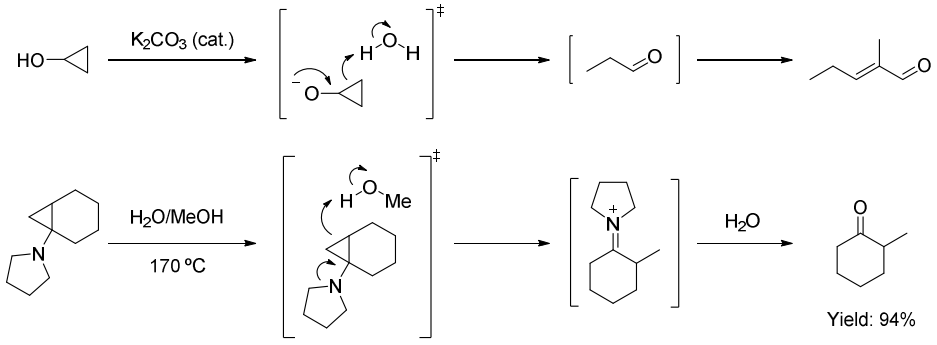
[10] Selected reviews on ring-opening reaction of donor cyclopropanes: (a) Guijarro, D.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1713. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Salaun, J. *Chem. Rev.* **1983**, *83*, 619. (d) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*,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

[11] (a) Kuehne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304. (b) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347. (c) Stahl, G. W.; Cottle, D. L. *J. Am. Chem. Soc.* **1943**, *65*, 1782.



Scheme 1.3. Ring-opening of hydroxy- and aminocyclopropane derivatives leading to the corresponding carbonyl compounds.

Donor cyclopropanes also react with transition metal salts under mild conditions, leading to the corresponding substituted organometallic compound, which can afterwards show typical organometallic reactivity (Scheme 1.4). Several studies have been carried out employing different transition metal salts, such as mercury, [12] zinc, [13] titanium,[14] copper,[15] iridium[16] and palladium.[17] As an example of this reactivity, mercury(II) acetate efficiently reacted with cyclopropanols obtaining acetoxy(3-oxopropyl)mercury as final aduct.

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12 DeBoer, A.; DePuy, C. H. *J. Am. Chem. Soc.* **1970**, *92*, 4008.

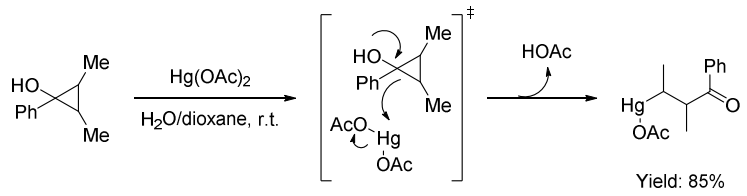
13 For a selected example, see: Urai, S.; Ay, T.; Renge, T.; Ryu, I.; Sonoda, N. *J. Org. Chem.* **1974**, *39*, 858.

14 For a selected example, see: Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651.

15 For a selected example, see: Das, P. P.; Belmore, K.; Cha, J. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 9517.

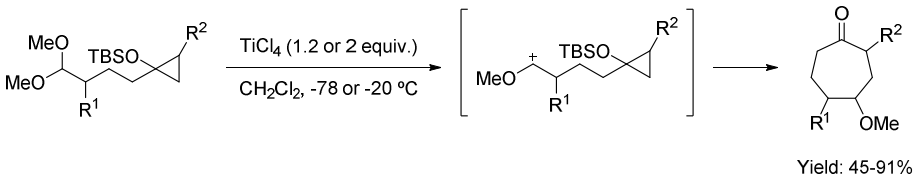
16 For a selected example, see: Ziegler, D. T.; Steffens, A. M.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 6726.

17 For a selected example, see: Nikolaev, A.; Nithiy, N.; Orellana, A. *Synlett* **2014**, *25*, 2301.



Scheme 1.4. Ring-opening of 2,3-dimethyl-1-phenylcyclopropanol by the addition of mercury.

This simple reaction provides access to structurally more complex substrates when using starting reagents bearing both a donor cyclopropane and an electrophilic position in the same molecule. In this sense, the ring-opening reaction could be followed by cyclization due to an intramolecular electrophilic addition.[18] This way, seven-membered carbocycles could be synthesised in good to high yields under Lewis acid catalysis, through the addition of cyclopropyl silyl ethers to the oxonium ion intermediates (Scheme 1.5).[18b]



Scheme 1.5. Ring-opening of cyclopropyl silyl ethers followed by intramolecular electrophilic addition.

On the other hand, silylmethylcyclopropanes, despite not having a heteroatom attached to the cyclopropane moiety, can also undergo the ring-opening process, as the silyl group stabilizes the positive charge in β to the silicon atom. In an example of the reactivity of these compounds, Scheme 1.6 shows that they can

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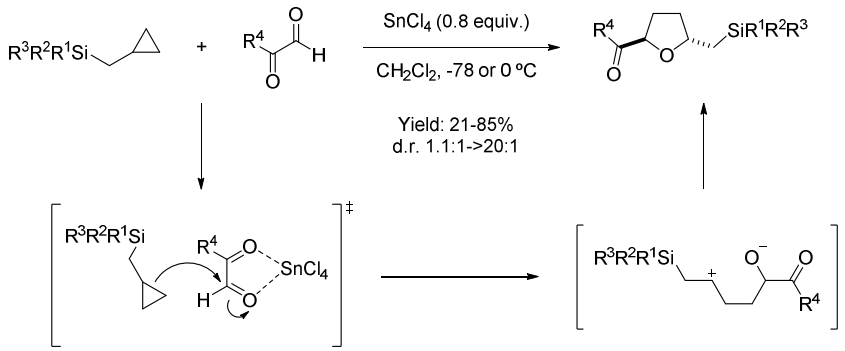
[18] (a) Lee, H. G.; Lysenko, I. L.; Cha, J. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3326. (b) Epstein, O. L.; Lee, S.; Cha, J. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 4988. (c) O´Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515.

react with glyoxals upon activation by a Lewis acid, promoting the ring-opening, which is followed by cyclization and leading to 2,5-disubstituted tetrahydrofurans in good yields and moderate to good diastereocontrol.[19]

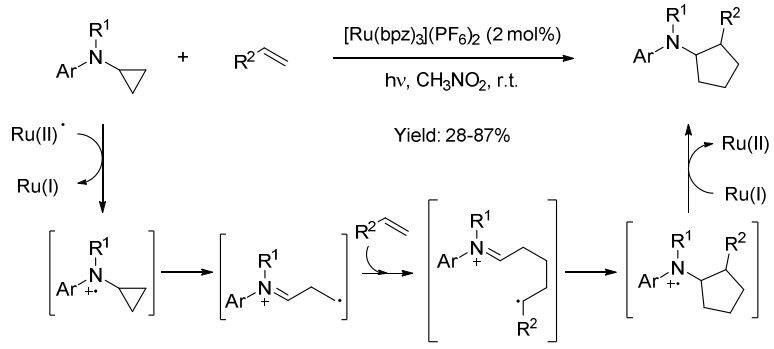


Scheme 1.6. Ring-opening reaction of silylmethylcyclopropanes in the presence of activated glyoxals.

Finally, the ring-opening process can also occur in oxy-, amino-, and thiocyclopropane derivatives *via* radical mechanisms (see an example in Scheme 1.7). The transformation would begin by the abstraction of the hydrogen atom attached to the heteroatom or by formation of the heteroatom radical cation, followed by cleavage of the C-C bond present in the three-membered ring, forming a β-heterocarbonyl radical, which subsequently reacts with different radical-trapping species. The formation of the radical can be promoted by various

[19] (a) Dunn, J.; Dobbs, A. P. *Tetrahedron* **2015**, *71*, 7386. (b) Dunn, J.; Motevalli, M.; Dobbs, A. P. *Tetrahedron Lett.* **2011**, *52*, 6974.

transition metals[20] as well as by non-metal based oxidants.[21] More recently, a visible-light mediated (3+2) cycloaddition of alkenes with cyclopropylamines catalysed by Ru(II) has been developed, under mild conditions. Both secondary and tertiary amines featured the transformation in high yields *via* radical intermediate.[22]



Scheme 1.7. Ring-opening of cycloproplylamines *via* radical mechanism.

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[20] For selected examples employing Fe(III), see: (a) Barnier, J. P.; Morisson, V.; Blanco, L. *Synth. Commun.* **2001**, *31*, 349. (b) Shirai, M.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 5331. (c) Booker-Milburn, K. I.; Thompson, D. F. *Tetrahedron Lett.* **1993**, *34*, 7291. For a selected example employing Cr(VI), see: (d) Martinez, A. M.; Cushmac, G. E.; Roček, J. *J. Am. Chem. Soc.* **1975**, *97*, 6502. For selected examples employing Mn(III), see: (e) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411. (f) Iwasawa, N.; Funahashi, M.; Narasaka, K. *Chem. Lett.* **1994**, 1697. For a selected example employing Pb(III), see: (g) Rubbotom, G. M.; Beedle, E. C.; Kim, C. W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230. For a selected example employing V(V), see: (h) Kulinkovich, O. G.; Astashko, D. A.; Tyvorskii, V. I.; Ilina, N. A. *Synthesis* **2001**, 1453. For a selected example employing Cu(II), see: (i) Barnier, J. P.; Morisson, V.; Blanco, L. *Synth. Commun.* **2001**, *31*, 349.

[21] For selected examples, see: (a) Churykau, D. H.; Kulinkovich, O. G. *Synlett* **2006**, 3427. (b) Abe, M.; Oku, A. *Tetrahedron Lett.* **1994**, *35*, 3551.

[22] Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 222.

1.2. Donor-Acceptor cyclopropanes

Cyclopropanes bearing both an electron-withdrawing and an electron-donating substituent are named donor-acceptor cyclopropanes. Usually, carbonyl, sulfonyl and nitro groups serve as electron-withdrawing substituents and electron-rich aryl groups, heteroatoms, alkyl or alkenyl groups act as electron-donating substituents (Figure 1.4). When the electron-withdrawing and electron-donating groups are installed vicinally, a synergistic effect can be achieved inducing high polarisation to the C-C bond that is between both substituents (push-pull effect), leading to a rather weak C-C bond, which undergoes an easy cleavage that allows the donor-acceptor cyclopropanes to be depicted as a source of 1,3-zwitterionic reactive species, in which the positive charge is stabilised by the donor group and the negative charge is stabilised by the acceptor group.

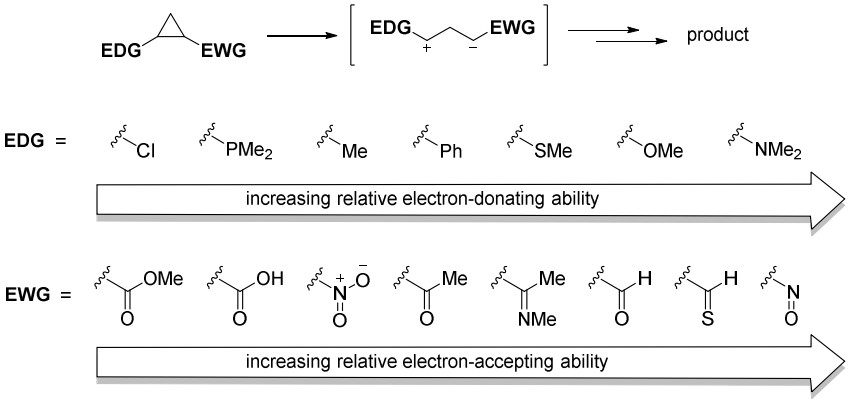

Figure 1.4. Substituents generally employed in donor-acceptor cyclopropanes.

Reissing introduced the term "donor-acceptor cyclopropane"[23d] in the 1980 and around that time the first golden age for these structures started.[23] Initially 2-

[23] For early work on donor-acceptor cyclopropanes, see: (a) Wenker, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778. (b) Piers, E.; Reissig, H.-U. *Angew. Chem. Int. Ed.*

alkoxycyclopropane carboxylates were mainly studied, as well as their analogues containing amino or alkylthio substituents as donor groups and carbonyl or nitrile functions as acceptor group. Nowadays, in what it has been called the second gold age of the donor-acceptor cyclopropanes, 2-alkenyl- and 2-(hetero)arylcyclopropane-1,1-diesters are the most surveyed (Figure 1.5).[24] Although all the fundamental reactions were basically reported in the 1980s and 1990s, these substrates are still part of ongoing investigations due to the possibilities they offer for enantioselective transformations and as key step of various natural products.

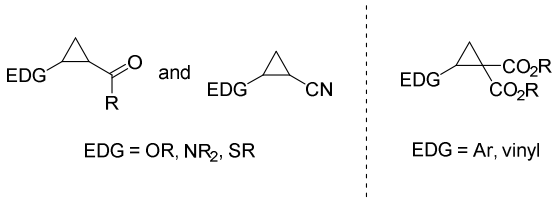

Figure 1.5. General structure of the most studied donor-acceptor cyclopropanes.

Despite the enhanced reactivity of donor-acceptor cyclopropanes, they usually need to be further activated in order to undergo the ring-opening reaction. To date, three main methods for the activation of donor-acceptor cyclopropanes have been reported. With no external catalysts in the media, thermal activation can lead to

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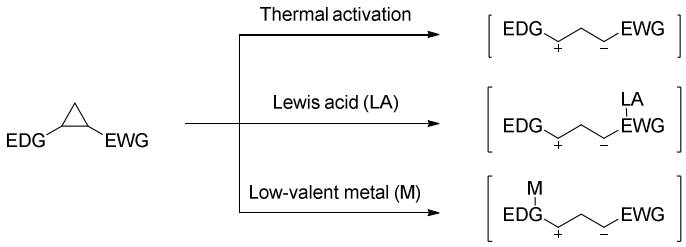
1979, *18*, 791. (c) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (d) Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed.* **1980**, *19*, 813. (e) Reissig, H.-U. *Tetrahedron Lett.* **1981**, *22*, 1981. (f) Doyle, M. P.; van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326. (g) Brückner, C.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **1985**, *24*, 588. (h) Brückner, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440. (i) Hoffmann, B.; Reissig, H.-U. *Synlett* **1993**, 27. (j) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

[24] For selected recent reviews on donor-acceptor cyclopropanes, see: (a) Gharpure, S. J.; Nanda, L. N. *Tetrahedron Lett.* **2017**, *58*, 711. (b) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13*, 655. (c) Schneider, T. F.; Johannes, K.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (d) Cavitt. M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (e) Mel´nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendelv. Commun.* **2011**, *21*, 293. (f) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

the C-C bond cleavage to afford the 1,3-ionic species.[25] Alternatively, the ring-opening could be promoted by increasing the polarisation of the C-C bond by the coordination of a Lewis acid to the acceptor group,[26] or by the interaction of low valent metals, such as palladium(0),[27] nickel(0),[28] iron(0)[29] or iridium(0)[30] (Scheme 1.8). Generally speaking, Lewis acid catalysis has been the most prolific approach for the activation of cyclopropanes as stated by the number of publications in this field.



Scheme 1.8. Activation methods of donor-acceptor cyclopropanes.

The capability that donor-acceptor cyclopropanes have to generate 1,3-zwiterionic reactive species, means that in addition to typical reactions of ring-opening promoted by external nucleophiles and electrophiles, they can also participate as dipoles in a variety of cycloaddition reactions. Moreover, many acceptors allow the transfer of the negative charge located in the carbon to the

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25 Berkowitz, W. F.; Grenetz, S. C. *J. Org. Chem.* **1976**, *41*, 10.

26 For some selected examples, see: (a) Yadav, V. K.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2669. (b) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (c) Horiguchi, Y.; Suehiro, I.; Sasaki, A.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6077.

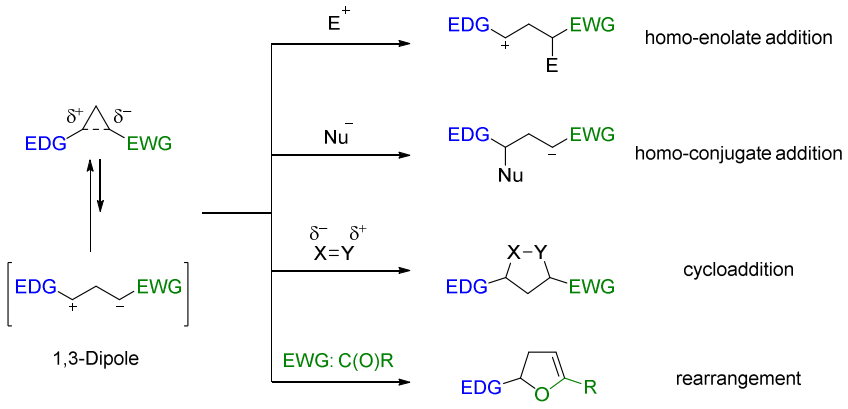
27 For a selected example, see: Parson, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541.

28 For a selected example, see: Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573.

29 For a selected example, see: Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. *J. Am. Chem. Soc.* **2012**, *134*, 5048.

30 For a selected example, see: Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618.

acceptor itself, which leads to rearrangement reactions by the insertion of the acceptor in the new structure (Scheme 1.9).



Scheme 1.9. Different reaction patterns of D-A cyclopropanes.

Mechanistically, a chirality loss would be expected by the formation of the ring-opened 1,3-zwitterionic equivalent, as a planar intermediate would be formed. However, they usually undergo stereospecific reactions through configurationally stable activated ion-paired intermediates where the chirality of the starting material is maintained.[31] However, it has to be highlighted that there are some enantioselective examples when chiral catalysts are employed (Figure 1.6).

[31] For some selected examples, see: (a) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844. (b) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014.

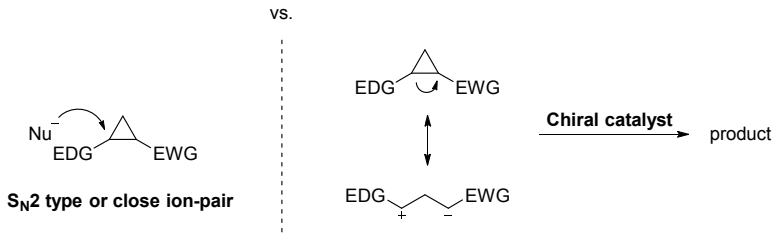
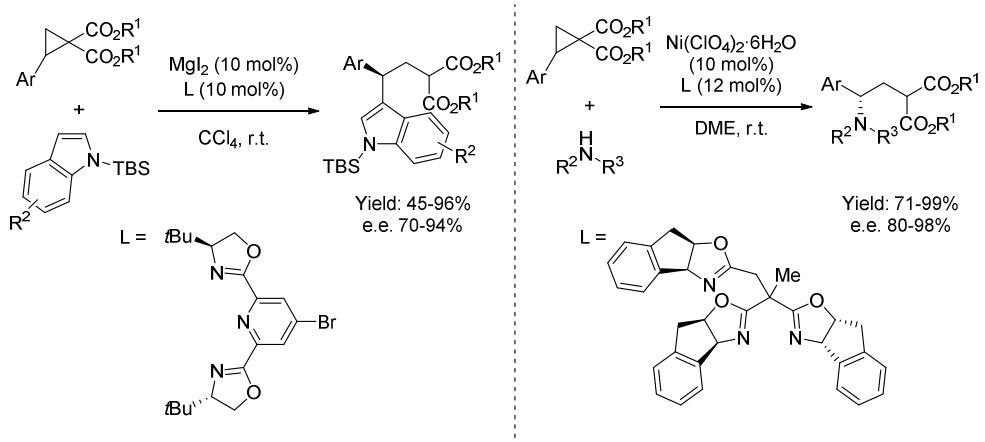


Figure 1.6. Two different approaches for obtaining enantioenriched final adducts after ring-opening of donor-acceptor cyclopropanes.

The most basic transformation of donor-acceptor cyclopropanes would be the ring-opening reaction that leads to the linear chain, which instantly reacts with external nucleophiles or electrophiles, giving access to 1,3-bifunctionalized products. Typically, heteroatom-containing nucleophiles or electron-rich arenes are employed to react with the positive charge, whereas a proton usually neutralizes the negative charge. In some cases, when the nucleophile and the electrophile are part of the same molecule an annulation process may occur through a domino sequence or as a tandem or one-pot reaction.

The nucleophilic ring-opening reaction of donor-acceptor cyclopropanes have been reported with various nucleophilic reagents. A good example of this reactivity is shown in Scheme 1.10. Johnson and co-workers reported an asymmetric Friedel-Crafts type alkylation between *N*-protected indoles and 2-arylcyclopropane-1,1-dicarboxylates, catalysed by a pybox·MgI_2 complex, obtaining the final products in high yields and e.e. values. The close-ion pair formed by the achiral catalyst and the cyclopropane led to a stereospecific nucleophilic addition of the indole derivative with inversion of the configuration. Moreover, the reaction proceeded *via* a dynamic kinetic asymmetric transformation, as an interconversion of the cyclopropane enantiomers was possible when the transition metal coordinated

them and the (*S*)-enantiomer reacted much faster than the (*R*)-enantiomer.[32] On the other hand, Tang´s group reported a successful methodology for the construction of enantioenriched γ-substituted γ-amino acid derivatives. 2-Aryl cyclopropane-1,1-dicarboxylates were activated with the Ni(II) complex of an indene-derived trioxazoline (In-TOX) ligand and reacted with secondary amines in a enantioselective fashion.[33]

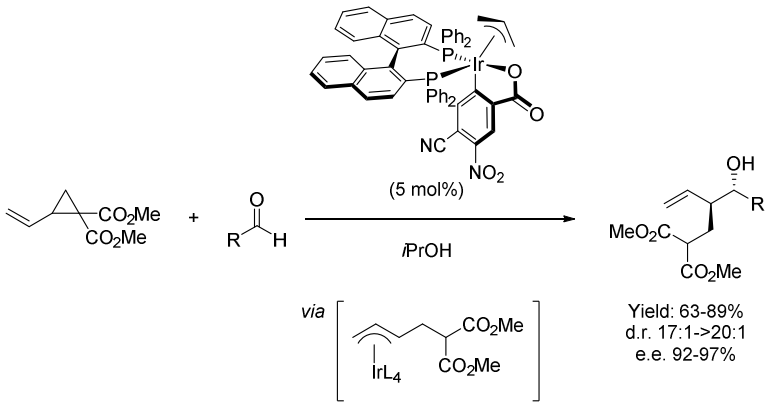


Scheme 1.10. Asymmetric nucleophilic addition to donor-acceptor cyclopropanes.

With respect to electrophilic additions to donor-acceptor cyclopropanes the most recent developments in the area include transition-metal catalysed ring-opening reactions of acceptor-substituted vinylcyclopropanes (see example on Scheme 1.11). The nucleophilic π-allyl-metal complex generated in the reaction media can react with electrophiles providing the donor-acceptor cyclopropane with a formally reversed polarity, as an electrophile would add to the carbon attached to the electron-donating substituent. In this sense, Krische and co-workers reported the asymmetric electrophilic addition of aldehydes to vinylcylopropane-

[32] Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558.
[33] Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066.

1,1-dicarboxylates achieving a high distereo- and enantiocontrol by using a chiral iridium complex based on BINAP as catalyst.[34]



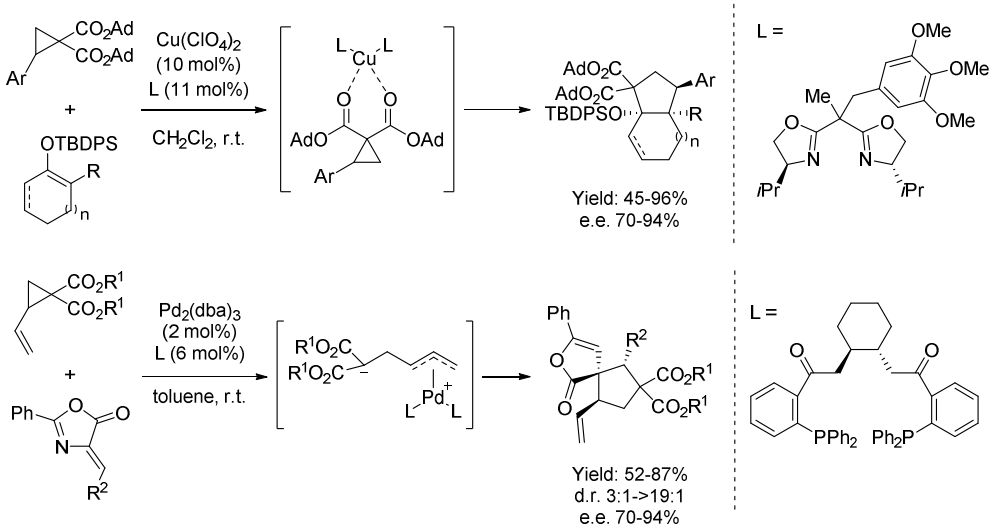
Scheme 1.11. Electrophilic addition of aldehydes to donor-acceptor cyclopropanes.

In addition, and as mentioned, the 1,3-zwitterionic species generated after the ring-opening event on donor-acceptor cyclopropanes, opens the possibility to develop cycloaddition reactions where cyclopropanes are used as dipoles. Through this type of reactivity highly functionalized five-, six-, or seven-membered cyclic scaffolds can be obtained in a very effective way. Most of the publications in this area are referred to (3+2) cycloadditions were both Lewis acids and transitions metals have been used for activating the substrate. Representative examples of both activation methods are shown in Scheme 1.12. A highly diastereo- and enantioselective formal (3+2) cycloaddition between cyclic enol silyl ethers and 2-aryl cyclopropane-1,1-diesters was realized using modified Cu(II)/BOX catalysts. After coordination of the Lewis acid with the carbonyl groups of the cyclopropane, the reaction proceed efficiently *via* a dynamic kinetic resolution process.[35] On the

[34] Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618.

[35] Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4004.

other hand, Trost developed the enantioselective cycloaddition between vinyl cyclopropanes and several alkylidene azalactones leading to enantioenriched spirocyclic, using a Pd(0)/chiral phosphine ligand as catalyst.[36] The transformation occurred through the formation of a stabilised palladium-allyl intermediate where the chiral ligand was able to block one of the faces controlling the stereochemical outcome of the reaction.

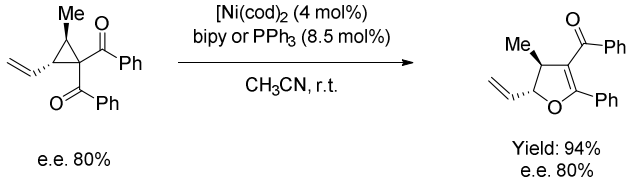


Scheme 1.12. (3+2) cycloaddition reactions of donor-acceptor cyclopropanes.

Donor-acceptor cyclopropanes have also the possibility to rearrange, forming a cyclic product with a larger ring in which strain has been released. For instance, some acceptor substituents on the donor-acceptor cyclopropane have the capacity to promote the ring-opening by attacking the carbon attached to the donor substituent and inserting themselves in the new structure. In particular when carbonyl groups are used as acceptors, furan derivatives are obtained after the

[36] Trost, B. M.; Morris, P. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 6167.

rearrangement. Scheme 1.13 shows the reaction of 1,1-diacyl 2-vinylcyclopropanes in the presence of Ni(0) leading to highly substituted dyhidrofurans in high yields.[37] The low-valent metal activated the cyclopropane upon formation of a π-allyl complex promoting the rearrangement process with retention of configuration.



Scheme 1.13. Rearrangement of donor-acceptor cyclopropanes leading to substituted dihydrofurans.

1.3. Acceptor cyclopropanes

Acceptor cyclopropanes are also known as electrophilic cyclopropanes as they usually bear two germinal electron-withdrawing substituents that increase their reactivity towards nucleophilic addition. Alternatively, less reactive cyclopropyl imines and ketones have also been able to perform the ring-opening reaction (Figure 1.7).

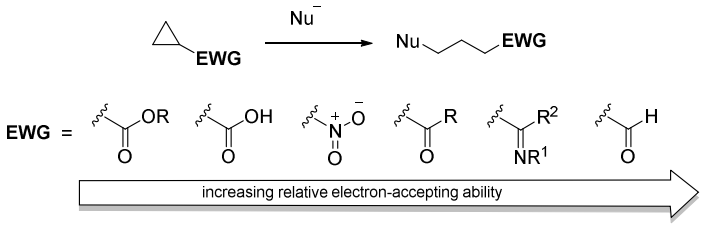
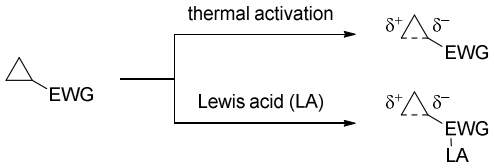


Figure 1.7. Substituents generally employed in acceptor cyclopropanes.

[37] Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573.

Most of the studied processes involving acceptor cyclopropanes have been focused on the identification of nucleophiles able to promote the ring-opening reaction.[38] In fact, for the transformation to occur, even the most reactive acceptor cyclopropanes need to be further activated and therefore the ring-opening reactions have to be usually carried out at high temperature or by enhancing the electrophilic nature of the electron-withdrawing substituents with the addition of Lewis acids, such as $Ni(ClO_4)_2 \cdot H_2O$,[39] BF_3,[40] $SnCl_4$[41] or TMSOTf (Scheme 1.14).[42]



Scheme 1.14. Different activation patterns of acceptor cyclopropanes.

In early experiments, the similarities between the cyclopropane and the C-C double bond reactivity were highlighted, as it has been already mentioned.[2] When one carbon of the C-C double bond is substituted with one or two electron-withdrawing groups (a Michael acceptor) 1,4-functionalization is achieved in Michael-type reactions, while electrophilic cyclopropanes would undergo formal 1,5-functionalization (Scheme 1.15).[43]

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

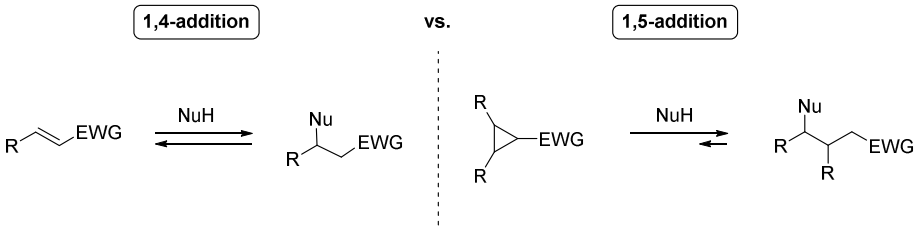
39 For a selected example, see: Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809.

40 For a selected example, see: Srinivasulu, M.; Reddy, V. L. N.; Reddy, S. M.; Ravikanth, V.; Raju, T. V.; Ramakrishna, S.; Venkateswarlu, Y. *Helv. Chim. Acta* **2005**, *88*, 2527.

41 For a selected example, see: Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709.

42 For a selected example, see: Shi, M.; Tang, X.-Y.; Yang, Y.-H. *J. Org. Chem.* **2008**, *73*, 5311.

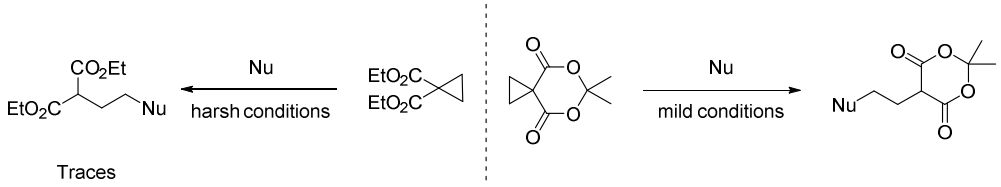
43 Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.



Scheme 1.15. Electrophilic cyclopropane as homologous Michael-acceptor.

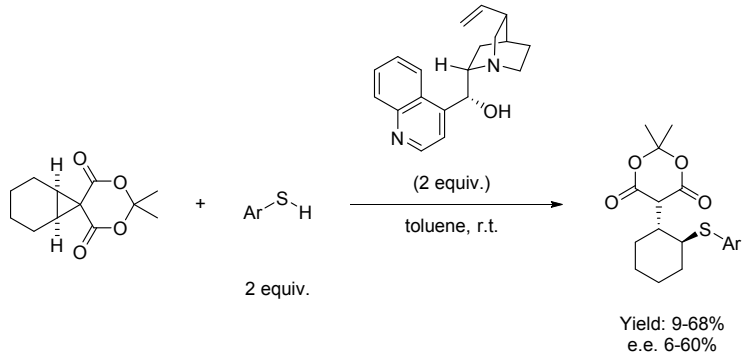
As mentioned, 1,1-cyclopropane dicarboxylic acid esters have been the most widely investigated electrophilic cyclopropanes. In the 1970s, Danishefsky extensively studied the ring-opening of these reagents promoted by external nucleophiles, always requiring harsh conditions. As an alternative Meldrum acid-related cyclopropanes were found to be more reactive, undergoing addition with nucleophiles under relatively milder conditions (Scheme 1.16).[9h,44] Meldrum acid has a higher acidity (with a pK_a of 4.97, which is 8 orders of magnitude more acidic than the related dimethyl malonate) and hence, the facility for this homo-Michael reaction to happen could be explained by the higher stability of the 1,3-dioxane-4,6-dione anion, which turns into a better capacity to stabilise the negative charge generated after cleave of the C-C bond, in comparison with the non-spiro diester.

[44] (a) Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239. (b) Stewart, J. M.; Westberg, H. H. *J. Org. Chem.* **1965**, *30*, 1951.



Scheme 1.16. 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione vs. 1,1- diester cyclopropane.

The enantioselective nucleophilic addition of thiophenols to this type of cyclopropanes was afterwards developed by using a chiral Brønsted base such a cinchonidine as catalyst. Cinchonidinium salt was proposed to form a close-ion pair with thiophenolate anion, hence providing a chiral environment to the transformation and promoting the nucleophilic insertion with a promising enantiocontrol (Scheme 1.17).[45]

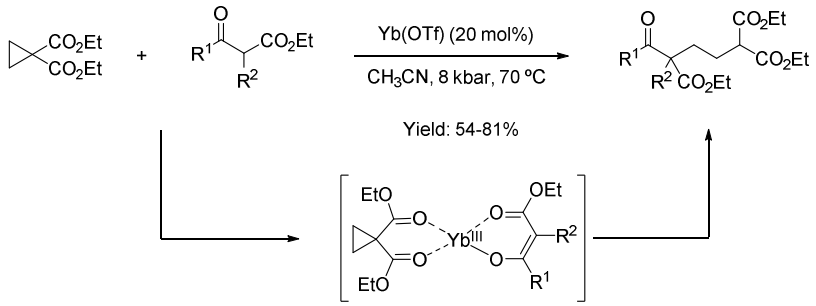


Scheme 1.17. Asymmetric ring-opening of the spiro-activated cyclopropane.

For electrophilic cyclopropanes that do not have the privileged spiro cyclopropane-based structure, the use of Lewis acids as catalysts gave the key for

[45] Müller, P.; Riegert, D. *Tetrahedron* **2005**, *61*, 4373.

performing the ring-opening without the necessity of carrying out the reaction in harsh conditions and also promoted a chance of testing less reactive nucleophiles. For example, ytterbium(III) triflate was found to be a Lewis acid that could be effectively used as catalyst for the homo-conjugate addition reaction of β-ketoesters to diethyl 1,1-cyclopropanedicarboxylate.[46] The Lewis acid was involved in enhancing the electrophility of the cyclopropane by coordination with the electron-withdrawing groups and it also facilitated the reaction by assembling both the cyclopropane and the nucleophile on its coordination structure (Scheme 1.18).



Scheme 1.18. Reaction between β-ketoesters and 1,1-cyclopropanedicarboxylate.

The doubly-activated acceptor cyclopropanes have also been evaluated in cycloaddition reactions in the presence of dipolarophiles. An example of this reactivity is shown in Scheme 1.19, where the reaction between dimethyl cyclopropane-1,1-dicarboxylate and benzonitrile leads to the corresponding (3+2) cycloadduct in high yield under acidic media. [47] A stepwise mechanism has been proposed, starting from the addition of the nitrile to the activated cyclopropane which promoted the ring-opening, followed by the ring-closure step.

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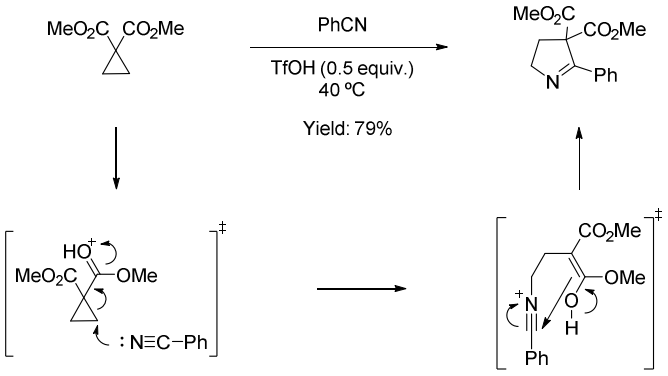
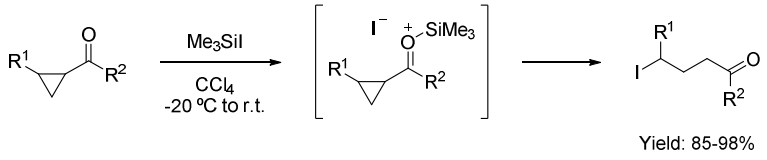
46 Kotsuki, H.; Arimura, K.; Maruzawa, R.; Ohshima, R. *Synlett* **1999**, *5*, 650.

47 Cui, B.; Ren, J.; Wang, Z. *J. Org. Chem.* **2014**, *79*, 790.



Scheme 1.19. Ring-opening of cyclopropane-1,1-diester leading to a cycloadduct after a second addition step.

Acceptor cyclopropanes with only one electron-withdrawing substituent are less reactive and require for further activating strategies. For example, cyclopropyl ketones react in the presence of trimethylsilyl iodide, under mild conditions, generating γ-iodo ketones (Scheme 1.20). The oxygen atom is proposed to coordinate with the silyl group forming a silyl oxonium cation which forms an ion-pair with the iodide. The increased electrophilicity of the cyclopropane facilitates the attack of the iodide, with complete regioselectivity as the addition occurs in the most substituted carbon.[48]

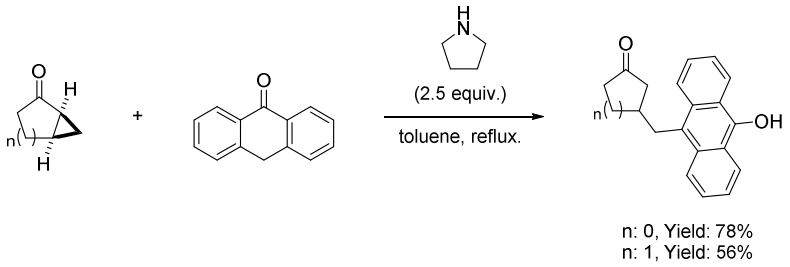


Scheme 1.20. Ring-opening of cyclopropyl ketones by trimethylsilyl iodide.

An alternative approach to activate these less reactive substrates involves including the cyclopropane as a substructure of a bicyclic molecule, increasing the

[48] Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412.

ring strain and facilitating the ring-opening reaction. For example bicycle[3.1.0]hexan-2-one and bicycle[4.1.0]heptan-2-one reacted with anthrone in a Friedel-Craft type reaction rendering the final ring-opening adduct in good yields and with total regiocontrol as the nucleophilic attack only happened at the less substituted carbon (Scheme 1.21). [49] The transformation was promoted by addition of stoiquiometric amounts of pyrrolidine, which led to the formation of the corresponding iminium ion upon condensation with the carbonyl group, hence, activating the electrophilic cyclopropane.



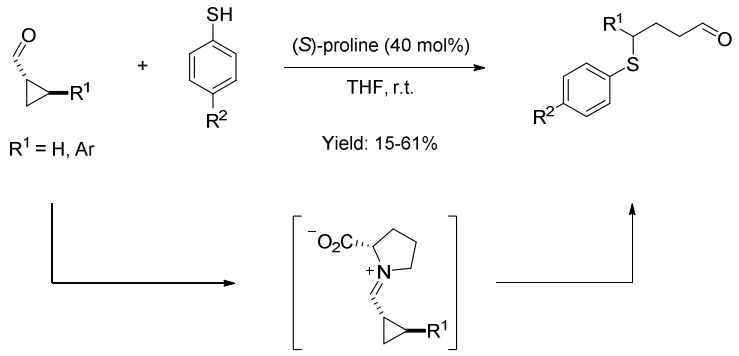
Scheme 1.21. Ring-opening of carbonyl bicyclic cyclopropane.

Enantioselective ring-opening reaction of acceptor cyclopropanes have remained scarce and attempts for synthesising chiral ligands that could interfere in the stereochemical outcome of the reaction have provided poor results.

Organocatalytic activation of electrophilic cyclopropanes has been very poorly developed. The first example corresponds to a report by Wang and co-workers who showed that formylcyclopropanes could be activated by a secondary amine, furnishing a cyclopropyl iminium ion, which resulted more electrophilic in comparison with the non-activated aldehyde. With this in mind, they optimised the proline-catalysed ring-opening of formylcyclopropanes by nucleophilic attack of

[49] Jiang, X.; Lim, Z.; Yeung, Y.-Y. *Tetrahedron Lett.* **2013**, *54*, 1798.

benzenethiols. The desired products were obtained in moderate to good yields with complete regioselectivity favouring the addition at the most substituted carbon, however no enantiomeric control was observed (Scheme 1.22).[50]



Scheme 1.22. Ring-opening of formylcyclopropanes *via* iminium ion.

Related to the previous example, Gilmour and co-workers reported the enantioselective desymmetrization of *meso*-formylcyclopropanes through nucleophilic chloride-initiated ring-opening, catalysed by a chiral secondary amine.[51] The reaction was carried out using MacMillan-type imidazolidinones as catalysts in the presence of 2,4,6-trimethylpyridine hydrochloride and an electrophilic chlorinating reagent, which had to be employed in order to quench the intermediate enamine formed after the nucleophile initiated ring-opening event. This led to the formation of α,γ-dichlorinated aldehydes as final products in good yields, high diastereocontrol and moderate to high enantiocontrol (Scheme 1.23).

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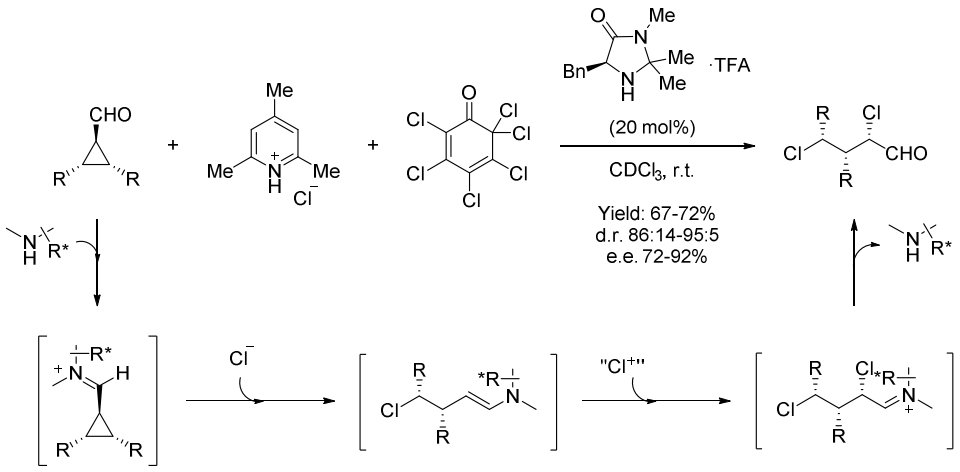
50 Li, L.; Li, Z.; Wang, Q. *Synlett* **2009**, *11*, 1830.

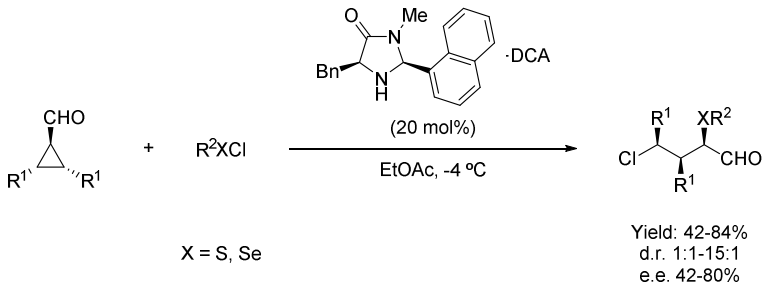
51 Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8391.



Scheme 1.23. Asymmetric ring-opening of formylcyclopropanes *via* iminium ion leading to α,γ-dichlorinated aldehydes.

A later report showed that highly polarized sulfenyl and selenyl chlorides can also trap the formed enamine in an asymmetric fashion, rendering the 1,3-disubstituted final adducts in moderate to high yields, poor to high diastereocontrol and moderate enantiocontrol (Scheme 1.24).[52] It should be mentioned that both organocatalytic asymmetric ring-opening reactions of formylcyclopropanes reported needed for a highly nucleophilic species such as the chloride anion in order to promote the ring-opening process.

[52] Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 18756.



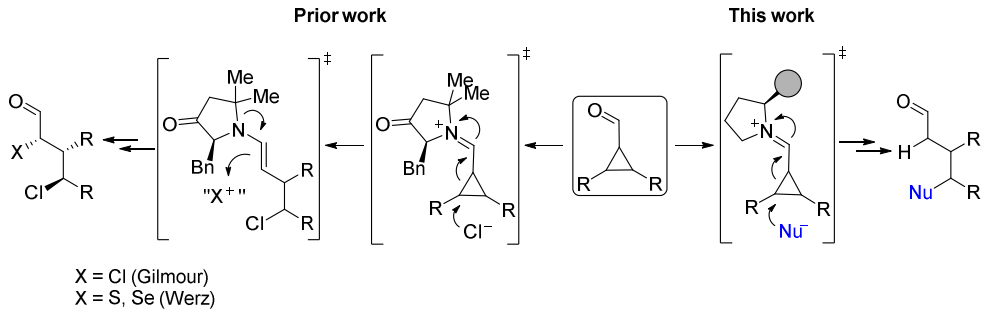
Scheme 1.24. Asymmetric 1,3-chlorochalcogenation of formylcyclopropanes *via* iminium ion.

In summary, it has been demonstrated that substituted cyclopropanes can participate in a wide range of reactions, through different activation methods. However, there is still a lot to investigate around the possibility to develop asymmetric versions of the most synthetically useful reactions involving the ring-opening.

2. SPECIFIC OBJECTIVES AND WORK PLAN

From the presented literature review, it has been clearly stated that most of the chemistry dealing with the use of cyclopropanes as reagents in synthesis has been focused on the use of donor-acceptor cyclopropanes. In contrast ring-opening reactions of acceptor cyclopropanes has been a field poorly covered in the chemical literature. Moreover, it should be noted that asymmetric ring-opening reactions using acceptor cyclopropanes is limited to the very specific examples and typically involve chiral cyclopropanes as starting materials when trying to achieve enantioenriched final products.

As mentioned before, Gilmour[51] and later on Werz[52] presented a ring-opening reaction very recently with great potential, which make use of the iminium activation approach on formylcyclopropanes. However it appears to have some scope limitations as they both used the same type of nucleophilic reagent (a chloride source) for promoting the ring-opening event. Moreover, a second electrophilic addition step has to take place in order to stabilise the final adduct. With this in mind, we decided to broaden the applicability of this reaction by finding conditions that would enable the use of other nucleophilic reactants to promote the ring-opening event (Scheme 2.1).

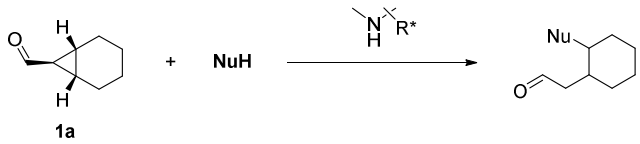


Scheme 2.1. Specific objective of the project.

Thus, the objective of the present project is to develop a **desymmetrization of formylcyclopropanes under iminium ion activation in the presence of different nucleophiles**. Furthermore, by the use of chiral secondary amines the final adduct will be yielded in an asymmetric fashion.

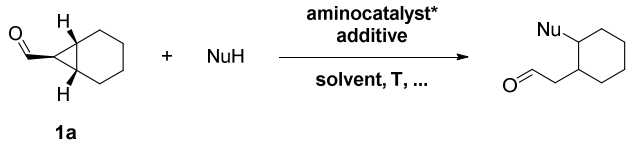
To accomplish the aforementioned objective, the subsequent work plan was followed:

1. *Proof of concept*: A varierty of nucleophiles of different natures will be tested in order to identify those reagents able to initiate the ring-opening process. Formylcyclopropane **1a** will be employed as model substrate as it has shown reactivity in previous studies (Scheme 2.2).[51,52]



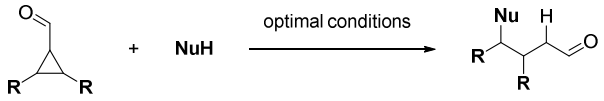
Scheme 2.2. Proof of concept.

2. *Optimization of the reaction conditions*: Using the model compound and a those nucleophiles initially identified to be capable to promote the ring-opening, a variety of catalysts will be tested under different reaction conditions to obtain the final product with the best yield, diastereo- and enantiocontrol (Scheme 2.3).



Scheme 2.3. Optimization of the reaction conditions.

3. *Scope of the reaction*: With the best reaction conditions in hand, the applicability of the methodology will be extended to the use of *meso*-formylcyclopropanes with different substitution patterns. In the same line, structural variations at the nucleophile will be also explored (Scheme 2.4).



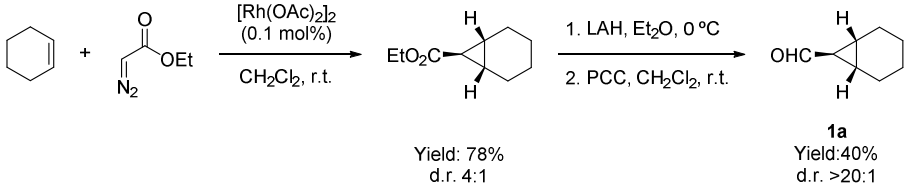
Scheme 2.4. Scope of the reaction.

3. RESULTS AND DISCUSSION

Now that the objective of the project has been defined and the work plan has been stablished, the most significant results gathered in the accomplishment of this research will be presented in the following paragraphs.

3.1. Proof of concept

In initial trials, it was decided to evaluate the ring-opening reaction of formylcyclopropane fused to a six membered ring with the attached ring in *trans* arrangement with respect to the formyl group **1a**, as it has shown enhanced reactivity in previous studies.[51,52] Moreover, this compound was easy to synthesize and to isolate as a single diastereoisomer (Scheme 3.1).[53]



Scheme 3.1. Synthesis of *meso*-formylcyclopropane **1a**.

With this substrate in hand, we next proceeded to evaluate a variety of potential nucleophiles able to initiate the ring-opening event. With respect to the aminocatalyst, Gilmour and Werz had obtained the best results employing MacMillan type imidazolidinones and therefore, the nucleophiles were tested in the presence of 2nd generation MacMillan catalyst **3a**. Moreover, it was also decided to survey the Jørgensen-Hayashi aminocatalyst **3b**, which is the other

[53] For experimental details, see Chapter 6.

archetypical catalyst employed in iminium ion activation chemistry.[54] The reaction was carried out in chloroform at room temperature, which are standard reaction conditions used in previous studies with similar catalysts in our group (Scheme 3.2). Nucleophiles that have been widely used in conjugate additions under iminium ion catalysis were first tested, such as typical 1,3-dicarbonyl compounds like diethyl malonate[55] and its analogue malonotrile,[56] as well as nitromethane.[57] These only rendered traces of the corresponding 1,2-addition product to the formyl group of the formylcyclopropan reagent. No reaction was observed with *N*-heterocyclic nucleophiles such as imidazole, 1*H*-benzotriazole and 1-phenyl-1*H*-tetrazole. [58] Phenol,[59] *N*-methylindole[60] and diethyl 2-aminomalonate[61] were also studied, but no reactivity was observed.

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54 (a) Gotoh, H.; Hayashi, Y. In *Sustainable Catalysis*, Dunn, P. J., Ed.; Wiley: Hoboken, New York, 2013: pp 287-316. (b) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (c) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821. (d) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (e) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.

55 Yamaguchi, M.; Yokota, N.; Ninami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

56 Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1101.

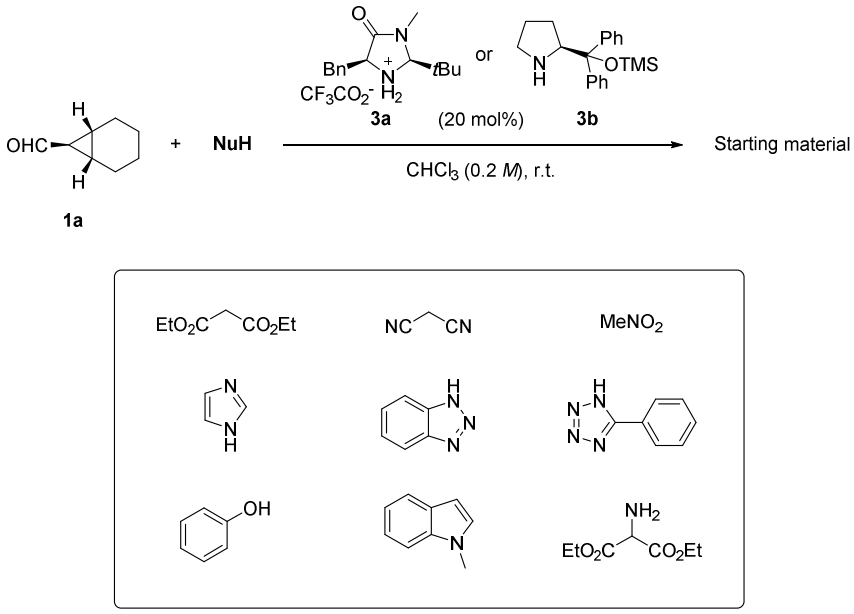
57 McMurry, J. E.; Melton, J. *J. Am. Chem. Soc.* **1971**, *93*, 5309.

58 (a) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509.

59 Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 3039.

60 Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

61 Riaño, I.; Díaz, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330.



Scheme 3.2. Nucleophiles tested for the ring-opening reaction of **1a**.

As not even traces of the desired product were observed, it was thought that perhaps and as it happened in the reactions reported by Gilmour and Werz, the presence of an external electrophile in the media was necessary in order to quench the enamine formed after the ring-opening. Hence, different reagents bearing both an electrophile and a nucleophile within their structure were tested under the same conditions as those employed before (Scheme 3.3). *Ortho*-hydroxy and amino benzaldehyes[62] were tested without any positive results. The same behaviour was observed when benzaldehyde oxime and diethyl 2-(benzylideneamino)malonate[63] were surveyed.

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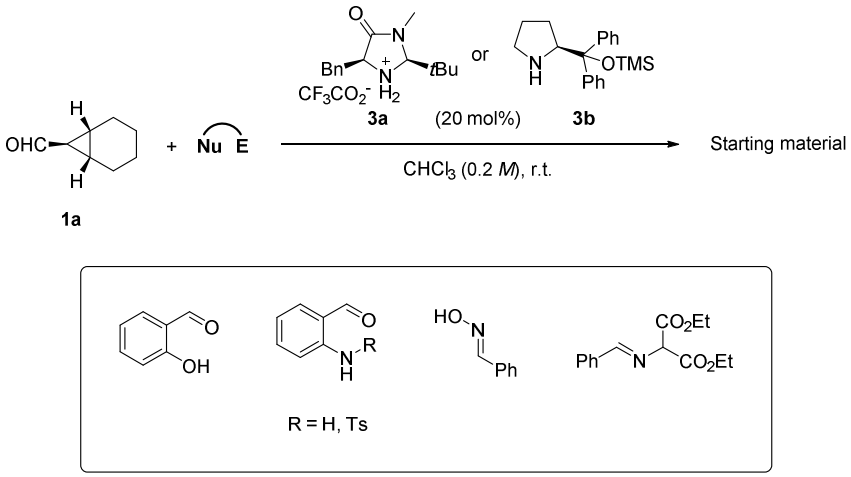
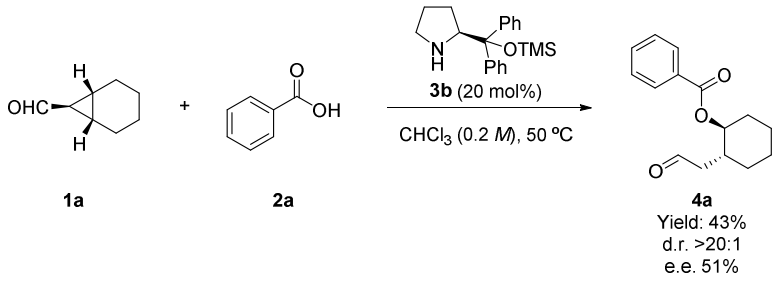
62 Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574.

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



Scheme 3.3. Bifunctional reagents containing both a nucleophile and electrophile surveyed in the ring-opening reaction of **1a**.

In view of these negative results, it was decided to re-evaluate all the nucleophilic reagents incorporating a Brønsted acid as co-catalyst, such as benzoic acid, in the reaction scheme. Typically, the presence of this type of additives in the reaction media is known to facilitate the condensation between the aminocatalyst and the substrate and/or favour the catalyst turnover. Interestingly, although none of the selected substrates was found to promote the projected ring-opening reaction, traces of γ-aciloxy aldehyde **4a** were detected when using Jørgensen-Hayashi aminocatalyst **3b**, meaning that benzoic acid **2a** was acting as the external nucleophile. In view of these results, the reaction between formylcyclopropane **1a** and stoichiometric amounts of benzoic acid **2a** under iminium ion catalysis was tested in chloroform at room temperature, employing the Jørgensen-Hayashi catalyst **3b**. Although the transformation occurred with a very low conversion, an acceptable yield could be obtained by increasing the temperature up to 50 °C (Scheme 3.4).



Scheme 3.4. Reaction between formylcyclopropane **1a** and benzoic acid **2a** under iminium ion catalysis.

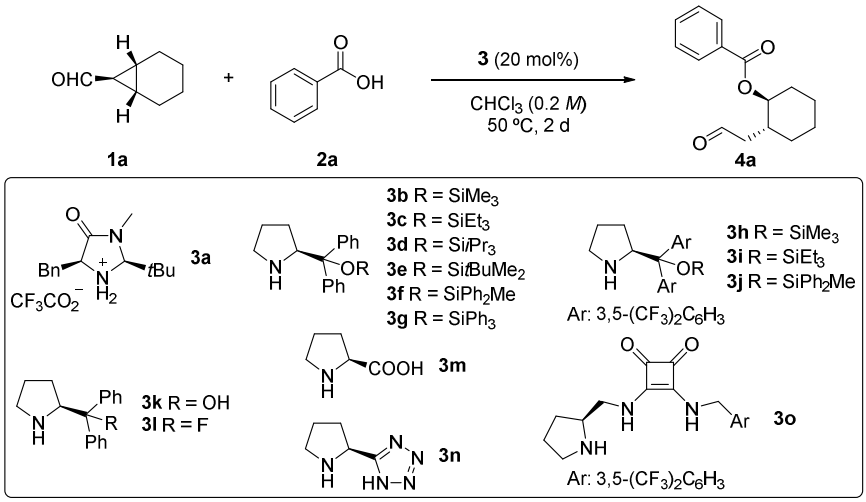
The ring-opening reaction proceeded efficiently in 2 days rendering the final product **4a** in a moderate yield of 43%, as a single diastereoisomer and with a promising enantiomeric excess of 51%. The adduct **4a** needed to be derivatized to the corresponding alcohol **7a** by reduction with sodium borohydride to enable the determination of the enantiomeric excess by chiral HPLC.

3.2. Optimization of the reaction conditions

With these promising results in hand, the next efforts were directed to the identification of the best catalyst for the reaction, focusing specially on the improvement of the enantiocontrol (Table 3.1). The transformation was first carried out in the absence of catalyst, observing that the starting materials remained untouched after 2 days and that the desired product was not formed (Table 3.1, entry 1); concluding that no background reaction was occurring. Next, MacMillan-type imidazolidinone **3a**, which was found to perform best in the aforementioned two literature examples,[51,52] was re-evaluated under same reaction conditions as those used with Jørgensen-Hayashi catalyst **3b** (Table 3.1, entries 2-3). As the formation of the adduct **4a** was observed in only low amount and with a lower enantiomeric excess, the imidazolidinone structure was discarded in favour of proline-based catalysts. In this sense, the reaction was surveyed with

other silylated analogues of catalyst **3b** (Table 3.1, entries 4-8). When more robust and bulkier silyl substituents were placed in the diphenylprolinol structure such as triethylsilyl (catalyst **3c**), triisopropylsilyl (catalyst **3d**) and triphenylsilyl (catalyst **3g**) an improvement of the enantiomeric excess was observed; *tert*-butyldimethylsilyl-containig catalyst **3e** provided almost racemic product, but a 70% e.e. value was observed when diphenylmethylsilyl-containing catalyst **3f** was used. Thinking of increasing the steric hindrance induced by the aminocatalyst, the bulkier 3,5-bis(trifluoromethyl)phenylprolinol analogues were surveyed (Table 3.1, entries 9-11). Although *O*-TMS diarylprolinol **3h** failed to promote the reaction, the enantiomeric excess with the bulkier triethylsilyl-containing catalyst **3i** and diphenylmethylsilyl-containing catalyst **3j**, provided improved e.e. values in comparison with their diphenylprolinol-protected analogues. In fact, the final product was obtained with an excellent enantiomeric excess of 92% when employing catalyst **3j**, although with a low yield. Other catalysts with architectures that could show other interactions apart from the steric shielding were surveyed. Thinking of structures without the silicon protecting group, the non-protected dihenylprolinol **3k** and a similar catalyst bearing a fluoride group (catalyst **3l**) were evaluated (Table 3.1, entries 12-13). Catalyst **3k** did not promote the reaction and with catalyst **3l** the final product was obtained with almost no enantiocontrol. L-proline **3m** and Ley´s catalyst **3n** were also surveyed but they induced lower enantiocontrol (Table 3.1, entries 14-15). Finally, the bifuctional pyrrolidine-squaramide catalyst **3p** developed by Jørgensen was unable to promote the reaction (Table 3.1, entry 16).

Table 3.1. Evaluation of a series of catalysts.[a]

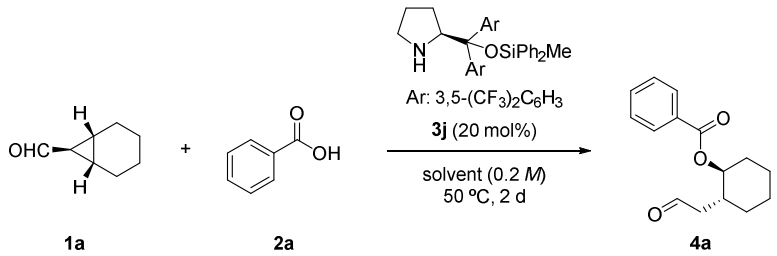


Entry	Catalyst	Yield (%)[b]	d.r.[c]	e.e. (%)[d]
1	-	<5	-	-
2	**3a**	8	>20:1	31
3	**3b**	43	>20:1	51
4	**3c**	33	>20:1	61
5	**3d**	42	>20:1	61
6	**3e**	41	>20:1	13
7	**3f**	40	>20:1	70
8	**3g**	59	>20:1	64
9	**3h**	<5	-	-
10	**3i**	40	>20:1	77
11	**3j**	40	>20:1	92
12	**3k**	<5	-	-
13	**3l**	50	>20:1	8
14	**3m**	17	>20:1	0
15	**3n**	38	>20:1	8
16	**3o**	<5	-	-

[a] Reactions performed in 0.1 mmol scale of **1a** and **2a**, using 20 mol% of catalyst **3** in 0.5 mL of $CHCl_3$ at 50 °C for 2 d. [b] Yield of pure product after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding reducted adduct **6a**.

At this point, catalyst **3j** provided an excellent diastereo- and enantioselectivity in the reaction. However, the yield of the transformation needed to be improved by further modifying the reaction conditions. For this reason, solvents of different nature were evaluated. Non-polar solvents negatively affected the yield (Table 3.2, entries 2-3), especially in the case of hexane, for which no reactivity was observed, probably due to solubility issues. In the same line, when increasing the polarity of the solvent from THF to MeCN, going through DME, AcOEt and DMF (Table 3.2, entries 4-8) no reactivity or just traces of the final product were detected. Polar protic solvents were also tested (Table 3.2, entries 9-10), but as with the previous polar solvents, the ring-opening did almost not happen; however, it should be mentioned that H_2O managed to provide the desired product in a low yield but with a moderately good enantiocontrol. As changing the nature of the solvent did not end up in any improvement and chloroform reminded the best (Table 3.2, entry 1), various halogenated solvents were tested, such as, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene and α,α,α-trifluorotoluene (Table 3.2, entries 11-14). Although, the enantiocontrol was maintained, the yielded decreased in all cases; hence, the further screening of the reaction conditions was performed employing chloroform as solvent.

Table 3.2. Evaluation of different solvents.[a]



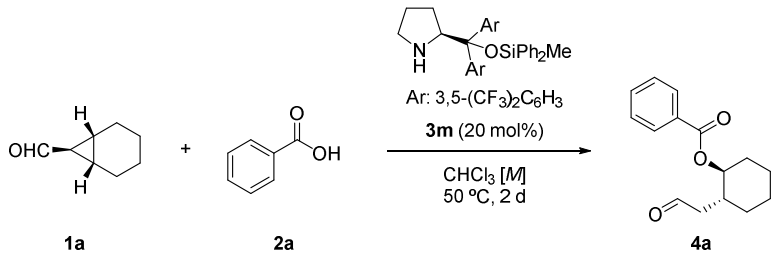
Entry	Solvent	Yield (%)[b]	d.r.[c]	e.e. (%)[d]
1	$CHCl_3$	40	>20:1	92
2	Toluene	28	>20:1	90
3	Hexane	<5	-	-
4	THF	<5	-	-
5	DME	<5	-	-
6	AcOEt	7	>20:1	89
7	DMF	<5	-	-
8	MeCN	8	>20:1	80
9	*i*PrOH	<5	-	-
10	H_2O	13	>20:1	70
11	$ClCH_2CH_2Cl$	20	>20:1	91
12	CCl_4	26	>20:1	90
13	ClC_3H_5	19	>20:1	89
14	$CF_3C_3H_5$	24	>20:1	90

[a] Reactions performed in 0.1 mmol scale of **1a** and **2a**, using 20 mol% of catalyst **3j** in 0.5 mL of solvent at 50 °C for 2 d. [b] Yield of pure product after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding reducted adduct **6a**.

Finally, the influence of the concentration and the molar ratio of reactants was evaluated, in the outcome of the reaction. Decreasing the concentration of **1a** to 0.1 *M* led to lower yield (Table 3.3, entry 1), while increasing it to 0.4 *M* slightly increased the yield as well as maintained the high stereocontrol (Table 3.3, entry 3). At higher concentration no further improvement was observed (Table 3.3, entry 4).With respect to the influence played by the molar ratio of reagents, using benzoic

acid **2a** as limiting reagent with a small excess of formylcyclopropane **1a** was not beneficial for the reaction (Table 3.3, entry 5), whereas the use of higher amounts of benzoic acid **2a** increased considerably the quantity of product obtained (Table 3.3, entries 6-7). Adding more than 3 equivalents of benzoic acid reduced the value of the obtained highest yield (Table 3.3, entry 6).

Table 3.3. Evaluation of concentration of the reaction and molar ratio of reagents.[a]

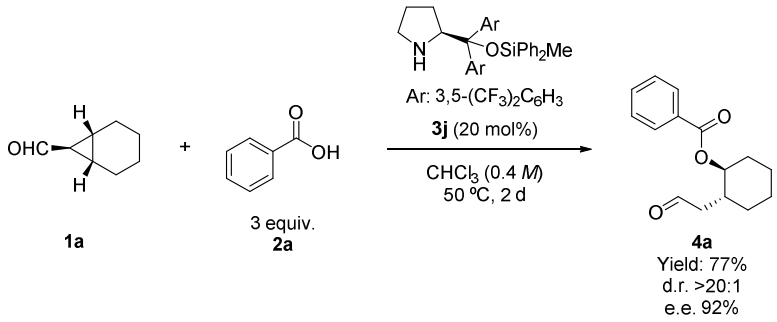


Entry	[*M*]	1a/2a ratio	Yield (%)[b]	d.r.[c]	e.e. (%)[d]
1	0.1	1:1	16	>20:1	92
2	0.2	1:1	40	>20:1	92
3	0.4	1:1	49	>20:1	92
4	0.8	1:1	39	>20:1	88
5	0.4	1.5:1	36	>20:1	91
6	0.4	1:1.5	61	>20:1	92
7	0.4	1:3	77	>20:1	92
6	0.4	1:5	60	>20:1	90

[a] Reactions performed in 0.1 mmol scale of limiting reagent, using 20 mol% of catalyst **3j** in $CHCl_3$ at 50 ºC for 2 d. [b] Yield of pure product after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding reducted adduct **6a**.

Once the most important reaction parameters had been evaluated, it was concluded that the optimal conditions for carrying out the reaction implied using formylcyclopropane as limiting reactant and adding an excess of 3 equivalents of

carboxylic acid in combination with secondary amine **3j** (20 mol%) as catalyst, in chloroform (0.4 *M*) at 50 °C and running the reaction for two days (Scheme 3.5).



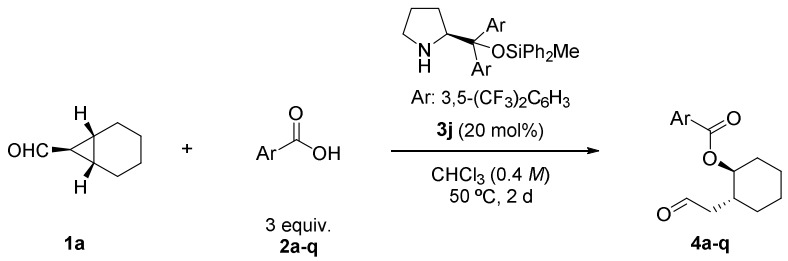
Scheme 3.5. Optimal conditions for the ring-opening reaction of *meso*-formylcyclopropanes with benzoic acids.

3.3. Scope of the reaction

In order to evaluate the effect that different carboxylic acids could have in the reaction, a wide variety of them was analysed (Table 3.4). Benzoic acid derivatives and other aromatic carboxylic acids were first tested. The reaction performed well in terms of yield and enantiocontrol with a large variety of substitution patterns in the aryl moiety of benzoic acid derivatives (Table 3.4, entries 1-16); the e.e. values were similar in all the cases, although the yield was influenced by the nature of the substituent and its position in the ring. The presence of an electron-withdrawing group in *para* position of the aromatic ring provided the final adduct in similar yields in comparison with benzoic acid (Table 3.4, entries 2-3) and in contrast, electron-donating groups negatively affected the formation of the ring-opening product (Table 3.4, entries 4-5). Remarkably, the excellent enantiocontrol was maintained in all the cases. The same effect could be observed with *ortho*-substituted benzoic acid derivatives (Table 3.4, entries 6-10). The presence of *o*-amino group resulted in the lowest yield and a moderate enantiocontrol, and the reaction did not take

place with the *o*-dimethylamino benzoic acid (Table 3.4, entries 11-12). Finally, an electron-donating group was placed in *meta*-position rendering the final product in high yield and excellent enantiocontrol (Table 3.4, entry 13). Interestingly, highly substituted benzoic acids were also tolerated by the reaction with satisfactory outcome (Table 3.4, entries 14-16), even when bulky substituents such as isopropyl groups where placed in the aryl moiety. It can be concluded that in terms of yield, benzoic acid derivatives which have a pK_a value lower than the benzoic acid, will perform in a similar way than the benzoic acid itself, and that higher pK_a values will end up lowering the yield. Heteroaromatic carboxylic acids such as 2- and 3-furanecarboxylic acid delivered the final product successfully (Table 3.4, entries 17-18), with the exception of nicotinic acid which failed to promote the reaction, possible due to the presence of a rather electron-poor aryl group (Table 3.4, entry 19).

Table 3.4. Scope of benzoic acid derivatives and heteroaromatic carboxylic acids.[a]

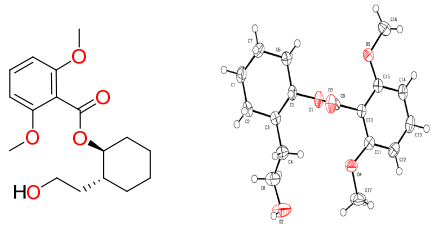


Entry	Product	Ar	pK_a (ArCOOH)	Yield (%)[b]	e.e. (%)[c]
1	**4a**	Ph	4.19	77	92
2	**4b**	4-(NO_2)C6H4	3.44	80	86
3	**4c**	4-FC_6H_4	4.14	76	91
4	**4d**	4-MeC_6H_4	4.37	45	93
5	**4e**	4-$MeOC_6H_4$	4.47	18	92
6	**4f**	2-(NO_2)C_6H_4	2.17	81	92
7	**4g**	2-FC_6H_4	3.27	75	98
8	**4h**	2-(OH)C_6H_4	2.97	79	95
9	**4i**	2-MeC_6H_4	3.95	44	93
10	**4j**	2-$MeOC_6H_4$	4.09	33	91
11	**4k**	2-(NH_2)C_6H_4	4.95	10	74
12	**-**	2-(NMe_2)C_6H_4	-	<5	-
13	**4l**	3-$MeOC_6H_4$	4.08	72	92
14	**4m**	2,4,6-$(Me)_3C_6H_2$	3.44	74	93
15	**4n**	2,4,6-(iPr)$_3C_6H_2$	-	84	91
16	**4o**	2,6-$(MeO)_2C_6H_3$	3.98	81	89
17	**4p**	Furan-2-yl	3.12	57	92
18	**4q**	Furan-3-yl	4.03	46	89
19	**-**	Pyrid-3-yl	4.75	<5	-

[a] Reactions performed in 0.25 mmol scale of **1a** and 0.75 mmol of **2a-q**, using 20 mol% of catalyst **3j** in 0.6 mL $CHCl_3$ at 50 °C for 2 d. d.r. >20:1 in all cases by ^{1}H-NMR. [b] Yield of pure product after flash column chromatography. [c] Determined by HPLC analysis of the corresponding reducted adduct **6a-q**.

It has been mentioned that a reduction step after the ring-opening event was necessary in order to determinate the e.e. values by HPLC analysis. And at this

point, the absolute configuration was assigned by X-ray diffraction on monocrystals of the aaducts obtained by reduction of 4**o**, observing a (1*S*,2*R*) stereostructure (Figure 3.1). The absolute configuration of the other adducts was established assuming an identical mechanistic pathway for all the reactions.



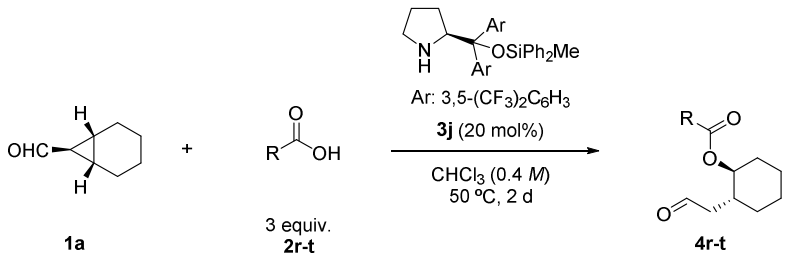
6o

Figure 3.1. ORTEP diagram for alcohol obtained by reduction of adduct **4o**.

On the other hand, aliphatic carboxylic acids also performed well in the reaction. As expected by the results obtained with the benzoic acid derivatives, pivalic acid, with the highest pK_a value, resulted unproductive in the reaction (Table 3.5, entry 1). On the other hand, acetic acid, phenylacetic acid and chloroacetic acid delivered the final product with an excellent enantiocontrol, although acetic acid provided the corresponding ring-opening product in lower yield compared to phenylacetic acid and chloroacetic acid (Table 3.5, entries 2-4). When the most acidic trichloro- and trifluoroactic acid were tested, despite observing complete transformation of the formylcyclopropane to the desired product, these final products resulted to be highly unstable, degrading almost immediately in the reaction media (Table 3.5, entries 5-6).[64]

[64] The ring-opening product could not be isolated nor derivatized *in situ*.

Table 3.5. Scope of aliphatic carboxylic acids.[a]



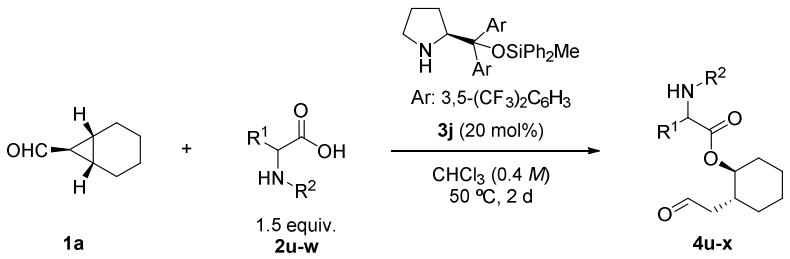
Entry	Product	R	pK_a (ArCOOH)	Yield (%)[b]	e.e. (%)[c]
1	-	*t*Bu	5.03	<5	-
2	**4r**	Me	4.76	26[d]	90
3	**4s**	Bn	4.31	79	91
4	**4t**	CH_2Cl	2.86	73	87
5	-	CCl_3	0.65	n.d.[e]	-
6	-	CF_3	-0.25	n.d.[e]	-

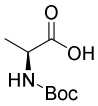
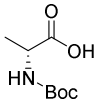
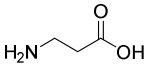
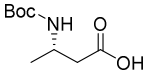
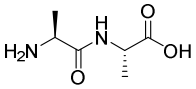
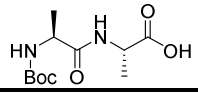
[a] Reactions performed in 0.25 mmol scale of **1a** and 0.75 mmol of **2r-t**, using 20 mol% of catalyst **3j** in 0.6 mL $CHCl_3$ at 50 ºC for 2 d. d.r. >20:1 in all cases by ^{1}H-NMR. [b] Yield of pure product after flash column chromatography. [c] Determined by HPLC analysis of the corresponding reducted adduct **6s** and benzoylated adduct **8a-b**. [d] Yield obtained after preforming reduction *in situ*. [e] n.d.: Not determined.

In view of the broad scope of carboxylic acids that delivered the final product in a high yields and with an excellent enantiocontrol, it seemed mandatory to next study the possibility of using amino acids in this ring-opening process. α- and β-amino acids and a dipeptide derived from two units of L-Alanine were chosen for the first trials, expecting at least a similar reactivity as the one observed with anthranilic acid, but all of them failed to react (Table 3.6, entries 1, 4, 6). As the amino group of the amino acid could be competing with the aminocatalyst for condensing with the carbonyl group of the formylcyclopropane, *N*-protected amino acids were surveyed. The reaction performed satisfactorily with both *N*-Boc-protected α- and β-amino acids (Table 3.6, entries 2-3, 5) and the desired product could also be obtained with the protected dipeptide as well (Table 3.6, entry 7).

Importantly, *N*-Boc-protected D- and L-Alanine provided the final adduct with the same diastereomeric ratio, which supports the theory of the ring-opening proceeding under exclusive catalyst control with respect to stereocontrol (Table 3.6, entries 2-3).

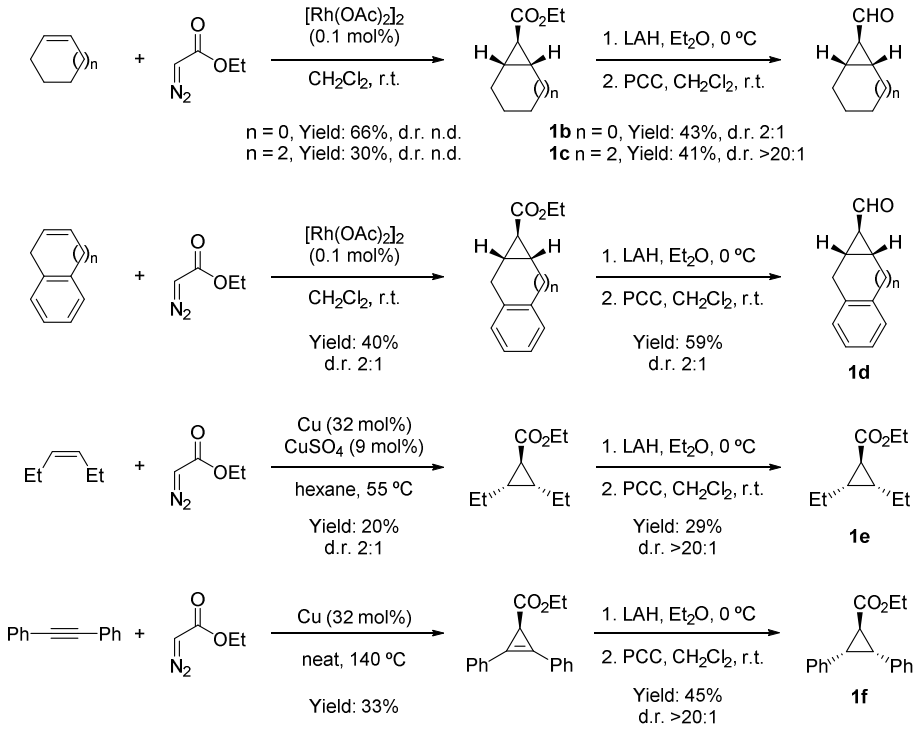
Table 3.6. Scope of amino acids.[a]



Entry	Product	Amino acid	Yield (%)[b]	d.r.[c]
1	-		<5	-
2	**4u**		67	11:1
3	**4v**		88	11:1
4	-		<5	-
5	**4w**		60	18:1
6	-		<5	-
7	**4x**		33	7.5:1

[a] Reactions performed in 0.25 mmol scale of **1a** and 0.38 mmol of **2u-x**, using 20 mol% of catalyst **3j** in 0.6 mL $CHCl_3$ at 50 °C for 2 d. [b] Yield of pure product after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

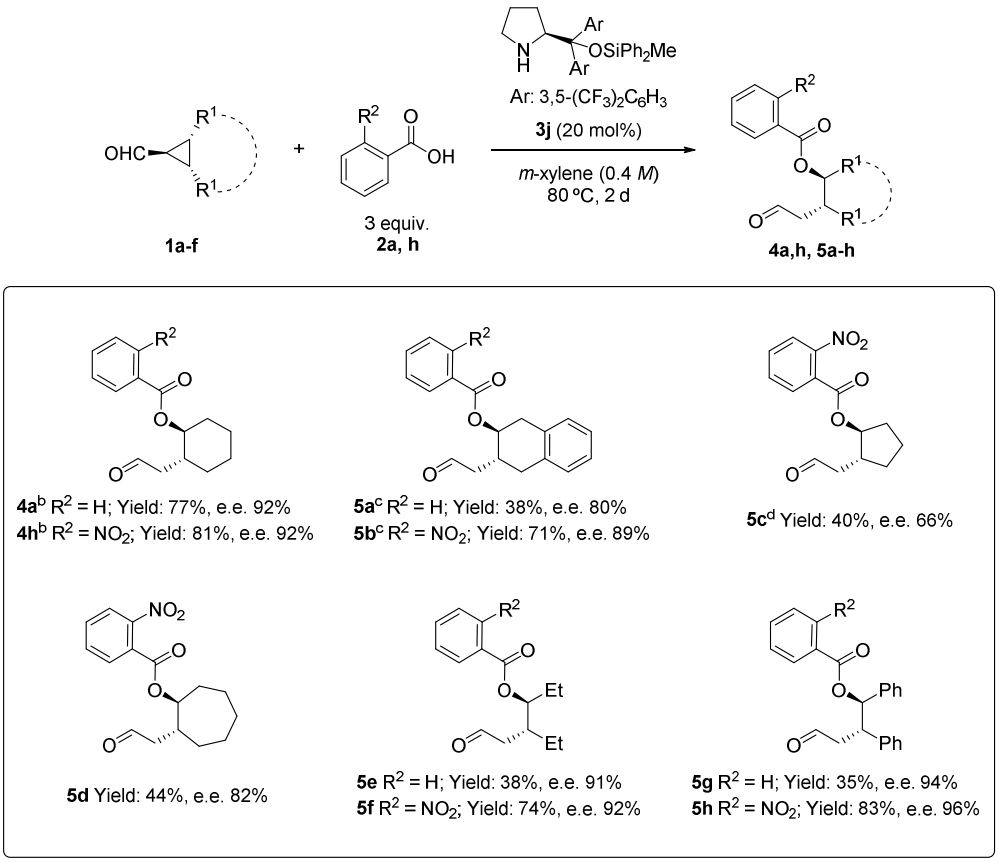
Once all the aspects of the nucleophile had been analysed, the possibility of using other formylcyclopropanes was evaluated. Formylcyclopropanes incorporated within a bicyclic framework such as bicyclo[3.1.0]hexane (**1b**), bicyclo[5.1.0]octane (**1c**) and 1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene (**1d**), as well as simpler *meso*-2,3-diethyl-substituted formylcyclopropane (**1e**) and *meso*-2,3-diphenyl-substituted derivative (**1f**) were synthesised. Formylcyclopropanes **1b-d** were prepared employing the same methodology as for the synthesis of **1a**, with rhodium. In the case of **1c** as for **1a**, the diastereoisomers could be separated in the purification of the cyclopropanation step and the final aldehyde was obtained as a single diastereoisomer. However, in the case of formylcyclopropanes **1b** and **1d** the separation of the diastereoisomers could not be done in any of the synthetic steps, and the final adducts were obtained as a diastereomeric mixture. The cyclopropanation step for the synthesis of formylcyclopropanes **1e** and **1f** was performed in the presence of copper using the corresponding alkene for **1e** and alkyne for **1f**, and the corresponding aldehyde of both products was obtained as a single diastereoisomer (Scheme 3.6). For the products obtained as diastereomeric mixture, the minor *cis* diastereoisomer isomerized to *trans* in the presence of a secondary amine, which allowed the improvement of the diastereomeric ratio of formylcyclopropanes **1b** and **1d**.



Scheme 3.6. General overview of the synthesis of formylcyclopropanes **1b-f**.

In an initial attempt, formylcyclopropanes **1b-f** showed lower reactivity than **1a**, as provided poor yields of the corresponding ring-opening products. For this reason it was decided to modify the reaction in order to be able to raise up the temperature and improve the conversion. After a short screening of other solvents, the reaction with these formylcyclopropanes **1b-f** was carried out in *m*-xylene at 80 ^{o}C and employing both benzoic acid **1a** and 2-nitrobenzoic acid **2h** as standard nucleophiles. Under these modified reaction conditions most of them reacted efficiently, showing a higher reactivity towards 2-nitrobenzoic acid in comparison with benzoic acid, as expected from previously obtained results and in all cases, the final adducts where isolated as highly enantioenriched materials (Scheme 3.7). It

has to be pointed out that, bicyclo[3.1.0]hexane **1b** and formylcyclopropanes bicyclo[5.1.0]octane **1c** depleted the reactivity, which is in agreement with the proposed mechanism that will be discussed afterwards.

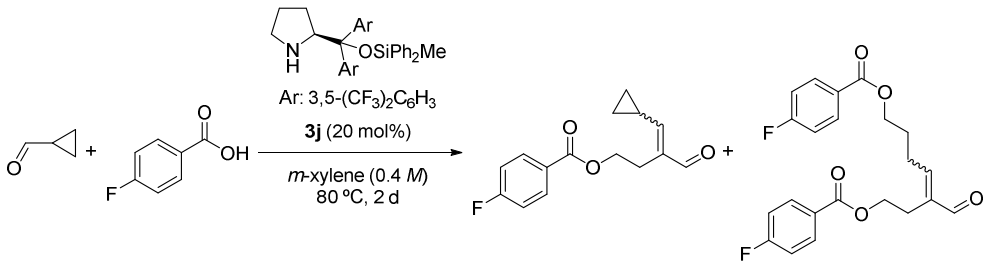


Scheme 3.7. Scope of the reaction using formylcyclopropanes **1b-f**.[65]

[65] Reactions performed in 0.25 mmol scale of **1a-f** and 0.75 mmol of **2a** or **2h**, using 20 mol% of catalyst **3j** in 0.6 mL *m*-xylene at 80 °C for 2 d. d.r. >20:1 in all cases by ^{1}H-NMR. Yield of pure product after flash column chromatography. e.e. determined by HPLC analysis of the corresponding reducted adduct **6a,h** and **7a-h**. Reactions performed in $CHCl_3$ at 50 °C. d.r. of starting material formylcyclopropane **1d** 18:1. d.r. of starting material formylcyclopropane **1b** 8:1.

Finally, it was decided to study the possibility of using the more challenging unsubstituted formylcyclopropane **1h**, despite expecting a final product with no stereocenters. Under optimised reaction conditions, **1h** was able undergo the ring-opening reaction, isolating compounds **5i** and **5j** in yields of 24% and 7% respectively. With this substrate the reaction did not stop in the γ-acyloxy aldehyde, as in all the previous cases, but the enamine intermediate further reacted with the starting formylcyclopropane leading to product **5i** or with the γ-acyloxy aldehyde providing product **5j** (Table 3.7). The formation of product **5j** could be inhibited by changing the limiting reactant and adding, for this specific case, formylcyclopropane in excess.

Table 3.7. Ring-opening of formylciclopropane **1h**.[a]



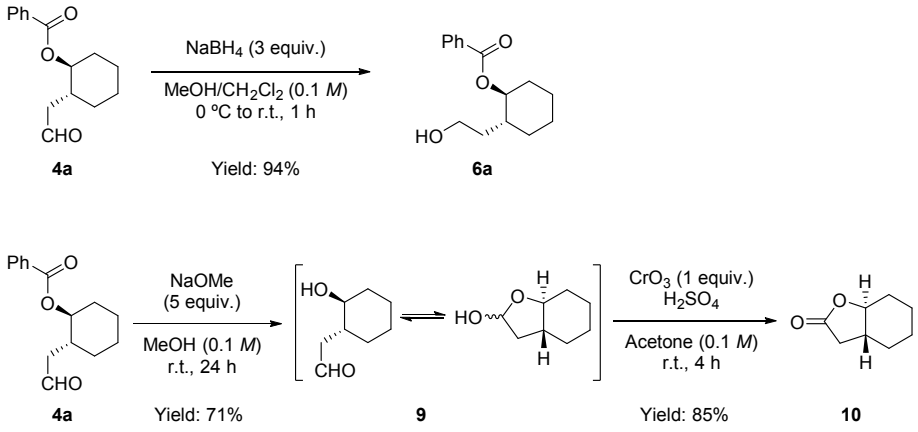
Entry	1h/2c ratio	Yield 5i (%)[b]	Yield 5j (%)[b]
1	1:3	24	7
2	3:1	77	Traces

[a] Reactions performed in 0.25 mmol scale of limiting reagent, using 20 mol% of catalyst **3j** in 0.6 mL *m*-xylene at 80 ºC for 2 d. d.r. >20:1 in all cases by ^{1}H-NMR. [b] Yield of pure product after flash column chromatography.

3.4. Synthetic manipulations on the γ-acyloxy aldehydes

Having observed that a wide variety of formylcyclopropanes and carboxylic acids could be satisfactory employed for the synthesis of γ-acyloxy aldehydes, some

selected transformation were carried out in order to prove the utility of the developed ring-opening reaction. For this aim, compound **4a** was selected as a representative model substrate to be subjected to various modifications. Reduction of the aldehyde was straightforward and quantitative to the primary alcohol **5a**, while the ester remained untouched; for this transformation $NaBH_4$ was selected as it satisfactorily reacts with aldehydes but is not reactive enough for reducing esters. Transformation of the ester to the corresponding alcohol, in the presence of the aldehyde was achieved by hydrolysis. The corresponding γ-hydroxyaldehyde **11** was obtained as a mixture of isomers in a high yield; this adduct provided access to γ-lactone **12** by an oxidation process in an excellent yield (Scheme 3.8).



Scheme 3.8. Transformations performed over adduct **4a**.

3.5. Mechanistic insights

In order to understand the origin of the stereocontrol and to propose a mechanism of the reaction, DFT calculations were carried out.[66] The proposal is based on the activation of the formylcyclopropane *via* iminium ion. Under this

[66] DFT calculations were carried out by Prof. Merino´s group in the University of Zaragoza.

catalysis, not only the LUMO-energy would be lowered by the formation of this activated intermediate, but also, the polarity of the C-C bond present in the cyclopropane moiety would be increased leading to an easier cleavage of it.

Cyclohexane-fused formylcyclopropane **1a** and benzoic acid **2a** were chosen as model substrates for studying the reaction. Initially the achiral process considering pyrrolidine as catalyst was analysed, obtaining the corresponding transition structure where it could be observed the perpendicular orientation of the iminium moiety with respect to the plane containing the three-membered ring (Figure 3.2). However, it was not possible to identify which C atom of the cyclopropane would be the most prone to react, thus, a real chiral non-racemic catalyst was used for further calculations. Catalyst **3b** was chosen in terms of computational convenience.

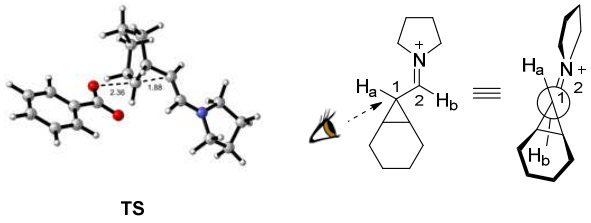
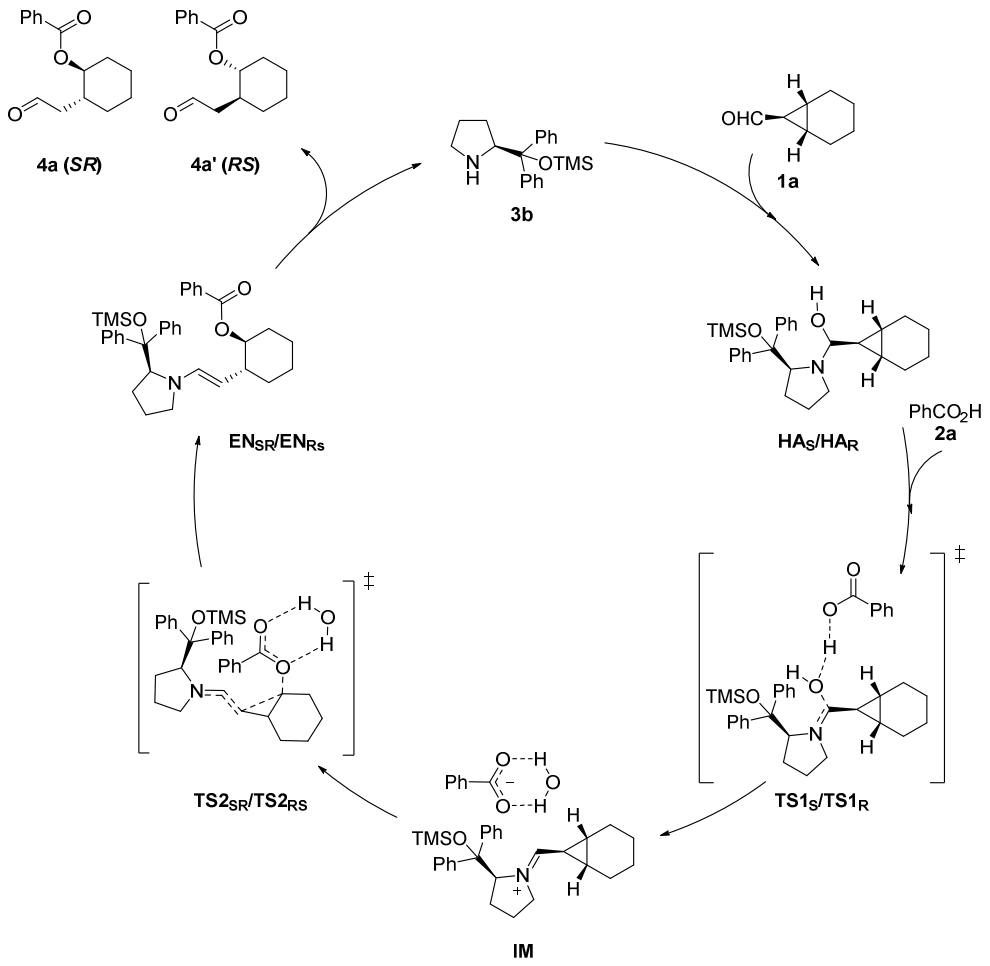


Figure 3.2. Iminium ion structure and TS.

The formation of the iminium ion starts with the 1,2-addition of the secondary amine to the formylcyclopropane which leads to the corresponding hemiaminal **HA** (Scheme 3.9). The stereocenter that is generated after this addition could have in principle both absolute configurations, however, this has no influence in the catalytic cycle because both diastereomers end up in the only possible iminium ion configuration. The iminium ion **IM** could be located as a minimum only when water was considered in the reaction media, this molecule being involved in the

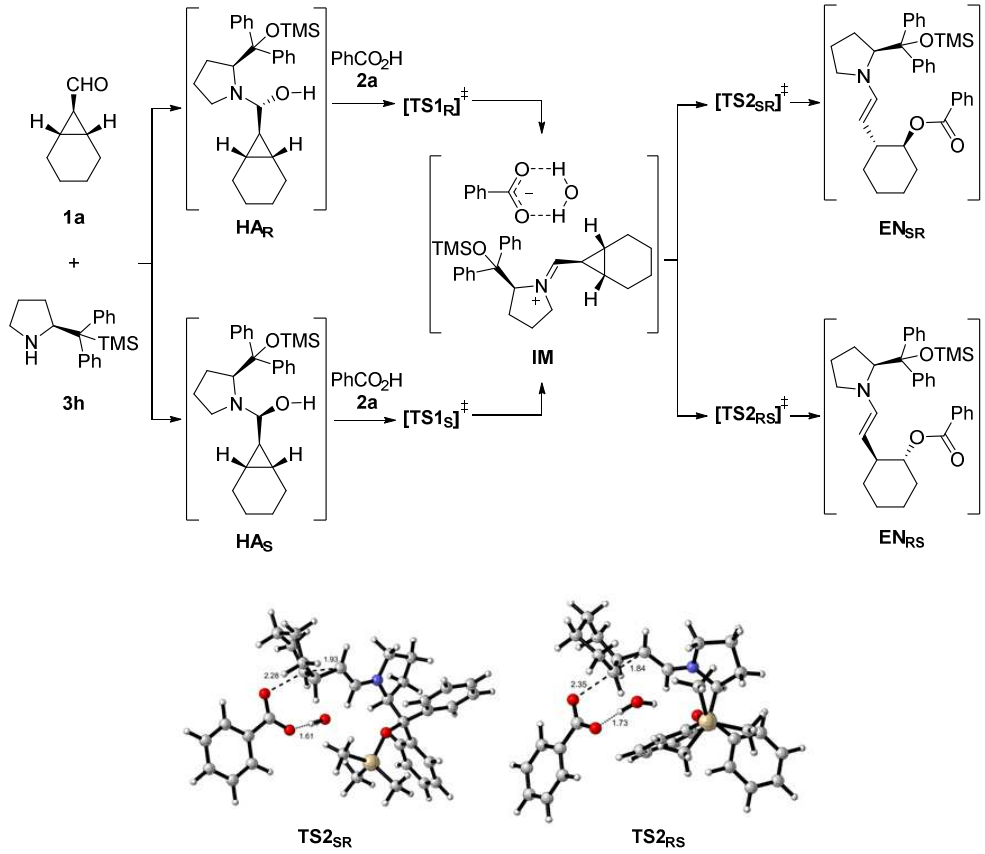
stabilization of the ion-pair formed by the iminium ion and the benzoate.[67] Once the cyclopropane moiety is activated the C-C bond cleavage would take place. The cyclopropane-ring opening **TS2** is the rate limiting step of the cycle and since a carbocationic intermediate could not be located, the step has been considered to be an S_N2-type reaction. In this sense, the attack should come from the opposite side of the breaking bond leading to a complete inversion of configuration.

[67] Examples of stabilization of the iminium ion through binding of the hydroxy-leaving group by an H-donor. For a example with bis-sulfonamides, see: Gu, Y.; Yu, T. Y.; Liang, Y. M.; Luo, Y. C.; Xu, P. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 14128. For an example with thioureas and squaramides, see: Juste-Navarro, V.; Prieto, L.; Ignacio, D.; Manzano, R.; Tejero, T.; Reyes, E.; Vicario, J. L.; Merino, P. *Adv. Synth. Catal.* **2017**, *359*, 4122.



Scheme 3.9. Catalytic cycle of the reaction between **1a** and **2a** catalysed by **3b**.

As the face of the addition is controlled by the substrate, only two possible enantiomeric products can be obtained, depending on in which C atom of the cyclopropane happens the attack of the benzoate anion. Calculations showed a clear preference (4.0 kcal/mol) for the attack that leads to the experimentally obtained mayor enantiomer **TS2$_{SR}$** (Scheme 3.10, Figure 3.3).



Scheme 3.10. Possible pathways for the reaction between **1a** and **2a** catalysed by **3b**.

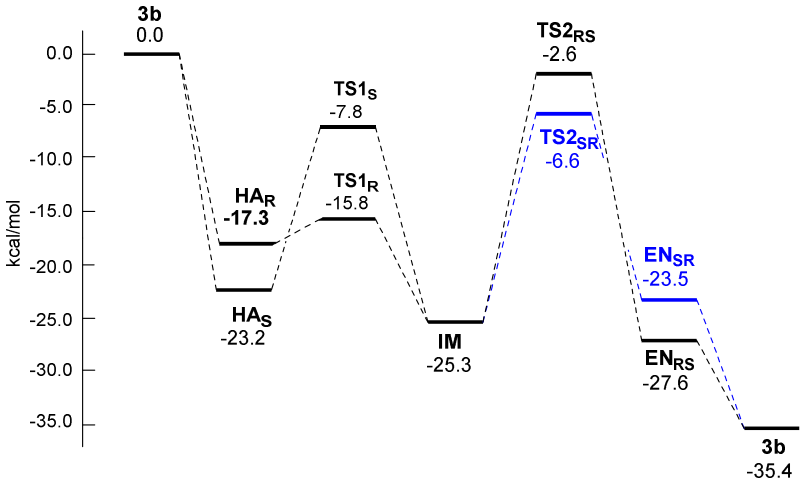


Figure 3.3. Comparative energy profiles of the two possible diastereomeric pathway for the reaction between **1a** and **2a** catalysed by **3b**.

It has been mentioned before that the fact of not having located a carbocation enamine species as a minimum in addition to the excellent diastereomeric control, led to consider the ring-opening as an S_N2-type reaction. However, a close inspection of the **TS2** and the corresponding IRC showed a slight asynchronicity in the process. In order to study the progress of the reaction a topological analysis of the electron localization function (ELF) was carried out.

The illustration of the ELF analysis (Figure 3.4) shows the moment when the cyclopropane C1-C3 bond breaks at point 56. From that moment until point 60, C3-C4 bond increases its electron population reaching values compatible with C-C double bond, and at the same time, V(C4,N5) decreases intensity until single bond values, while V(N5) increases. From these events, it can be concluded that the ring-opening happens at the same time as the evolution from the iminium ion towards the enamine, which will be formed at point 60. The absence of monosynaptic basins for C1 is characteristic of their carbocationic character. Moreover, the formation of

the enamine carbocation is supported by the fact that O6 remains with the same electron population until point 72. The formation of the bond C1-O6 happens after the transition state, at the same time as the V(O6) drops its intensity.

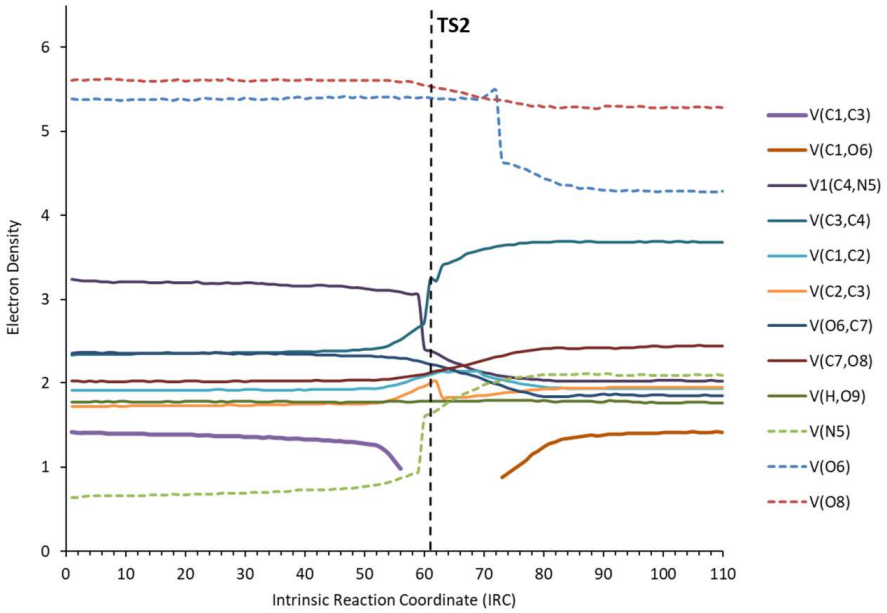
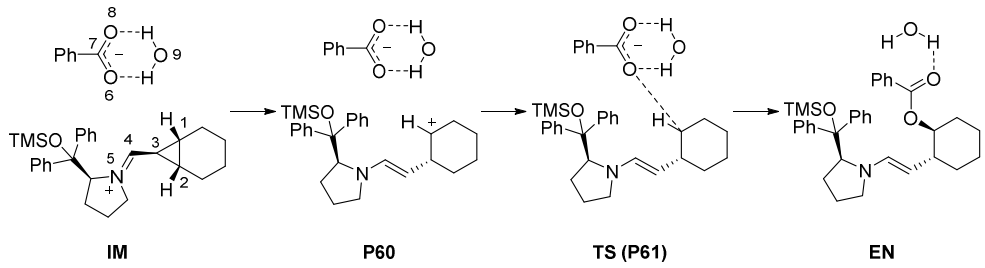


Figure 3.4. Graphical representation of ELF analysis for the reaction between **1a** and **2a** catalysed by **3b**.

The observed gap between the C1-C3 bond breaking (P56) and the formation of C1-O6 bond (P72) is compatible with the formal existence of an incipient carbocation, which cannot be localized neither as a minimum nor as an intermediate. The developing positive charge forms an intimate ion-pair leading to an inverting-S_N1 process[68] rather than to a typical S_N2 mechanism. However, as no intermediates are located, the reaction is considered to occur in one kinetic step,

[68] For a S_N1-type reactions showing a complete inversion of configuration due to the formation of intimate-ion pairs, see: Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *28*, 328.

as a concerted but asynchronous transformation since two events can be identified along the reaction coordinate (Scheme 3.11). Moreover, the existence of the incipient carbocation explains the differences in reactivity between the cyclohexane- and cycloheptane-/cyclopentane-fused formylcyclopropanes. The formylcyclopropanes fused to the seven- and five-membered ring show a lower reactivity due to the formation of less stable carbocations, in comparision with the more stable six-membered ring carbocation. This would be in agreement with the expected differences in stability, calculated through the solvolysis of the corresponding 1-aryl-1-cycloalkyl alcohols, for the cyclohexyl, cyclopentyl and cycloheptyl carbocataions.[69]



Scheme 3.11. Formation of an incipient carbocation forming an intimate ion pair during the reaction course.

[69] Brown, H. C.; Periasamy, M. *J. Org. Chem.* **1981**, *46*, 3161.

4. CONCLUSIONS

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

- Carboxylic acids proved to be reactive enough to promote the ring-opening of *meso*-formylcyclopropanes under iminium ion activation, obtaining highly enantioenriched γ-acyloxy aldehydes when using diphenylmethylsilyl protected diarylprolinol catalyst.

- The method has demonstrated to have a wide scope regarding both the carboxylic acid and the formylcyclopropane reagents. In regard of the nucleophile, aromatic and aliphatic carboxylic acids were satisfactorily tolerated, as well as *N*-Boc-protected α- and β-amino acids.

- Mechanistic studies suggested that the reaction should be considered concerted but asynchronous, since two events can be identified along the reaction coordinate even though it occurs in a single kinetic step. The bulky substituent of the chiral catalyst differentiated the stereotopic C atoms of the cyclopropane, obtaining enantioenriched final adducts as the attack of the benzoic acid mainly occurred in one C atom.

Chapter 3

3

Total Synthesis of Speciosin H

1. OXIGENATED CYCLOHEXANOIDS ISOLATED FROM *HEXAGONIA SPECIOSA*

Oxygenated cyclohexanoids, which are usually generated in bacteria, fungi, higher plants and molluscs are known to have a wide range of bioactivities, such as, antifungal, [1] antibacterial,[2] antibiotic[3] and phytotoxic.[4] In this sense, *Hexagonia speciosa*, a fungus present in the tropical and subtropical zones of China, generates as second metabolites 19 compounds named speciosin A-T (Figure 1.1).[5] Even though all these metabolites are oxygenated cyclohexanoids, they present important structural differences. All of them can be described as cyclohexanes with different degrees of unsaturation that also present two or more positions of the cyclic scaffold in different oxidation states. They also have in common the presence of one or two lateral chains that are probably derived from a terpene. According to their structures, these compounds could be classified into four groups. The first ones present an epoxyquinone backbone with a trisubstituted oxirane (speciosin A-F and L-O), whereas the second ones are mono- or disubstituted hydroxyenones (speciosin K and T). Alternatively, the third group presents an aromatic structure, being the two of them monosubstituted hydroquinones (speciosin G and P) and the last ones present a completely saturated cyclohexanediol as backbone with one lateral chain (speciosin H-J and Q-S).

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1 (a) Li, J. Y.; Harper, J. K.; Grant, D. M.; Tombe, B. O.; Bashyal, B.; Hess, W. M.; Strobel, G. A. *Phytochemistry* **2001**, *56*, 463. (b) Kim, H.-J.; Vinale, F.; Ghisalberti, E. L.; Worth, C. M.; Sivasithamparam, K.; Skelton, B. W.; White, A. H. *Phytochemistry* **2006**, *67*, 2277.

2 Shah, R.; Neuss, N.; Gorman, M.; Boeck, L. D. *Antibiot.* **1970**, *23*, 613.

3 Nair, M. S. R.; Anchel, M. *Phytochemistry* **1977**, *16*, 390.

4 Nagata, T.; Ando, Y.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810.

5 (a) Jiang, M.-Y.; Zhang, L.; Liu, R.; Dong, Z.-J.; Liu, J.-K. *J. Nat. Prod.* **2009**, *72*, 1405. (b) Jiang, M.-Y.; Li, Y.; Wang, F.; Liu, J.-K. *Phytochemistry* **2011**, *72*, 923.

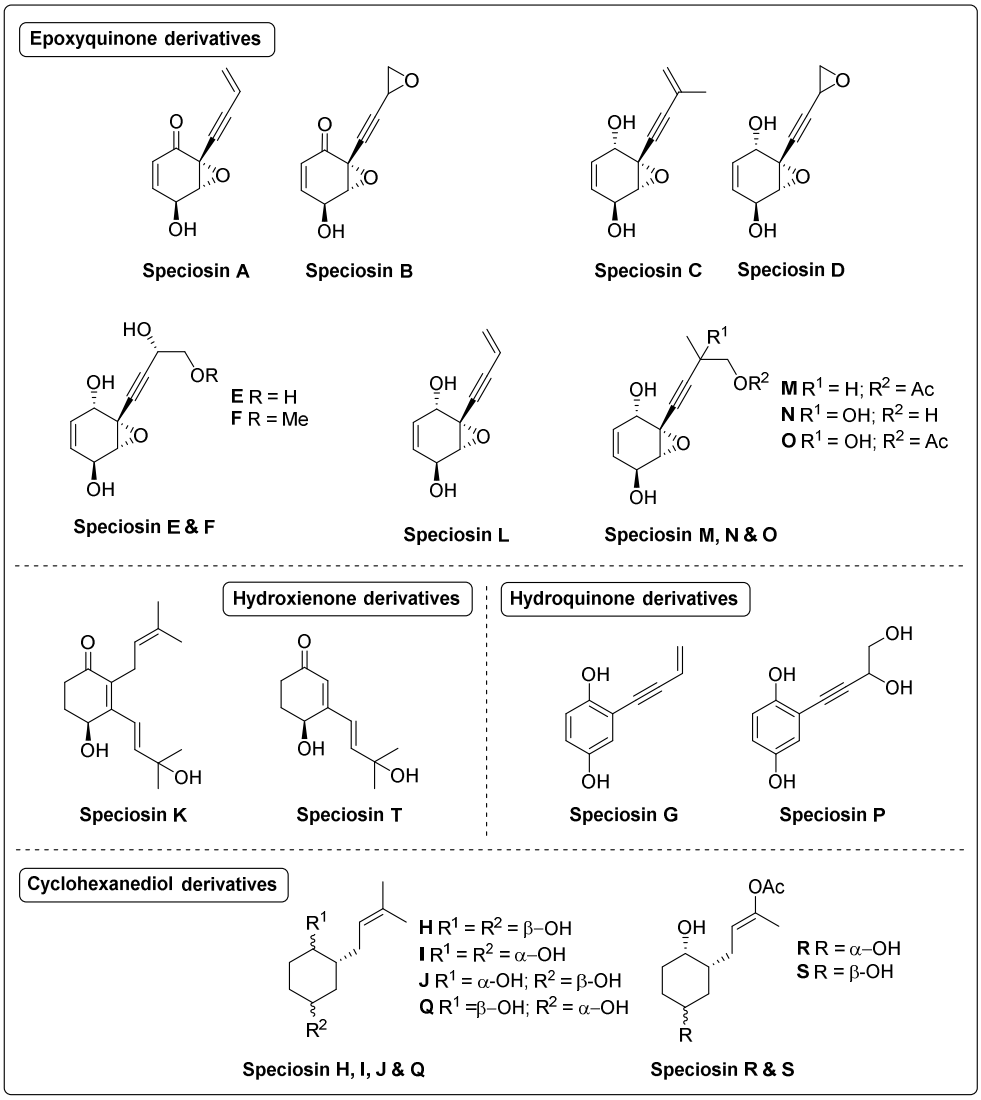
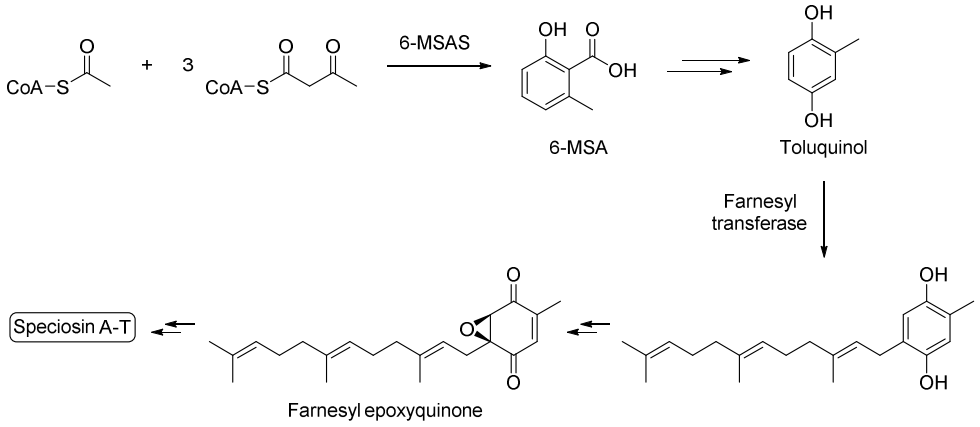


Figure 1.1. Structures of speciosin A-T.

Although the biosynthesis of the secondary metabolites speciosin A-T has not been described, it has been recently postulated that they could be derived *via*

polyketide synthase-terpene synthase (PKS-TPS) hybrid pathway.[6] A biosynthetic pathway was proposed for the synthesis of farnesyl epoxyquinone; where toluquinol is biosynthesised through 6-methylsalicilic acid from condensation of one acetyl-CoA and three malonyl-CoA in the presence of 6-methylsalicylic acid synthase, which would afterwards suffer farnesylation followed by an epoxidation or vice versa, leading to farnesyl epoxyquinone (Scheme 1.1).[7] However, it is not clear if this biosynthesis can be extended to speciosin A-T.



Scheme 1.1. Proposed biosynthetic pathway for farnesyl epoxyquinone, possible intermediate in the biosynthesis of speciosin A-T.

Finally, it should be mentioned that out of the 19 isolated metabolites, the total synthesis of just a few of them has been described up to date.

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6 Mehta, G.; Sengupta, S. *Tetrahedron* **2017**, *73*, 6223.

7 (a) Teng, L.-L.; Song, T.-Y.; Xu, Z.-F.; Liu, X.; Dai, R.; Chen, Y.-H.; Li, S.-H.; Zhang, K.-Q.; Niu, X.-M. *Org. Lett.* **2017**, *19*, 3923. (b) Matsuda, Y.; Abe, I. *Nat. Prod. Rep.* **2016**, *33*, 26.

1.1. Total synthesis of speciosin A-C

Taylor and co-workers envisioned a synthesis for epoxiquinones containing trisubstituted epoxides that could give access to speciosins A-C.[8] They postulated that the final products could be obtained through two main key steps: a palladium-catalysed coupling of a halogen-substituted 1,4-benzoquinone monoketal, and a Diels-Alder/reto-Diels-Alder sequence to protect the less-substituted alkene present in the quinone structure and to stereodirect the epoxidation and reduction processes (Scheme 1.2). A final epoxidation step on sepeciosin A would lead to speciosin B, and by slightly modifying the substituent of the alkyne that participates in the palladium-catalysed coupling, the synthesis of SDEF 678 metabolite would be possible, which would give access to speciosin C. The starting material 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone was converted to the corresponding enyne quantitatively under Stille coupling conditions. Afterwards the disubstituted quinone double bond was satisfactorily protected performing a Diels-Alder reaction with cyclopentane, although a racemic product was obtained and therefore the asymmetric synthesis of speciosin A-C would not be possible. A stereoselective reduction of the carbonyl group and acetal removal produced the corresponding enones after 3 steps in high yields. The epoxide moiety could be inserted by a nucleophilic epoxidation with a satisfactory yield, although with no diastereocontrol. Finally, the retro-Diels-Alder reaction gave the desired final speciosin A and SDEF 678 as racemic products, by heating up the previous compound at 250 ^{o}C in diphenyl ether.

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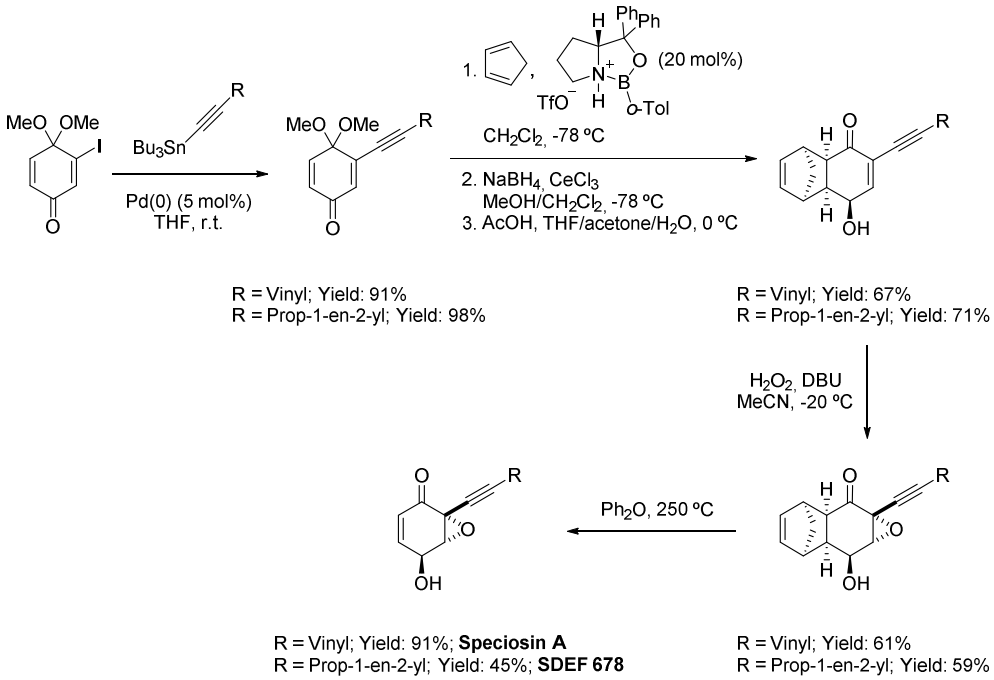
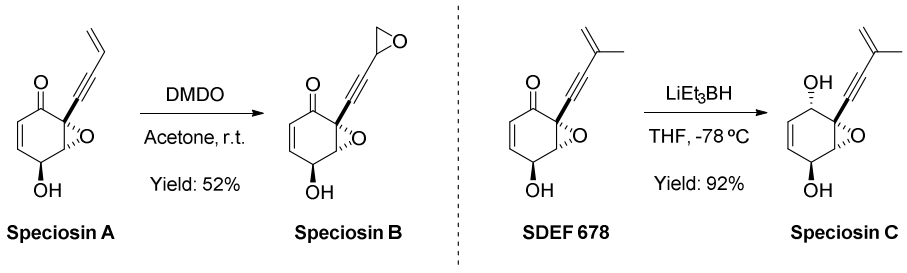
8 Hookins, D. R.; Burns, A. R.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 451.



Scheme 1.2. Total racemic synthesis of speciosin A.

Speciosin B could be obtained by epoxidation of speciosin A with DMDO in acetone, in a moderate yield; and reduction of SDEF 678 with $LiEt_3BH$ led to speciosin C as a single diastereoisomer in an excellent yield (Scheme 1.3).

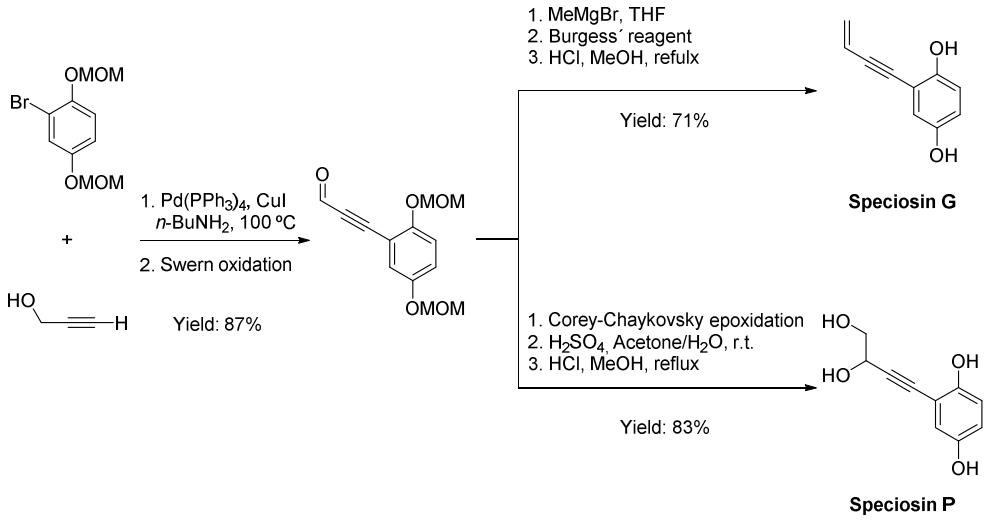


Scheme 1.3. Final step for the synthesis of speciosins B and C in racemic form.

1.2. Total synthesis of speciosin G and P

In 2014 Macías and co-workers reported the total synthesis of speciosin G and P from readily available starting materials.[9] The key step of the strategy would be the attachment of the carbon chain to an aromatic nucleous, which is indeed a common intermediate of the two metabolites. Although speciosins G and P are in principle simple products, a multi-step and convergent synthesis was necessary for their preparation. The common product could be generated by a Sonogashira coupling of the protected bromohydroquinone with propargyl alcohol, followed by a Swern oxidation, in an excellent yield. The synthesis of speciosin G required of the olefination of the aldehyde that was accomplished through Grignard addition, followed by dehydration using Burgess´ reagent. Finally, deprotection under acidic conditions yielded the target product satisfactorily. Speciosin P was obtained by performing a Corey-Chaykovsky epoxidation and subsequently hydrolysing the epoxide, leading to the corresponding diol. The last deprotection was carried out in the same conditions as for speciosin G (Scheme 1.4). Both products were obtained in remarkable high overall yields.

9 Guerrero-Vásquez, G. A.; Chinchilla, N.; Molinillo, J. M. G.; Macías, F. A. *J. Nat. Prod.* **2014**, *77*, 2029.



Scheme 1.4. Total synthesis of speciosin G and P.

In general, it can be said that a wide variety of oxygenated cyclohexanoids generated as metabolites in different species have been synthesised,10 however, none of the procedures describes a useful synthetic route that could be applied for the synthesis of speciosin K and T or speciosin H-J and Q-S. Thus, brand new methodologies should be studied for the obtention of these substrates.

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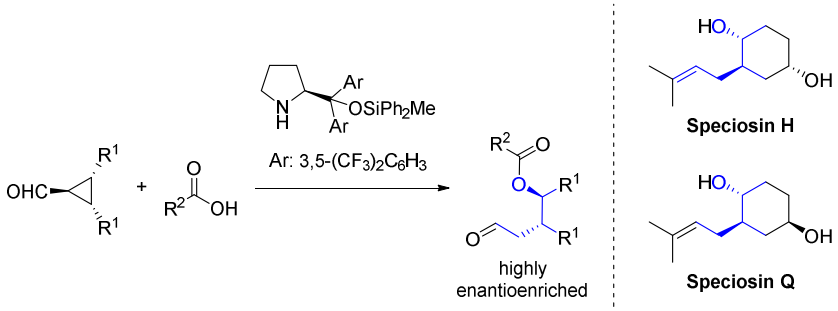
10 For selected examples on the synthesis of oxygenated cyclohexanoids, see: (a) Mehta, G.; Kumar, Y. C. S.; Khan, T. B. *Tetrahedron Lett.* **2010**, *51*, 5112. (b) Fujimura, T.; Shibuya, M.; Ogasawara, K.; Iwabuchi, Y. *Heterocycles* **2005**, *66*, 167. (c) Mehta, G.; Pujar, S. R.; Ramesh, S. S.; Islam, K. *Tetrahedron Lett.* **2005**, *46*, 3373.

2. SPECIFIC OBJECTIVES

From the literature examples shown it can be concluded that, up to date, there is no synthetic route described for the obtention of 2-substituted 1,4-cyclohexanediols speciosin H-J and Q-S. With this in mind, it is decided to demonstrate the synthetic potential of the previously described asymmetric cyclopropane ring-opening reaction of *meso*-compounds through application in the total synthesis of one of these natural products. As the two stereocenters are obtained with *trans* configuration after the ring-opening, it is envisioned that either speciosin H or/and Q could be potential target compounds by employing the opposite enantiomer of the secondary amine catalyst (Scheme 2.1).

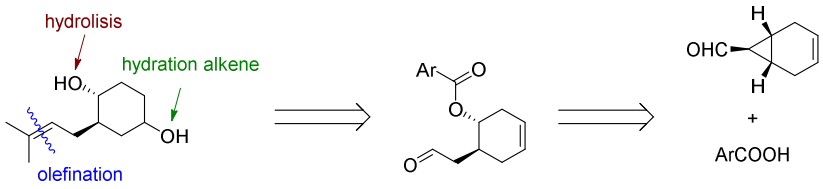


Scheme 2.1. Envision of the applicability of the ring-opening reaction for the synthesis of speciosin H and/or Q.

Therefore, the objective of the present work is to develop a **synthetic rout for speciosin H and/or Q employing the previously described asymmetric desimetrization of *meso*-formylcyclopropanes as key step**.

The proposed disconnections of speciosin H and Q in Scheme 2.2 show the possibility of synthesising these two products *via* an approach where the key step would be the ring-opening of bicycle[4.1.0]hept-3-ene-7-carbaldehyde. Therefore,

by selecting the starting formylcyclopropane with the appropiate ring fusion, the desired cyclohexanoid should be generated containing an oxidised position (C1) and the corresponding lateral chain in the continuous carbon. The ring-opening reaction would lead to a final adduct with the two substituents in *trans* relative configuration, same as in the case of speciosin H and Q. On the other hand, for the obtaining of the correct enantiomer, the pyrrolidine derived aminocatalyst with the opposite configuration to the one employed in the previously optimized transformation will have to be used.

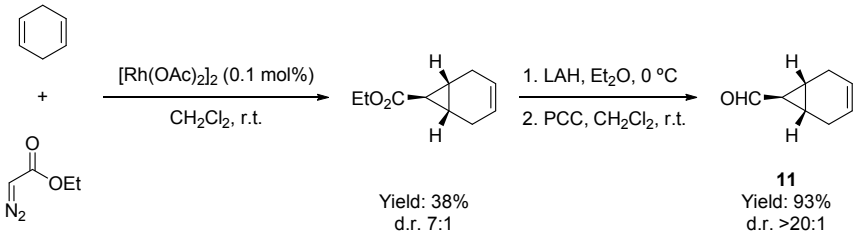


Scheme 2.2. Proposed disconnections for the synthesis of speciosin H and Q.

In regard to the transformations that will have to be carried out in order to transform the two substituents present in the adduct obtained after the ring-opening, the ester moiety could be converted into the hydroxy group through hydrolysis and the aldehyde would give access to the alkene performing an olefination. Finally, the oxidation of the position C4 should be possible through hydration of the alkene moiety. The order of the proposed transformations will be decided depending on the selected reaction conditions.

3. RESULTS AND DISCUSSION

The synthesis was started with the preparation of the key starting material. Formylcyclopropane **11** was synthesized following the methodology employed for the preparation of the previously tested formylcyclopropanes **1a-d**.[11] In the initial cyclopropanation step only one C-C double bond out of the two present in the 1,4-cyclohexadiene reacted, leading to the expected product in a moderate yield and with a diastereoselectivity of 7:1 in which the mayor diastereoisomer presented a *trans* relation between the etoxycarbonyl and the cyclohexene moiety. Reduction and oxidation, as previously shown, provided de final formylcyclopropane **11** quantitatively, achieving an overall yield of 31% in 3 steps (Scheme 3.1).



Scheme 3.1. Synthesis of cyclohexene-fused formylcyclopropane **11**.

With formylcyclopropane **11** in hand, the reaction between **11** and salicylic acid **2h** under iminium ion catalysis was tested in chloroform at 50 °C, employing the diphenylmethylsilylated diarylprolinol catalyst ***ent*-3p** (Scheme 3.2). The ring-opening reaction proceeded with outstanding results, rendering the desired product **12** in an excellent yield of 94%, as a single diastereoisomer and with almost complete enantiocontrol.[12]

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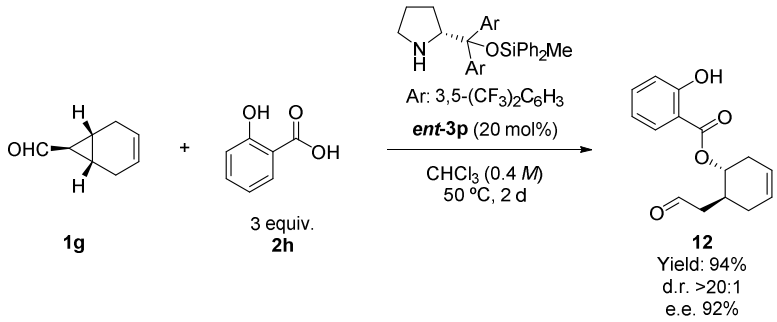
11 For experimental details, see Chapter 6.

12 The e.e. was determined on compound **13**, product of the reduction of **12** with $NaBH_4$. For experimental details, see Chapter 6.



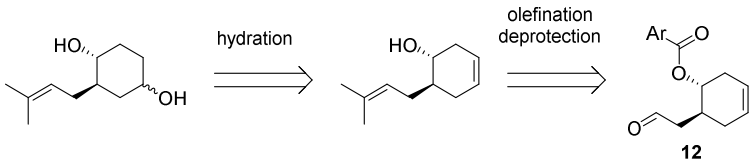
Scheme 3.2. Ring-opening reaction between formylcyclopropane **11** and salicylic acid **2h**.

As it has been aforementioned, the opposite enantiomer of the catalyst employed in the ring-opening reaction was necessary in order to obtain the final product that would lead to the target natural products with the appropriate stereochemistry. On the other hand, between all the carboxylic acids that have been previously tested under the optimised conditions, salicylic acid **2h** was selected as it provided excellent results in terms of yield and enantiocontrol. Moreover, the higher solubility of this benzoic acid derivative in water, was also beneficial in the work up step where the excess of carboxylic acid is separated from the organic layer and this facilitated the reaction when it was scaled up to 0.82 mmol of **11**.

3.1. Synthesis of speciosin H by hydroboration

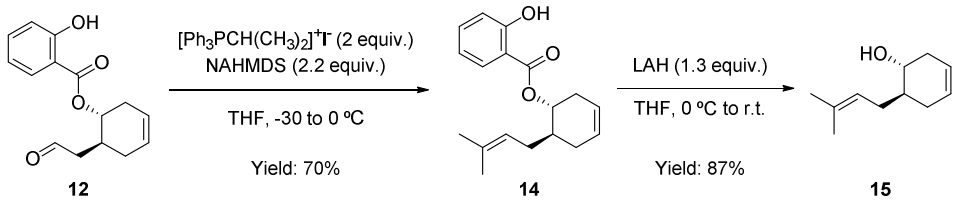
Once the ring-opening reaction had been proved to give excellent results when employing formylcyclopropane **11**, a directed strategy for the synthesis of speciosin H and/or Q was proposed based on the analysis shown in Scheme 3.3. In the initially presented retrosynthesis, after the ring-opening reaction the aldehyde would be converted into the corresponding alkene through an olefination and the oxidised

carbon (C1) would be deptrotected. Finally, a hydration of the C-C double bond would provide the second hydroxy group.



Scheme 3.3. Initial retrosynthetic analysis for the synthesis of speciosin H and/or Q.

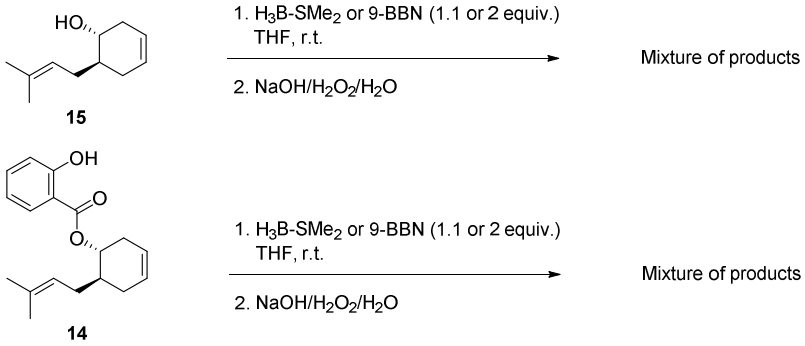
In this sense, for the formation of the desired olefin moiety starting from compound **12** it was decided to test the Wittig reaction as a similar transformation had been described in the bibliography[13]. Triphenylphosphoranylidene isopropane was generated from the corresponding phosphonium salt in the presence of NaHMDS, obtaining the desired alkene **14** in 70% yield. Next, the reduction of the ester moiety was accomplished quantitatively leading to the corresponding alcohol **15** by the addition of lithium aluminium hydride (Scheme 3.4). At this point, two of the three substituents of the final product were present in the structure with the appropriate configuration and none of the stereocenters had epimerized neither under the Wittig reaction conditions nor in the reduction step.



Scheme 3.4. Wittig reaction over compound **12**, followed by reduction of the ester moiety.

[13] Vassilikogiannakis, G.; Chronakis, N.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1998**, *120*, 9911.

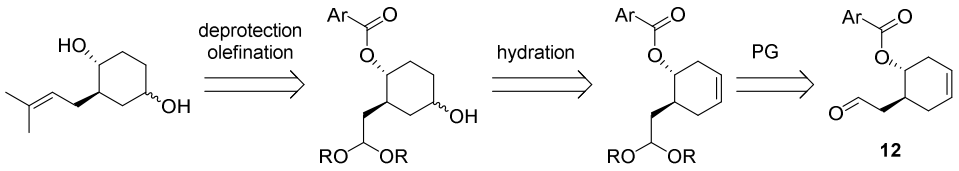
Hydroboration/oxidation of compound **15** was thought to be the more straightforward strategy for the insertion of the hydroxy group attached to the C4 carbon. It had been proved that the hydroboration tends to occur at the less substituted double bond, leaving the more substituted alkene unaltered, although, it should be mentioned that monohydroboration of differentially substituted non-conjugated dienes has usually been described when a terminal alkene is present in the structure.[14] With this in mind, the bulkier 9-borabicyclo[3.3.1]nonane (9-BBN) was surveyed. However, when testing the hydroboration in compound **15** a mixture of products was observed indicating that both alkenes present in the structure reacted similarly, obtaining a mixture of products where both alkenes had been hydroborated separately with no regiocontrol. Borane dimethyl sulphide complex was also tested with similar results (Scheme 3.5). At this point, it was evaluated to perform the hydroboration/oxidation before the reduction step. However, similar results were observed when performing the reaction in compound **14**. In addition, transesterification took place under the oxidation step, obtaining non desired products.



Scheme 3.5. Hydroboration/oxidation of compounds **14** and **15**.

[14] Graham, T. J. A.; Poole, T. H.; Reese, C. N.; Goess, B. C. *J. Org. Chem.* **2011**, *76*, 4132.

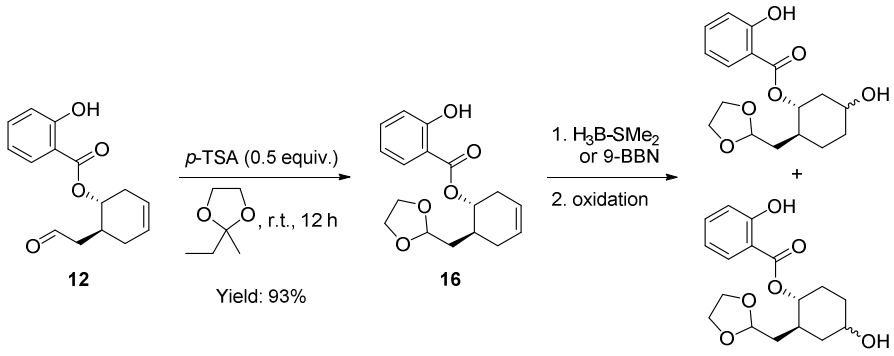
The results obtained until the moment when trying to hydroborate various non-conjugated alkenes suggested that a structure with only one alkene and with a protected aldehyde[15] was necessary. Thus, the carbonyl group should be protected before the hydration of the alkene and the Wittig reaction should be carried out as final step, after the necessary deprotection of the hydroxy group placed in C1 position (Scheme 3.6).



Scheme 3.6. Alternative retrosynthetic analysis for speciosin H and Q.

It was decided to protect the carbonyl group of compound **12** converting it into an acetal, as this transformation does not alter the oxidation stage of the carbon that participates in the transformation. In this sense, aldehyde **12** could be protected as its corresponding acetal **16** almost quantitatively in the presence of 1,3-dioxalane and *p*-toluenesulfonic acid. However, when trying the hydroboration reaction on this compound the two possible regioisomers were obtained as a diastereomeric mixture (Scheme 3.7).

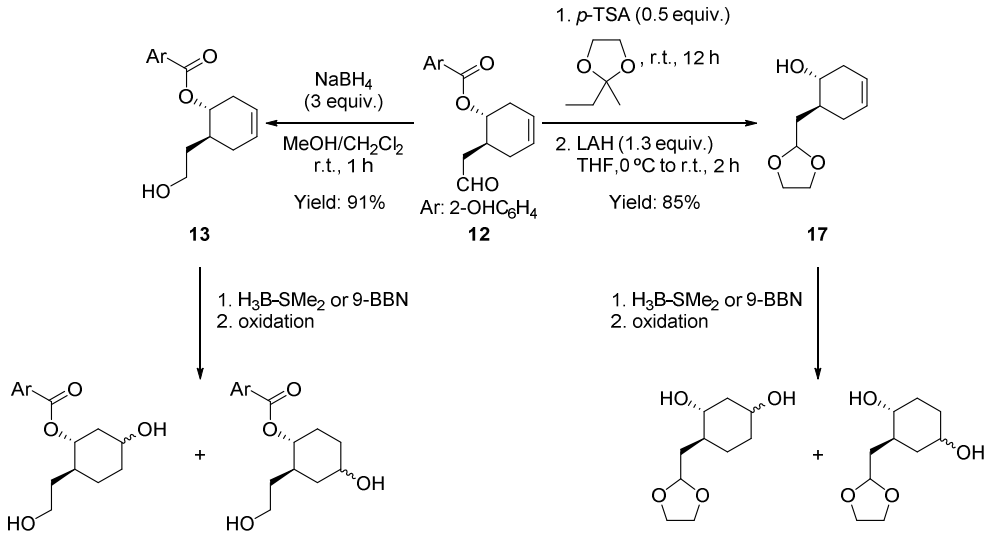
[15] When trying the hydroboration with compound **13**, the borane mainly promoted the reduction of the carbonyl group.



Scheme 3.7. Hydroboration/oxidation of compound **16**.

As no selectivity had been observed in any of the hydroboration/oxidation trials, based on previous studies, it was thought that the hydroboration could be regio- and diastereodirected by the hydroxy group present at the starting material.[16] For this strategy, alcohols **13** and **17** were chosen as starting materials. However, the transformation did not gave any good results, as there was no regio- nor diastereocontrol in any of the cases (Scheme 3.8).

[16] For selected examples of oxygen-directed intramolecular hydroborations, see: (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (b) Jung, M. E.; Karama, U. *Tetrahedron Lett.* **1999**, *40*, 7907. (c) Rarig, R.-A. F.; Scheideman, M.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 9182.



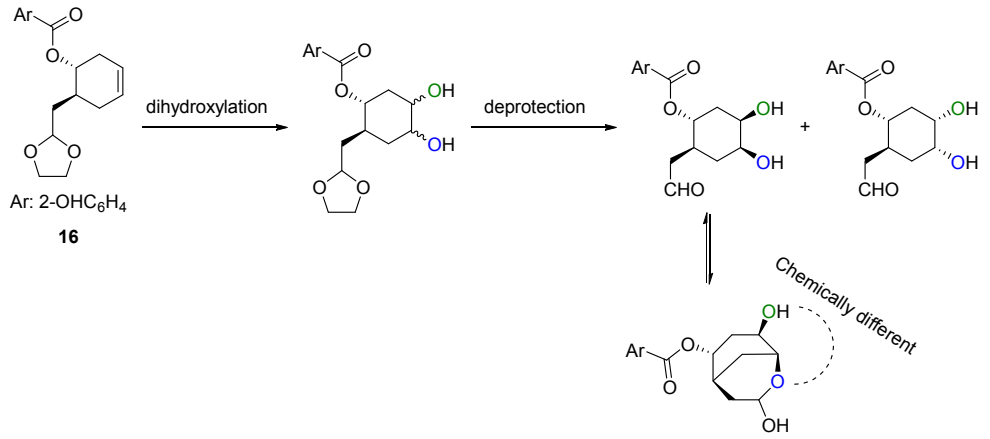
Scheme 3.8. Hydroboration/oxidation trials with compounds **13** and **17**.

After all the performed trials, it was concluded that the hydroboration/oxidation strategy for the hydration of the C-C double bond had to be discarded as no regiocontrol was achieved in any of the tested products.

3.2. Synthesis of speciosin H and/or Q by asymmetric dihydroxylation

As the C-C double bond hydration step could not be performed through previously designed hydroboration/oxidation reaction regioselectively, finding a way for chemically differentiating C4 and C5 carbons seemed a good idea to try next. It was thought that by a dihydroxylation proccess, despite both carbons of the C-C double bond would be hydroxilated, the presence of an aldehyde in the molecule would make them chemically differentiated. The hydroxy group attached to C4 carbon could react with the aldehyde forming a hemiacetal, if both functional groups were oriented in a *cis* configuration; for that, it was envisioned that an asymmetric dihydroxylation (AD) could lead to the appropriate diastereoisomer.

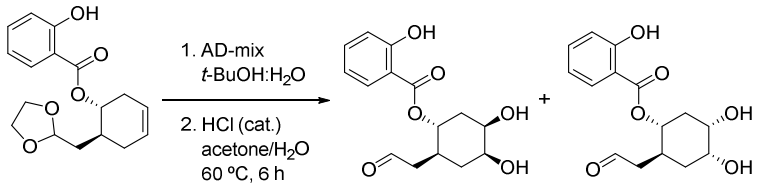
This cyclization would lead to chemically different hydroxy groups, giving the possibility of eliminating the OH group attached to the C5 carbon leaving the other OH untouched (Scheme 3.9).



Scheme 3.9. Strategy for chemically differentiating the OH groups attached to C4 and C5 carbons.

As the carbonyl groups are usually incompatible with dihydroxylation reaction conditions, the transformation had to be performed to the protected compound **16** (Table 3.1)**.** The *syn* addition occurred without diastereocontrol when running the reaction at room temperature despite the AD-mix used. Luckily, the combination of lowering the temperature down to 0 ^{o}C and adding AD-mix-β promoted the final diol with a satisfactory diastereomeric ratio of 4:1. Once the asymmetric dihydroxylation had been optimized, the aldehyde moiety of compound **18** could be deprotected through a transacetalization, however, aldehyde **19** did not cyclise to the corresponding hemiacetal.

Table 3.1. Optimization of the asymmetric dihydroxylation of compound **16**, followed by deprotection of the aldehyde.[a]

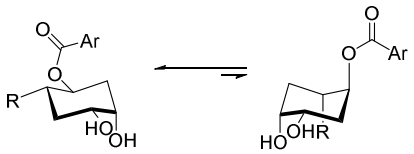


17 **19**

Entry	T (ºC)	AD agent	Yield (%)[b]	d.r.[c]
1	r.t.	AD-mix-α	70	1:1
2	r.t.	AD-mix-β	59	1:1
3	0	AD-mix-α	61	1.5:1
4	0	AD-mix-β	66	4:1

[a] Reactions performed in 0.20 mmol scale of **16** using 208 mg of AD-mix in *t*-BuOH: H_2O 1:1 (0.1 *M*). [b] Yield of pure product after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture of dihydroxilated acetal **18**.

Analysing the results obtained in the previously surveyed strategies for the hydration of the alkene, the fact that the OH directed hydroboration did not control the regio- nor the diastereoselectivity at all and that none of the diol **19** diastereoisomers cyclised leading to the corresponding hemiaminal, could suggest that the conformational equilibrium of the substituted cyclohexane is shifted towards the conformer with the substituents in equatorial position. This way, the substituents placed in equatorial position would not be able to cyclise with another position of the substrate as they are directed away from the molecule (Scheme 3.10).

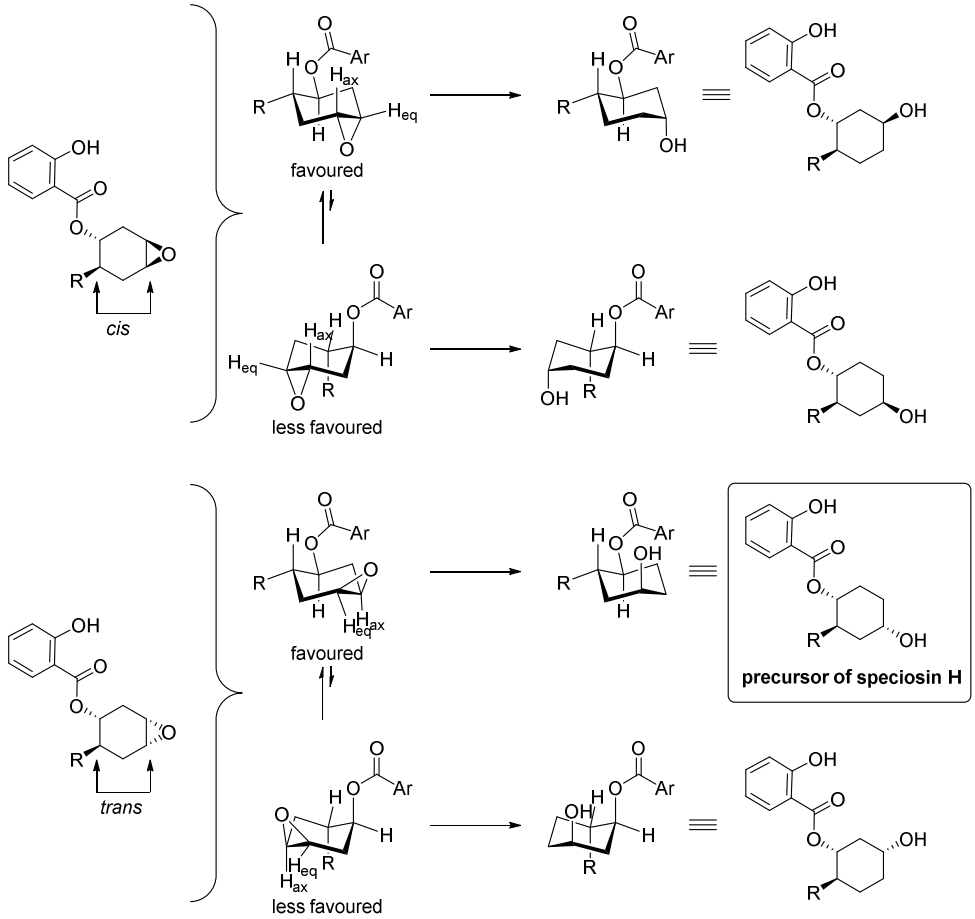


R: aldehyde, alcohol, acetal

Scheme 3.10. Conformational equilibrium shifted towards conformer with substituents in equatorial position.

3.3. Synthesis of speciosin H and/or Q by epoxidation

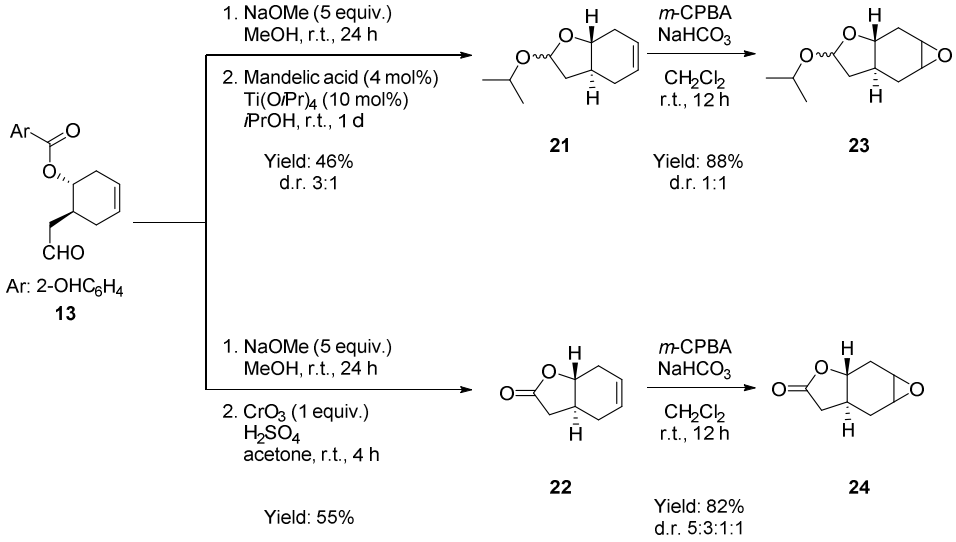
Based on the presumed conformational rigidity, epoxidation followed by ring-opening reaction appeared as a feasible alternative for obtaining the addition of the desired hydroxy group with high regio- and diastereocontrol. When opening an epoxide by a hydride addition, the S_N2 type attack happens in the less substituted carbon and in cyclic systems there is a strong preference for *trans* diaxial ring-opening. In this case, even though both carbon atoms are equally substituted, the conformational restriction would favour the formation of one single product by each of the epoxide diastereoisomers, as only one conformation would mainly exist in solution and the hydride attack would presumably happen in the carbon with the hydrogen in the axial position (Scheme 3.11).



Scheme 3.11. Hypothesis of regio- and diastereocontroled epoxide ring-opening reaction.

After this analysis, it appeared clear that only one epoxide diastereoisomer would lead to a precursor of one of the target molecules, whereas the other one would lead to a product with the new hydroxy group in the C5 position, instead of the C4. Hence, the development of a diastereoselective epoxidation seemed mandatory. It was first thought that a rigid bicyclic compound would direct the diastereoselectivity of the reaction more easily than the monocyclic one. In order

to verify the hypothesis,[17] compounds **21** and **22** were synthesised through a hydrolysis[18] followed by formation of the corresponding acetal or lactone respectively. However, when trying the epoxidation with *m*-chloroperbenzoic acid, a commonly used epoxidation agent, none of the substrates induced any diastereocontrol (Scheme 3.12).



Scheme 3.12. Epoxidation of bicyclic compounds **21** and **22**.

As the bicyclic compounds did not provide any type of diastereocontrol in the epoxidation reaction, it was decided to evaluate the transformation directly on acetal **16** with the idea of finding the best reaction conditions that would only generate one epoxide diastereosiomer. When employing *m*-chloroperbenzoic acid and dimethyldioxirane as epoxidation agents similar diastereomeric ratios were observed, obtaining the final product quantitatively in the first case (Scheme 3.13).

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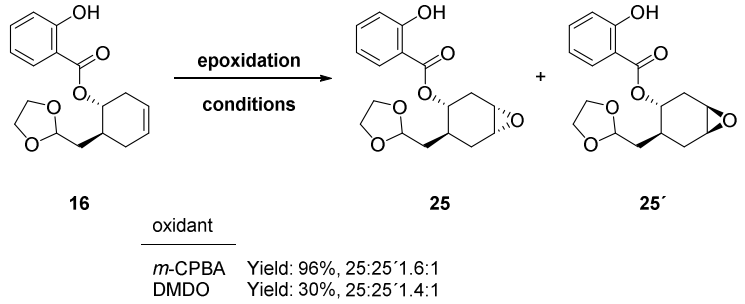
17 Krawczyk, A. R.; Jones, J. B. *J. Org. Chem.* **1989**, *54*, 1795.

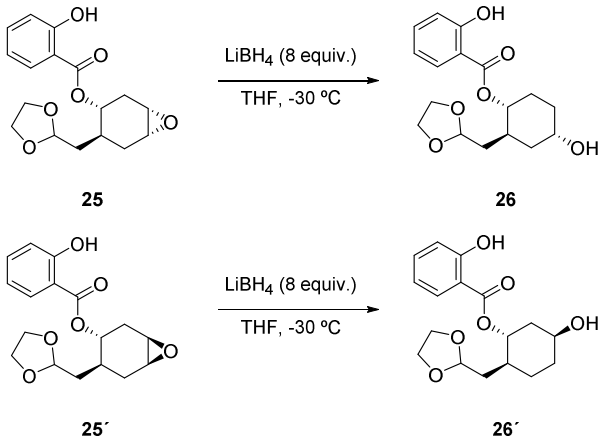
18 Compound **20** was synthesised *via* the hydrolysis that had been previously tested as a derivatisation of the ring-opening adducts, for more details see Chapter 2.

With these results in hand, it was decided to proceed with the synthesis of the natural product identifying *m*-chloroperbenzoic acid as the best epoxidation agent; it should be mentioned that under this reaction conditions epoxide **25** was isolated with a satisfactory 59% yield.



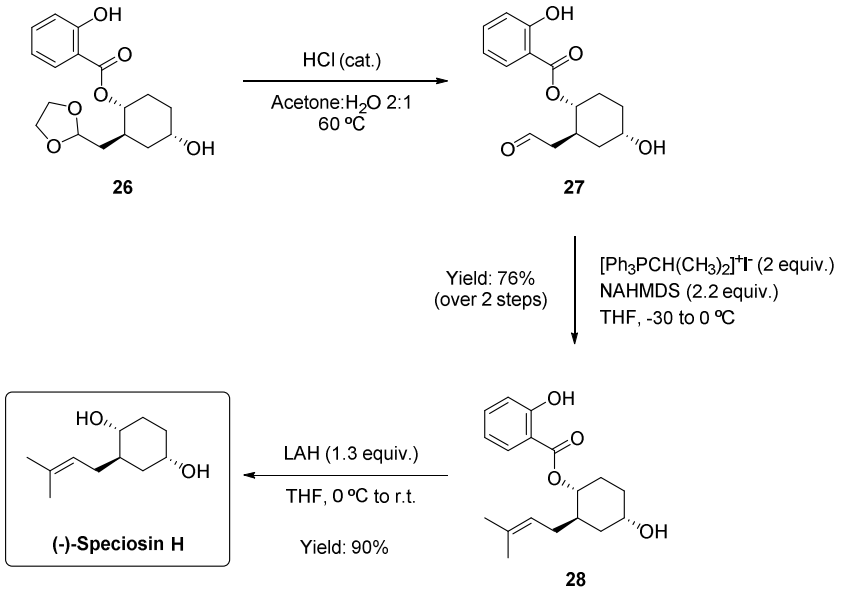
Scheme 3.13. Epoxidation on compound **16**.

Once the appropriate epoxide diastereoisomer had been isolated, the S_N2 type ring-opening reaction was tested and several reducing agents were surveyed. Sodium borohydride did not react with the epoxide and when carrying out the reaction with lithium aluminium hydride or lithium borohydride apart from the epoxide, the ester moiety was reduced as well obtaining the final adduct with the hydroxy group in the presumed C4 position but as a diastereomeric mixture. The epoxide could be selectively opened, maintaining the ester unreacted when using lithium borohydride at -30 ^{o}C, obtaining the desired compound **26** as a unique product in an 86% yield (Scheme 3.14). On the other hand, epoxide ring-opening reaction of **25´** led to the regioisomer of compound **26** as a unique diastereisomer, confirming the hypothesis that each epoxide diastereoisomer **25** and **25´** would lead to a different regioisomer of compound **26**, as a single diastereoisomer.



Scheme 3.14. Regio- and diastereoselective ring-opening on compounds **25** and **25´**.

Finally, once the hydration of the alkene had been optimised obtaining the hydroxy group in C4 position with the appropriate stereochemistry, the last steps for the synthesis of the target molecule were carried out. The aldehyde could be quantitatively deprotected under aqueous acidic media obtaining aldehyde **27** and, without need of further purification, the Wittig reaction was performed, leading to compound **28** in a yield of 76% over two steps. Lastly, the reduction of the ester with lithium aluminium hydride rendered the natural product (-)-speciosin H in an excellent yield (Scheme 3.15). NMR data matched with the data reported in the literature.[5a]



Scheme 3.15. Final steps for the synthesis of (-)-speciosin H.

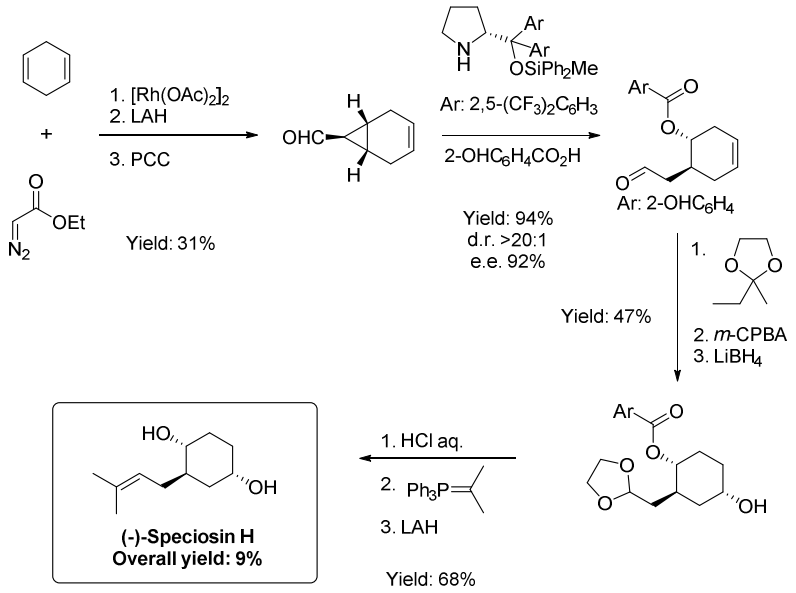
4. CONCLUSIONS

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

- The enantioselective total synthesis of (-)-speciosin H has been accomplished for the first time using the asymmetric ring-opening of *meso*-formylcyclopropanes under iminium ion catalysis, as key step.

- The reaction between bicycle[4.1.0]hept-3-ene-7-carbaldehyde **11** and salicylic acid **2h** under iminium ion catalysis, delivered the ring-opening product in a high yield and with an excellent diastereo- and enantiocontrol, using the methodology developed in our group.

- The ring-opening product could be further transformed into natural product speciosin H with an overall yield of 9% (Scheme 4.1), demostrating the applicability of the aforementioned asymmetric desymmetrization of *meso*-formylcylopropanes.



Scheme 4.1. General overview of the synthesis of speciosin H.

Chapter 4

4

Phosphine Catalysed Enantioselective [8+4] High-Order Cycloaddition

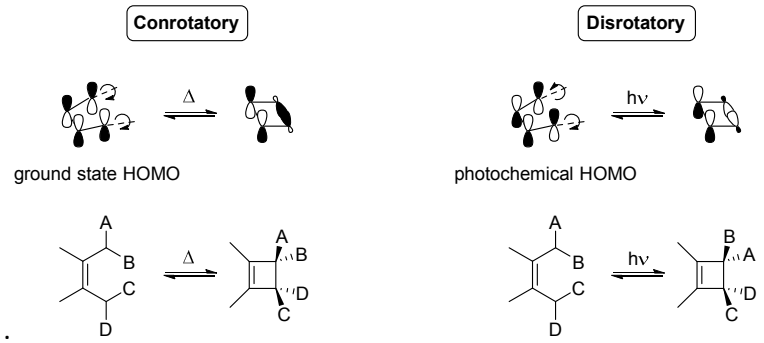
1. HIGH-ORDER CYCLOADITIONS

In the middle of the 1960s, Woodward and Hoffmann published a series of papers describing the stereochemical outcome and activation energy of pericyclic reactions.[1] They enunciated several rules by analysing the correlations between reactant and product orbitals, which led to understand that the pathway of concerted reactions are determined by the symmetry properties of the orbitals that are directly involved, since the symmetry of each participating orbital must be conserved during the transformation.

The rules were first formulated to explain the stereospecificity of electrocyclic reactions under thermal and photochemical control. The almost complete stereospecificity observed in these type of transformations is due to the fact that the groups bonded to the termini of the linear system (or to the breaking bond in the reverse process) do not rotate in a random way during the ring-closing (or ring-opening) reaction. The symmetry of the HOMO of the reacting system is the one controlling the stereochemical outcome of the transformation, as an overlap of the orbital lobes of the same sing must happen for the new bond to be formed. In this sense, for the 1,3-butadiene/cyclobutene system the symmetry of the HOMO ground state orbital is such that a bonding interaction between both termini must involve overlap between orbital lobes on opposite faces of the π-system, and this can only be achieved by a conrotatory process. On the other hand, the photochemically excited system must follow a disrotatory course, as the orbital lobes to be overlap are on the same face of the π-system (Scheme 1.1). Moreover, it was found that 4*n*-electron thermal and (4*n*+2)-electron photochemical

[1] (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395. (b) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 2046. (c) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388. (d) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781.

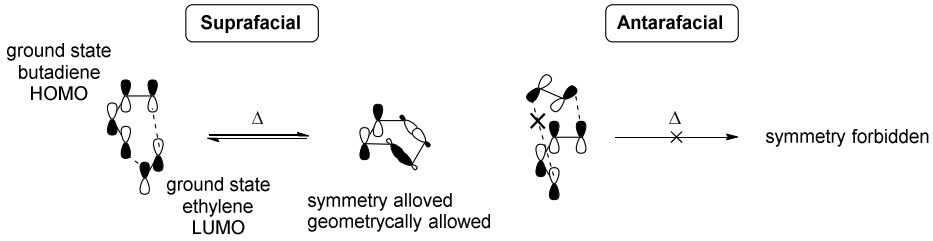
electrocyclic reactions are conrotatory in general, whereas 4*n*-electron photochemical and (4*n*+2)-electron thermal electrocyclic reactions are disrotatory in general.



Scheme 1.1. 1,3-butadiene/cyclobutene electrocyclic reaction.

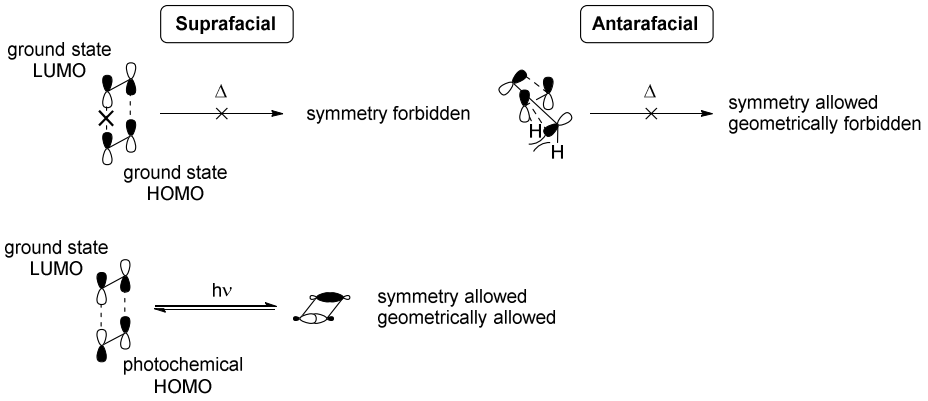
As it has been abovementioned, the Woodward-Hoffmann rules were first stated for the understanding of electrocyclic processes, but they can be generalised to all pericyclic reactions. For this, the bond rotation terms *conrotatory* and *disrotatory* are subsumed by the bond faciality terms *antarafacial* and *suprafacial*, which can better explain the interaction of orbital lobes of different components in transformations such as cycloaddition reactions.

In the thermal [4+2] cycloaddition reaction, usually the HOMO of the diene reacts with the LUMO of the dienophile. A suprafacial approach of the reactants provides of an overlap of orbital lobes with the same sign allowing the new bond to be formed, whereas the antarafacial approach is symmetry forbidden. The high selectivity of the approach leads to a stereospecific transformation as it happens in the case of the electrocyclic reactions (Scheme 1.2).



Scheme 1.2. [4+2] cycloaddition reaction.

On the other hand, the [2+2] cycloaddition is symmetry forbidden when a suprafacial approach occurs, whereas the antarafacial approach leads to the correct overlap of the orbital lobes. However, in most cases the antarafacial approach is geometrically forbidden, which leads to a forbidden transformation in ground state. On the contrary, the photochemical transformation would be allowed as the HOMO excited state of one of the olefins can satisfactorily overlap the LUMO of the other olefin in a suprafacial fashion (Scheme 1.3).



Scheme 1.3. [2+2] cycloaddition reaction.

Based on the observations made for the [2+2] and [4+2] cycloaddition reactions and assuming that in general the antarafacial approach is geometrically

disallowed, Woodward and Hoffman predicted which reactions would be allowed in thermal or photochemical conditions and they correctly envisioned the possibility of carrying out concerted cycloadditions of order greater than [4+2] (Table 1.1). For reactions involving more than four π-components, despite being also allowed by orbital symmetry they have to overcome too high entropic barriers and that is the reason why multicomponent systems with more than four π-systems have not been observed until the moment. It should be noted that in case of having highly polarized reactants, a stepwise mechanism might be favoured and, in this case, the selection rules would be inapplicable.[2]

Table 1.1. Prediction of the allowed concerted cycloaddition reactions involving ≤10π-electrons by Woodward and Hoffmann.

Type of Cycloaddition	Thermal	Photochemical
Two π-component	4+2	2+2
	6+4	4+4
	8+2	6+2
Three π -component	2+2+2	
	2+4+4	4+2+2
	6+2+2	
Four π -component	4+2+2+2	2+2+2+2

Cycloaddition reactions that involve more than 6π-electrons are considered high-order cycloadditions and they have become extremely useful tools for the synthesis of medium and large rings, which are otherwise quite difficult to prepare.[3]

[2] (a) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192. (b) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (c) Houk, K. N.; Li, Y.; Storer, J.; Raimondi, L.; Beno, B. *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1599.

[3] For selected reviews on high-order cycloadditions, see: (a) Palazzo, T. A.; Mose, R.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 10033. (b) Inglesby, P. A.; Evans, P. A. In *Comprehensive Organic Synthesis*; 2nd ed.; Knochel, P.; Molander, G. A., Eds; Elsevier: Amsterdam, 2014; pp 656-702. (c) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (d) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H.; Mingos, M. P., Eds.; Elsevier: Oxford, 2007; pp 603-647. (e) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.

As the Diels-Alder reaction, they show a high level of convergence, they can accommodate extensive functionalization in all the reactants, and they show a high degree of stereoselectivity. However, these reactions have some limitations due to the extended π-system, which makes them prone to participate in multiple pericyclic transformations that result in a mixture of several products with none of them predominating over the others.[4]

1.1. Two π-component cycloadditions

Diels-Alder reaction[5], Huisgen 1,3-dipolar cycloaddition[6] and related transformations constitute the mainstay of ring-forming processes when two π-components are involved in the reaction, forming six- or five-membered rings, respectively. Despite the utility of these transformations, they can only be used for the synthesis of small four to seven-membered rings and in this sense, the reactions between larger π-systems have become extremely useful, especially in total synthesis as they enable the formation of medium-size cycles in one single step. General examples of high-order cycloadditions between two π-components include [4π+4π], [6π+2π], [6π+4π] and [8π+2π] cycloaddition reactions.

1.1.1. [4+4] Cycloaddition

According to the aforementioned Woodward-Hoffmann rules, based on the conservation of the orbital symmetry along the reaction path, the [4+4] cycloaddition reaction is allowed in the excited state and forbidden in the ground state (Scheme 1.4).

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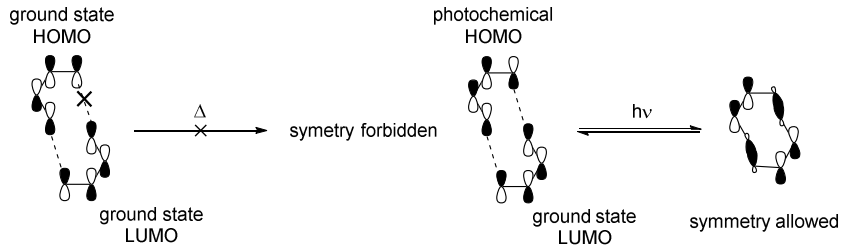
4 Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143.

5 (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Diels, O.; Alder, K. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 554.

6 Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494.



Scheme 1.4. [4+4] cycloaddition.

The earliest reported [4+4] cycloaddition was the photodimerization of anthracene initially described by Fritzsche,[7] who also observed that the photodimer could revert back to the monomer thermally. Later on, Chandross recognized that the photodissociation could be also effective (Scheme 1.5).[8] This reactivity could be extended to substituted anthracenes[9] and nitrogen derivatives[10] with a high regiocontrol, due to the predictable concerted mechanism. Despite the reduced scope presented by the transformation, it should be mentioned that several applications have been found for this reversible thermo/photochromic system, such as photochemical upconversion[11] and molecular switches.[12] On the other hand, anthracenes also constitute an excellent scaffold for the [4+4] cycloaddition reaction with other dienes, such as 1,3-cyclohexadiene or cyclopentadiene;[13]

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7 Fritzsche, I. *J. Prakt. Chem.* **1867**, *101*, 333.

8 Chandross, E. A. *J. Chem. Phys.* **1965**, *43*, 4175.

9 (a) Kawanami, Y.; Pace, T. C. S.; Mizoguchi, J.; Yanagi, T.; Nishijima, M.; Mori, T.; Wada, T.; Bohne, C.; Inoue, Y. *J. Org. Chem.* **2009**, *74*, 7908. (b) Becker, H.-G.; Langer, V. *J. Org. Chem.* **1993**, *58*, 4703. (c) Kaupp, G.; Teufel, E. *Chem. Ber.* **1980**, *113*, 3669.

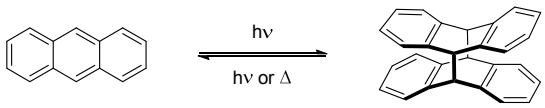
10 (a) Ihmels, H. *Tetrahedron Lett.* **1998**, *39*, 8641. (b) Wagner, J.; Bendig, J.; Felber, A.; Sommerer, A.; Kreysig, D. Z. *J. Org. Chem.* **1985**, *25*, 64. (c) Bradesher, C. K.; Beavers, L. E.; Jonese, J. H. *J. Org. Chem.* **1957**, *22*, 1740.

11 Islangulov, R. R.; Castellano, F. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 5957.

12 Zhao, P.; Fang, C. F.; Xia, C. J.; Wang, Y. M.; Liu, D. S.; Xie, S. J. *Appl. Phys. Lett.* **2008**, *93*, 13113.

13 For selected examples on [4+4] cycloaddition reactions involving anthracene, see: (a) Kaupp, G. *J. Liebigs Ann. Chem.* **1977**, 254. (b) Yang, N. C.; Libman, J. *J. Am. Chem. Soc.* **1972**, *94*, 1405.

whereas smaller aromatic rings, naphthalene[14] and benzene,[15] show lower reactivity.



Scheme 1.5. Reversible photodimerization of anthracene.

Other than the cyclic systems, open-chain nonaromatic diene compounds can also undergo the [4+4] cycloaddition, although they usually afford the corresponding cyclooctanodiene final product in low yields, as various competitive reactions occur at the same time, such as [2+2] and [4+2] cycloadditions.[16] An example of this multiple reactivity would be isoprene, although it was found out that acetophenone could be used as a triplet sensitizer, favouring the photocycloaddition reactions over the thermal transformations and therefore, obtaining the [4+4] cycloadducts in a 60% yield (Scheme 1.6).[17] The final product was obtained as a mixture of regioisomers as the two isoprene molecules could approach each other as mirror images or as inverted mirror images.

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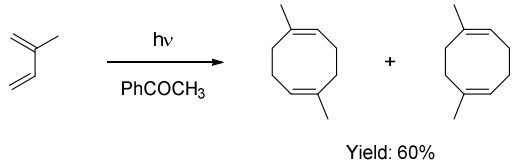
[14] For the photodimerisation of a naphthalene derivative, see: (a) Bradshaw, J. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1963**, *85*, 3953. For selected examples on [4+4] cycloadditions involving naphthalene, see: (b) Mak, K. T.; Srinivasachar, K.; Yang, N. C. *J. Chem. Soc., Chem. Commun.* **1979**, 1038. (c) Pac, C.; Sugioka, T.; Sakurai, H. *Chem. Lett.* **1972**, 39, 42.

[15] For selected examples on [4+4] cycloaddition reactions involving benzene, see: (a) García, H.; Gilbert, A.; Griffiths, O. *J. Chem. Soc., Perkin Trans 2* **1994**, 247. (b) Yang, N. C.; Horner, M. G. *Tetrahedron Lett.* **1986**, *27*, 543.

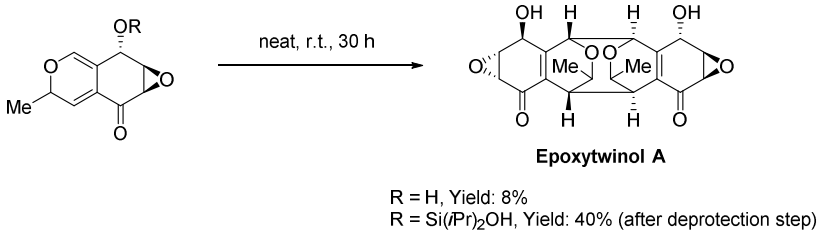
[16] Srinivasan, R.; Sonntag, F. I. *J. Am. Chem. Soc.* **1965**, *87*, 3778.

[17] Shimo, T.; Iwakiri, T.; Somekawa, K.; Suishu, T. *J. Heterocyclic Chem.* **1992**, *29*, 199.



Scheme 1.6. Photodimerization of isoprene.

The dimerization of 4π-systems has been successfully applied on the total synthesis of epoxytwinol A, in this case through a disfavoured thermal [4+4] cycloaddition that has been inspired in a biosynthesis. Up to date, this is the only natural product which is prepared in Nature *via* a [4+4] cycloaddition pathway, and it coexists in the same fungus with the [4+2] dimers. The dimerization of the starting monomeric species showed unsatisfactory results due to the competing [4+2] pathway, obtaining the desired product in a low yield.[18] Further investigations proved that the utilization of diorganosilanol protecting groups favoured the formation of the [4+4] cycloadduct improving the yield up to a 40% (Scheme 1.7).[19]



Scheme 1.7. Thermal [4+4] cycloaddition for the synthesis of epoxytwinol A.

Metal-catalysed cycloadditions are not classified as pericyclic reactions, in contrast to the photocycloadditions and the thermally promoted ones; therefore, they are not rationalized by the Woodward-Hoffmann rules and usually follow a

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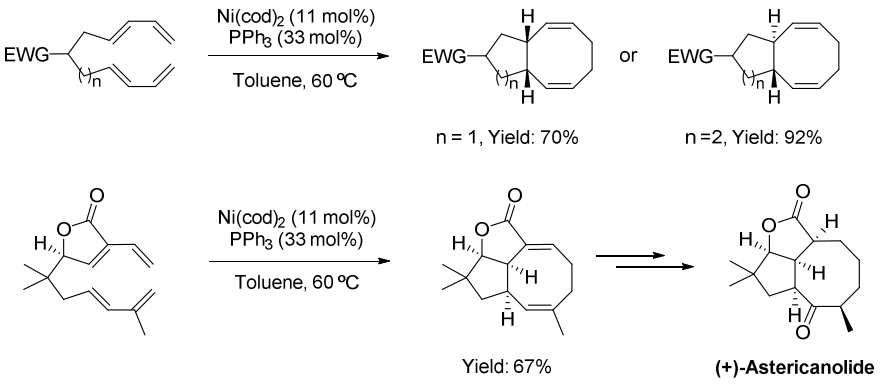
[18] Shoji, M.; Imai, H.; Mukaida, M.; Sakai, K.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2005**, *70*, 79.

[19] Li, C.; Porco, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 1310.

stepwise mechanism. The majority of the work around the [4+4] cycloadditions involves transition metal catalysis, as the metal activation allows to trigger transformations that otherwise would not occur. In this sense, Wender developed a nickel-catalysed intramolecular [4+4] cycloaddition of bis-dienes (Scheme 1.8).[20] It could be observed that dienes connected by a three-atom chain selectively led to the *cis*-fused product, whereas those connected by a four-atom chain were converted mainly into the *trans*-adduct; it should be pointed out that high yields were obtained under this reaction conditions. Moreover, the methodology could be applied to the total synthesis of (+)-astericanolide.[21]



Scheme 1.8. Ni-Catalysed intramolecular [4+4] cycloaddition of bis-dienes.

The scope of the transformation could be expanded to the dimerization of *in situ* generated vinyl allenes, which showed to be suitable synthons for the [4+4] cycloaddition reaction under palladium catalysis.[22] The reaction between α-

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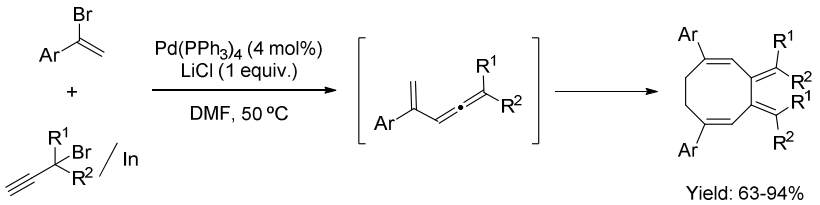
[20] (a) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (c) Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. (d) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678.

[21] Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.

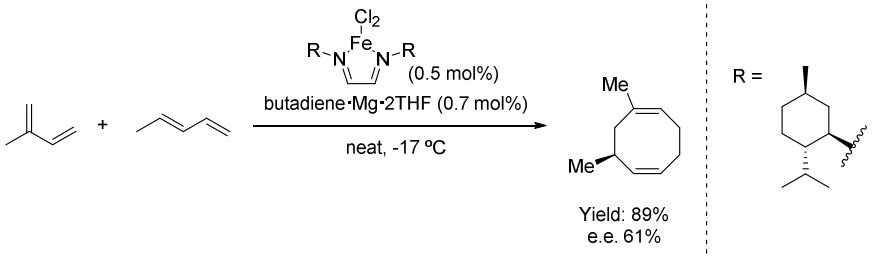
[22] (a) Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139. (b) Lee, P. H.; Lee, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3253.

bromovinyl arenes and propargyl bromides rendered eight-membered carbocycles in a rapid synthesis and in high yields. It is noteworthy that four molecules are assembled into one product *via* this procedure (Scheme 1.9).



Scheme 1.9. [4+4] cycloaddition between *in situ* generated vinyl allenes.

Finally, an asymmetric version of the [4+4] cycloaddition has been developed using a chiral iron-based complex as catalyst. Under this conditions, open-chain nonaromatic dienes, which gave multiple reactivity patterns in the aforementioned photocycloaddition, delivered the final 1,5-cyclooctadiene with a moderate enantiocontrol. Remarkably one mayor product was formed despite the possibility of several constitutional isomers (Scheme 1.10).[23]

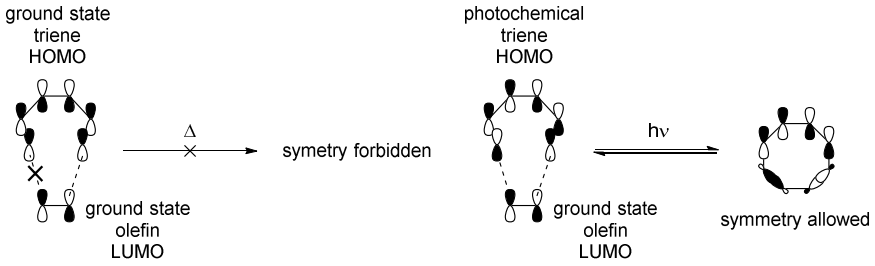


Scheme 1.10. Metal-catalysed asymmetric intermolecular [4+4] cycloaddition.

[23] Baldenius, K.-U.; tom Dieck, H.; König, W. A.; Icheln, D.; Runge, T. *Angew. Chem. Int. Ed.* **1992**, *31*, 305.

1.1.2. [6+2] Cycloaddition

The [6+2] cycloaddition reaction is another alternative for the formation of eight-membered rings, in this case a 6π-component reacts with a 2π-component. By the time the first [6+2] cycloaddition was reported, in 1974, a wide range of examples about the Diels-Alder transformation were already known, probably due to the fact that the latter is allowed in the ground state according to the Woodward-Hoffmann rules, whereas the former is forbidden in the ground state and allowed in the excited-state (Scheme 1.11).

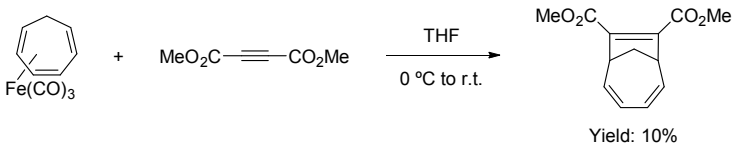


Scheme 1.11. [6+2] cycloaddition reaction.

Since the use of acyclic trienes usually leads to the Diels-Alder adduct as the mayor product, most robust cyclic structures are required for the [6+2] cycloaddition to happen, such as cycloheptatriene. Thereby, [6+n] cycloadditions often generate highly functionalised fused or bridged polycyclic structures. As the ground state reaction is orbital forbidden and the photochemical induction led to competitive [2+2] cycloaddition as the main reaction, the metal-catalysis played an important role in the development of the [6+2] cycloaddition.[24] Indeed, in the early

[24] For selected reviews on [6+2] cycloadditions, see: (a) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521. (b) Rigby, J. H. *Org. React.* **1997**, *49*, 331.

examples of the reaction, precomplexed metalled cycloheptatrienes proved able to act as 6π-synthons and react with acetylene dicarboxylic esters (Scheme 1.12).[25]



Scheme 1.12. [6+2] Cycloaddition reaction between metalled cyclohepatriene and acetylene dicarboxylic ester.

The stoichiometric transition metal amounts and precomplexed reactants needed when the first investigations around the topic started, were overcome with the development of catalytic systems based on transition metals.[26,] In 2008 the first enantioselective [6+2] cycloaddition between cycloheptatriene and terminal alkynes under cobalt catalysis was reported. The presence of a chiral monodentate phosphoramidite ligand delivered the final product in a high yield and moderate to excellent enantiocontrol (Scheme 1.13).[27]

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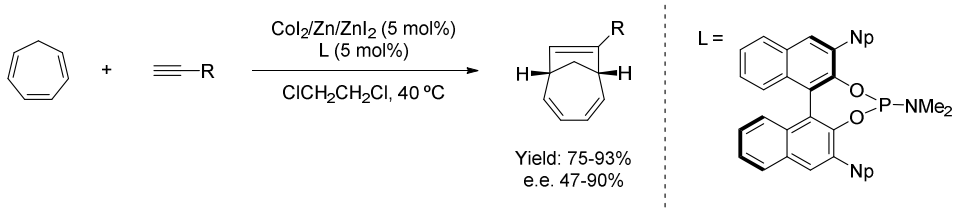
[25] For the earliest example, see: (a) Davis, R. E.; Dodds, T. A.; Hseu, T. H.; Wagnon, J. C.; Devon, T.; Tancrede, J.; McKennis, J. S.; Pettir, R. *J. Am. Chem. Soc.* **1974**, *96*, 7562. For other selected examples, see: (b) Ura, Y.; Utsumi, T.; Tsujita, H.; Wada, K.; Kondo, T.; Mitsudo, T. *Organometallics* **2006**, *25*, 2934. (c) Chen, W.; Chaffee, K.; Chung, H. J.; Sheridan, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 9980. (d) Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851. For an intramolecular version, see: (e) Rigby, J. H.; Kirova, M.; Niyaz, N.; Mohammadi, F. *Synlett* **1997**, 805.

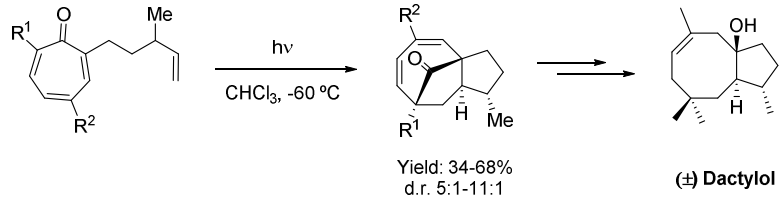
[26] For selected examples on titanium-catalysis, see: (a) Kaagman, J.-W. F.; Rep, M.; Horáček, M.; Sedmera, P.; Čejka, J.; Varga, V.; Mach, K. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1722. (b) Mach, K.; Antropiusová, H.; Petrusová, L.; Hanuš, V.; Tureček, F.; Sedmera, P. *Tetrahedron* **1984**, *40*, 3295. For selected examples on cobalt-catalysis, see: (c) Achard, M.; Mosrin, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2006**, *71*, 2907. (d) Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353. For selected examples on chromium-catalysis, see: (e) Kündig, E. P.; Robvieux, F.; Kondratenko, M. *Synthesis* **2002**, *14*, 2053. (f) Rigby, J. H.; Kondratenko, M. A.; Fiedler, C. *Org. Lett.* **2000**, *2*, 3917.

[27] Toselli, N.; Martin, D.; Achard, M.; Tenaglia, A.; Bürgi, T.; Buono, G. *Adv. Synth. Catal.* **2008**, *350*, 280.



Scheme 1.13. Asymmetric [6+2] cycloaddition reaction under cobalt catalysis.

On the other hand, the photochemical [6+2] cycloaddition has also been studied as it is orbital symmetry allowed. In this sense, Feldman reported the intramolecular photocycloaddition reaction of tropones and terminal olefins in a diastereoselective fashion when running the reaction at low temperatures (Scheme 1.14);[28] moreover, the methodology could be applied to the total synthesis of Dactylol.[29] However, there have not been many studies on this topic, mainly due to the difficulty of avoiding the [2+2] pathway when photoactivating the starting material.



Scheme 1.14. [6+2] Photocycloaddition reaction.

In these reactions, where a triene is used as the 6π-synthon, not only cycloheptatrienes and tropones have shown to be useful 6π-components, but also fulvenes provided satisfactory results. It was observed that 6-aminofulvenes

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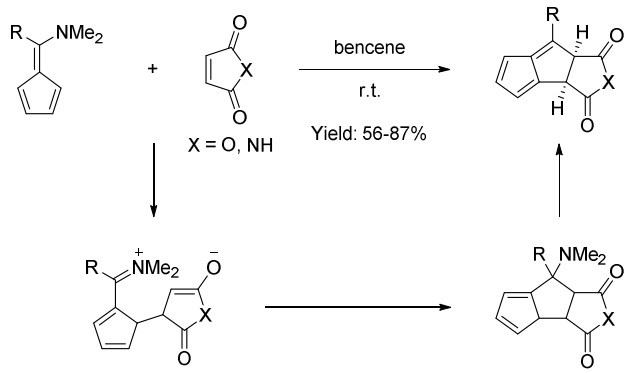
[28] Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M. J. *J. Org. Chem.* **1989**, *54*, 592.

[29] Feldman, K. S.; Wu, M. J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490.

spontaneously reacted at room temperature with maleic anhydride or maleimide to afford a tricyclic product in high yield.[30] For this transformation, a stepwise mechanism was proposed which involves a conjugate addition of the fulvene to the trienophile leading to a zwitterionic intermediate. Enolate addition to the previously formed iminium ion, followed by the elimination of the dimethyl amine provided the final cycloadduct (Scheme 1.15).

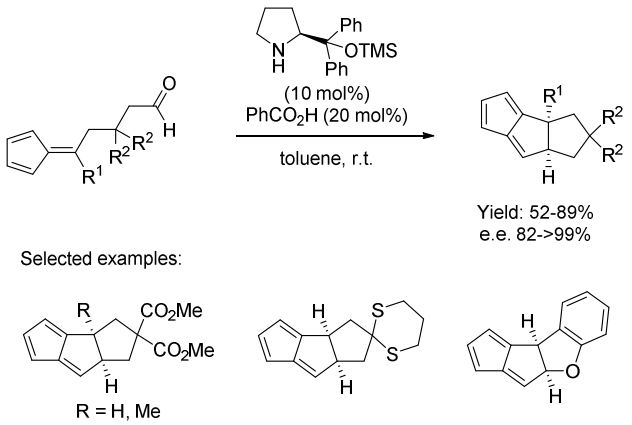


Scheme 1.15. Spontaneous [6+2] cycloaddition of fulvenes with alkenes.

An intramolecular version of the reaction employing a fulvene moiety as the 6π-component was developed, based on enamine catalysis; by this procedure linearly fused tricyclopentanoids could be synthesised in good yields.[31] This first example set the basis for the organocatalytic asymmetric version of the reaction reported by Hayashi and co-workers. [32] The aminocatalyst diphenylprolinol silyl ether successfully promoted the intramolecular [6+2] cycloaddition of fulvenes substituted at the exocyclic 6-position with a formylalkyl group, affording linear triquinane derivatives as a single diastereoisomer in good yields and excellent

[30] Hong, B.-C.; Shr, Y.-J.; Wu, J.-L.; Gupta, A. K.; Lin, K.-J. *Org. Lett.* **2002**, *4*, 2249.
[31] Wu, T. C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308.
[32] Hayashi, Y.; Gotoh, H.; Honma, M.; Sankar, K.; Kumar, I.; Ishikawa, H.; Konno, K.; Yui, H.; Tsuzuki, S.; Uchimaru, T. *J. Am. Chem. Soc.* **2011**, *133*, 20175.

enantioselectivities (Scheme 1.16). Computational investigations showed that the reaction between the fulvene (6π) and the enamine (2π) functionalities proceeded through a concerted mechanism *via* a highly asynchronous transition state.



Scheme 1.16. Asymmetric [6+2] cycloaddition reaction *via* enamine catalysis.

1.1.3. [6+4] Cycloaddition

In 1965 Woodward and Hoffmann predicted that thermal [6+4] cycloadditions were orbital symmetry allowed pericyclic transformations[1] and they envisioned that linear trienes would react with linear dienes leading to cyclodecane derivatives (Scheme 1.17). Although theoretical studies have been carried out proving that acyclic compounds could act as 6π-components in this transformation,[33] all known examples of [6+4] cycloaddition reactions yield bridged-ring products. Since acyclic substrates usually show [4+2] reactivity and in the cases that the [6+4] adduct is formed, a [3,3]-sigmatropic shift of the product occurs leading to cyclohexane derivatives, only cycloalkatrienes have been able to undergo the transformation.

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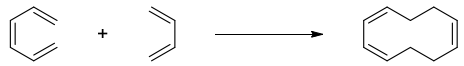
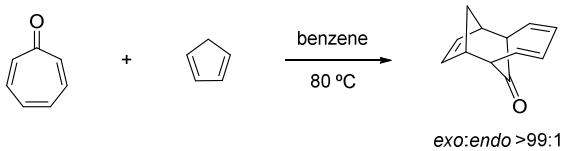
33 Alder, R. W.; Harvey, J. N.; Lloyd-Jones, G. C.; Oliva, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 8325.



Scheme 1.17. Predicted [6+4] cycloaddition reaction.

Cookson and Itô independently reported the first [6+4] cycloaddition reaction.[34] They discovered that tropone and cyclopentadiene afforded the *exo* [6+4] cycloadduct selectively minimizing the possible [4+2] cycloaddition and the aforementioned Cope rearrangement (Scheme 1.18). After this transformation was discovered, several reports were published employing cyclic trienes such as tropones, cycloheptatrienes and fulvenes,[35] however in many cases the competing Diels-Alder cycloaddition was more prone to happen leading to low yields, thus, the utility of the [6+4] cycloaddition has remained rather limited.

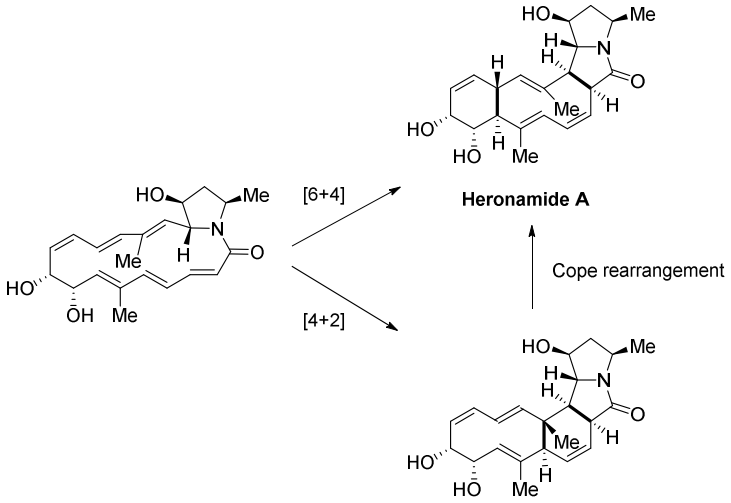


Scheme 1.18. [6+4] Cycloaddition between tropone and cyclopentadiene.

[34] (a) Cookson, R. C.; Drake, B. V.; Hudec, J.; Morrison, A. *Chem. Commun*. **1966**, 15. (b) Itô, S.; Fujise, Y.; Okuda, T.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1351.

[35] For selected examples on [6+4] cycloadditions, see: (a) Moiseev, A. M.; Balenkova, E. S.; Nenajdenko, V. G. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 141. (b) Rigby, J. H.; Chouraqui, G. *Synlett* **2005**, 2501. (c) Rigby, J. H.; Fleming, M. *Tetrahedron Lett.* **2002**, *43*, 8643. (d) Hong, B.-C.; Jiang, Y.-F.; Kumar, E. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1981. (e) Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 8237. (f) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382. (g) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (h) Garst, M. E.; Roberts, V. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 3882. (i) Mukherjee, D.; Watts, C. R.; Houk, K. N. *J. Org. Chem.* **1978**, *43*, 817. (j) Sasaki, T.; Kanematsu, K.; Iizuka, K. *J. Org. Chem.* **1976**, *41*, 1105. (k) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143.

On the other hand, mechanistic studies suggest that Nature is able to obtain unbridged 10-membered rings through a [6+4] cycloaddition reaction.[36] The transannular transformation proposed as a step in the biosynthesis of heronamide A is highly stereoselective, affording a single product. The reaction could proceed through [4+2] or [6+4] pathway as ambimodal transition states are involved in the mechanism, although the facile interconversion of the two possible adducts *via* Cope rearrangement would lead to a mayor formation of the thermodynamically more stable [6+4] adduct (Scheme 1.19).

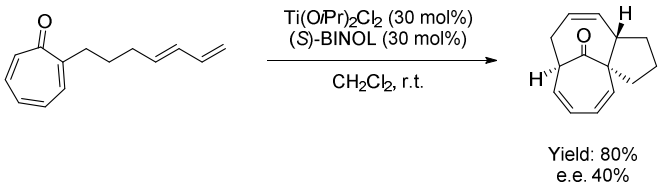


Scheme 1.19. Transannular [6+4] cycloaddition in the biosynthesis of heronamide A.

Probably due to the moderate amount of publications about this cycloaddition, there has been a remarkable lack of reported catalytic asymmetric versions. In 2002, Rigby presented a chiral titanium(IV) Lewis acid capable of inducing stereocontrol in the intramolecular cyclisation between a tropone and a

[36] (a) Patel, A.; Chen, Z.; Yang, Z.; Gutiérrez, O.; Liu, H.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 3631. (b) Yu, P.; Patel, A.; Houk, K. N. *J. Am. Chem. Soc.* **2015**, *137*, 13518.

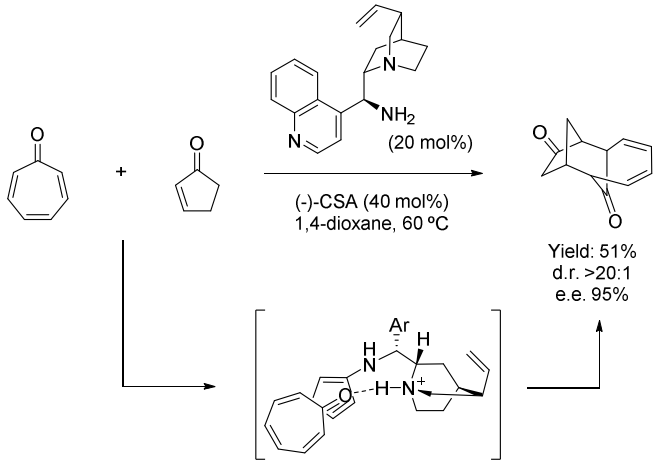
diene. The final cycloadduct was obtained as a single diastereoisomer in high yield and with a promising enantiocontrol (Scheme 1.20).[35c]



Scheme 1.20. Titanium catalysed asymmetric intramolecular [6+4] cycloaddition reaction.

In this sense, it was not until 2017 that the synthesis of a highly enantioenriched [6+4] adduct was achieved. Jørgensen and co-workers reported the first organocatalytic enantioselective intermolecular [6+4] cycloaddition with an excellent enantiocontrol, using primary amines as catalyst to activate the 2-cyclopentenone (Scheme 1.21).[37] They observed that the linear dienamine formed after condensation of the aminocatalyst with the cycloalkenone served as a 2π-component in [4+2] and [8+2] cycloadditions, whereas the cross-dienamine could serve as a 4π-component in [6+4] cycloadditions. Varying the ring size of the cycloalkenones and modifying the triene from tropone to various heptafulvenes the periselectivity of the reaction could be influenced. For the case of the [6+4] cycloaddition, the stereochemical outcome of the transformation can be explained by an *exo*-selective interaction between the tropone and the cross-dienamine, directed through hydrogen-bonding.

[37] Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iversen, E. H.; Jørgensen, K. A. *Nat. Chem.* **2017**, *9*, 487.



Scheme 1.21. Asymmetric intermolecular [6+4] cycloaddition *via* cross dienamine.

1.1.4. [8+2] Cycloaddition

[8+2] Cycloaddition reactions are symmetry allowed transformations under thermal conditions, according to the Woodward-Hoffmann rules. However, most of the reported examples employ a transition metal catalyst in order to promote the cycloaddition, hence, they probably do not follow a concerted mechanism.[38] Heptafulvenes and their heteroanalogues offer a rigid system of 4π-bonds which makes them suitable 8π-components for the [8+2] cycloaddition; in addition a few other rigidly fused systems such as dienylisobenzofurans and indolizines have been found to also undergo the transformation (Figure 1.1).

---

[38] For a selected review on [8+2] cycloadditions, see: (a) Nair, V.; Abhilash, K. G. *Synlett* **2008**, 301. For a selected chapter, see: (b) Nair, V.; Abhilash, K. G. In *Topics in Heterocyclic Chemistry*; Hassner, A., Ed.; Springer: Berlin, 2008; pp 173-207.

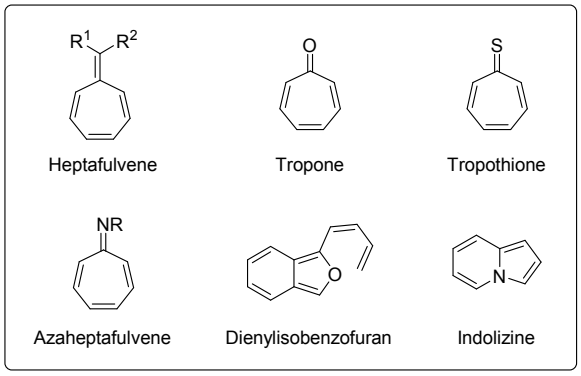
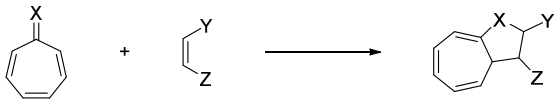


Figure 1.1. Reported 8π components in various [8+2] cycloadditions.

Among these substrates, heptafulvene derivatives have been the most studied ones due to their high capacity to act as 8π-compounds, although they also tend to undergo competitive [6+n], [4+n] and [2+n] cycloadditions. It should be mentioned that they provide access to highly functionalized bicyclico[5.3.0]decane scaffolds through the [8+2] pathway, which are core scaffolds in numerous natural and non-natural products (Scheme 1.22).[39]



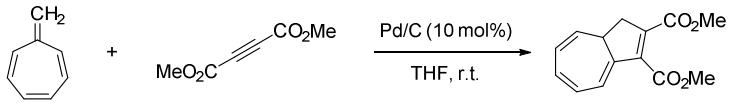
Scheme 1.22. Access to bicyclic [5.3.0] rings *via* [8+2] cycloaddition.

The first [8+2] cycloaddition reaction was describe in 1960 by Doering and Wiley.[40] They observed that methylenecycloheptatriene could act as an 8π-component in the presence of dimethyl acetylene dicarboxylate (Scheme 1.23),

[39] (a) Zhou, X.; Xiao, T.; Iwama, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 4909. (b) Zhao, X.; Zhang, E.; Tu, Y.-Q.; Zhang, Y.-Q.; Yuan, D.-Y.; Cao, K.; Fan, C.-A.; Zhang, F.-M. *Org. Lett.* **2009**, *11*, 4002. (c) Daub, J.; Hirmer, G.; Jakob, L.; Maas, G.; Pickl, W.; Pirzer, E.; Rapp, K. M. *Chem. Ber.* **1985**, *118*, 1836. (d) Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393.

[40] Doering, W. E.; Wiley, D. W. *Tetrahedron* **1960**, *11*, 183.

also noticing that dienophiles with a higher electron-rich character failed to promote the reaction.



Scheme 1.23. [8+2] Cycloaddition reaction between methylenecycloheptatriene and dimethyl acetylene dicarboxylate.

Once this initial transformation had been reported, it was observed that depending on the exocyclic substituent, heptafulvenes can have an electron-rich or electron-deficient character and this influences on the role the can play on different cycloaddition reactions. In general, electron-rich heptafulvenes tend to react as 8π-components, whereas electron-deficient heptafulvenes exhibit multiple reactivity profiles. In 1972, Prinzbach reported a highly efficient [8+2] cycloaddition reaction between electron-rich 7-alyllidenecycloheptatriene and tetracyanoethylene, affording the desired product quantitatively.[41] Since then, several methodologies employing more challening electron-poor heptafulvenes such as 8-oxoheptafulevene[42] and dicyanoheptafulvene[43] have been described, as well as intramolecular versions (Scheme 1.24).[44]

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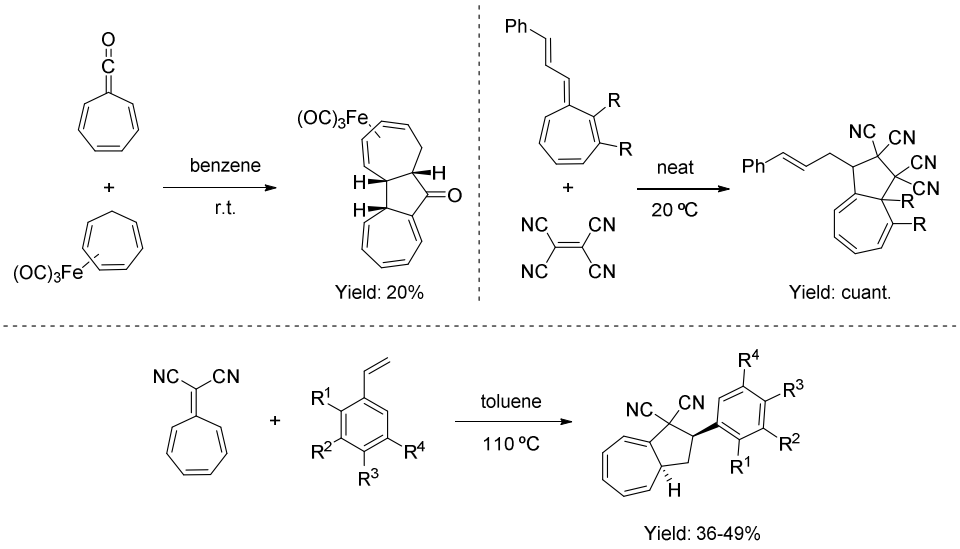
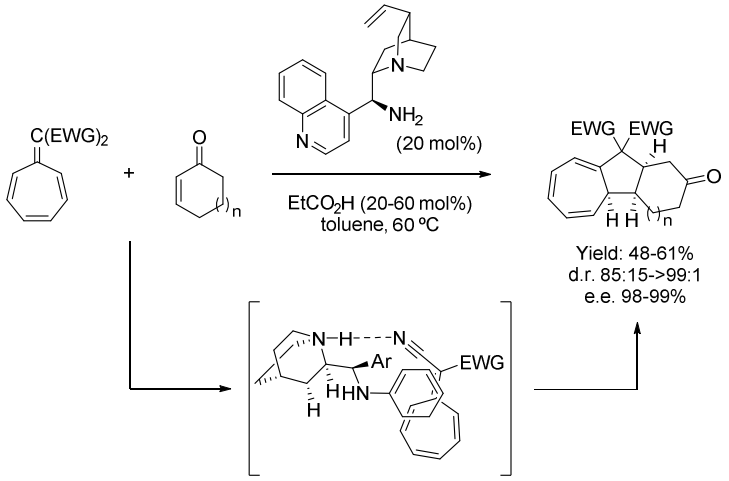
41 Prinzbach, H.; Herr, H.-J.; Regel, W. *Angew. Chem. Int. Ed.* **1972**, *11*, 131.
42 Morita, N.; Yokoyama, R.; Asao, T.; Kurita, M.; Kikuchi, S.; Ito, S. *Organomet. Chem.* **2002**, *642*, 80.
43 Nair, V.; Abhilash, K. G.; Zeimer, B. *Tetrahedron Lett.* **2005**, *46*, 2307.
44 Liu, C. Y.; Mareda, J.; Houk, K. N.; Fronczek, F. R. *J. Am. Chem. Soc.* **1983**, *105*, 6714.



Scheme 1.24. [8+2] Cycloaddition of several heptafulvenes.

Very recently, Jørgensen has described the first asymmetric [8+2] cycloaddition reaction *via* aminocatalysis, employing heptafulvenes as the 8π-components. As it has been mentioned before (Scheme 1.21), the formation of a cross-dienamine after condensation of the 2-cyclopentenone with the primary amine serveed as a 4π-component that further reacted with tropone through a [6+4] cycloaddition. However, by changing the cycloalkenone from 2-pentenone to 2-hexenone or 2-heptenone, the reaction pathway occurred *via* linear dienamine which reacted as a 2π-system. When cyanoesterheptafulvene and dicyanoheptafulvene were applied, the [8+2] cycloadducts were isolated in good yields and excellent stereoselctivities. The catalyst directed the approach of the heptafulvene through hydrogen-bonding with the cyano group, placing the 8π-component of the heptafulvene and the 2π-component of the linear dienamine in an *endo* transition state. (Scheme 1.25).[37]



Scheme 1.25. Enantioselective [8+2] cycloaddition of 2-cycloalkenones with heptafulvenes.

On the other hand, heteroheptafulvenes have also been reported as effective 8π-components. The studies carried out on the cycloaddition chemistry of tropone have revealed its preference to react as a 4π- or 6π-component in cycloaddition reactions;[45] hence, there are only few examples where it serves as an 8π-component. The initial studies were done using ketenes and obtaining the [8+2] adduct in low to moderate yields.[46] Later on, the scope of the transformation could be expanded to employ azalactones[47] as 2π-components (Scheme 1.26).

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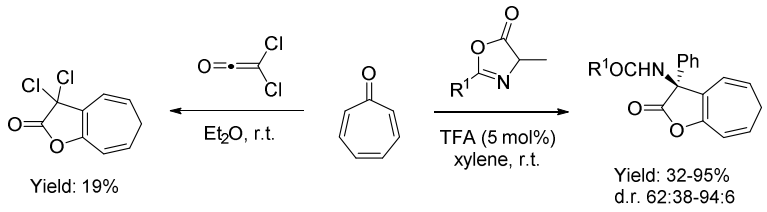
[45] (a) Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628. (b) Isakovic, L.; Ashenhurst, J. A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4189. (c) Ishar, M. P. S.; Gandhi, R. P. *Tetrahedron* **1993**, *49*, 6729.

[46] (a) Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512. (b) Morita, N.; Kitahara, Y.; Asao, T. *Tetrahedron Lett.* **1972**, *9*, 869. (c) Ciabattoni, J.; Anderson, H. W. *Tetrahedron Lett.* **1967**, *35*, 3377.

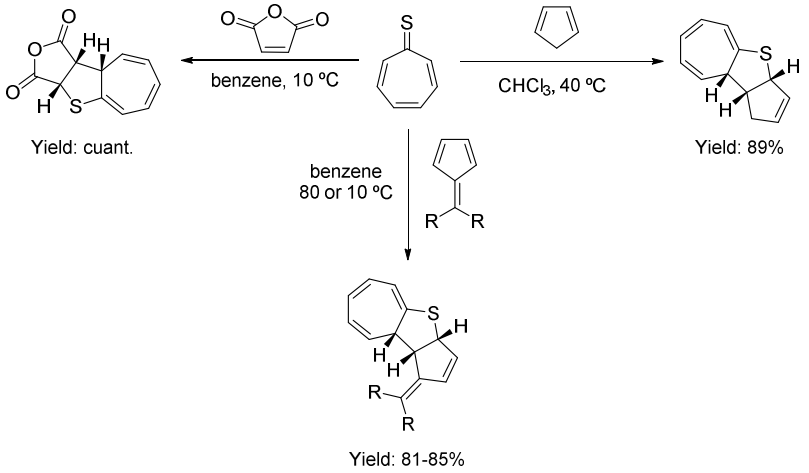
[47] Esteban, F.; Alfaro, R.; Yuste, F.; Parra, A.; García, J. L.; Alemán, J. *Eur. J. Org. Chem.* **2014**, 1395.



Scheme 1.26. [8+2] Cycloaddition of tropone with various 2π-components.

In contrast to tropone, tropothione usually reacts as a 8π-component in cycloaddition reactions. In fact, the molecule has been found to be stable at -78 °C under nitrogen, but it dimerizes readily at 0 °C, leading to a head-to-tail [8+8] type dimer.[48] Machiguchi reported the first [8+2] cycloaddition of tropothione in 1973, reaction with maleic anhydride rendered the desired adduct in high yield. [49] Furthermore, whereas tropone gave a double [6+4] adduct with dimethyl pentafulvene, tropothione reacted with dimethyl and diphenyl pentafulvenes, [50] as well as with pentadiene[51] *via* an [8+2] cycloaddition pathway; theoretical calculations suggested that the large lobe of the HOMO on the sulphur atom is responsible for the selective [8+2] cycloaddition (Scheme 1.27).

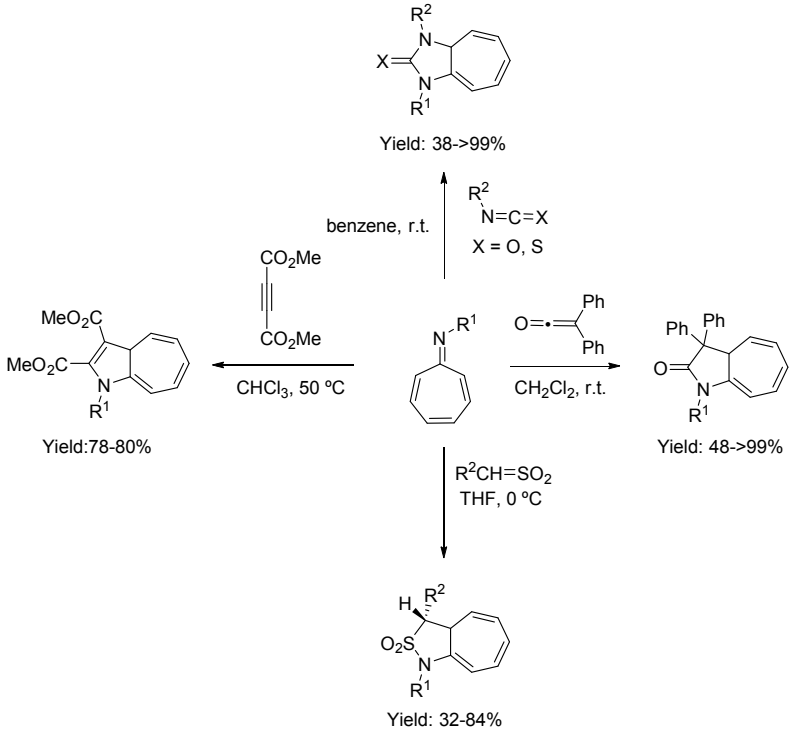
48 Machiguchi, T.; Hasegawa, T.; Itoh, S.; Mizuno, H. *J. Am. Chem. Soc.* **1989**, *111*, 1920.
49 Machiguchi, T.; Hoshino, M.; Ebine, S.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 196.
50 Machiguchi, T.; Hasegawa, T.; Ishii, Y.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1993**, *115*, 11536.
51 Machiguchi, T.; Hasegawa, T.; Otani, H.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1375.



Scheme 1.27. [8+2] Cycloaddition of tropothione with various 2π components.

Finally, azaheptafulvenes are also appealing 8π-components as they are stable, easy to prepare and rarely react as 6π-systems. Since the first efficient method for their synthesis was developed in 1977,[52] they have been mainly used with electron-deficient 2π-systems such as isocyanates, isothiocyanates,[53] sulfenes,[54] ketenes[55] and dimethyl acetylene dicarboxylate[56] providing the [8+2] cycloadducts in good yields (Scheme 1.28).

52 Sanechika, K.-I.; Kajigaeshi, S.; Kanemasa, S. *Synthesis* **1977**, *6*, 85.
53 Yamamoto, K.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1977**, *6*, 85.
54 Truce, W. E.; Shepherd, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 6453.
55 Yamamoto, K.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1977**, *6*, 91.
56 Sanechika, K.-I.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1977**, *6*, 861.

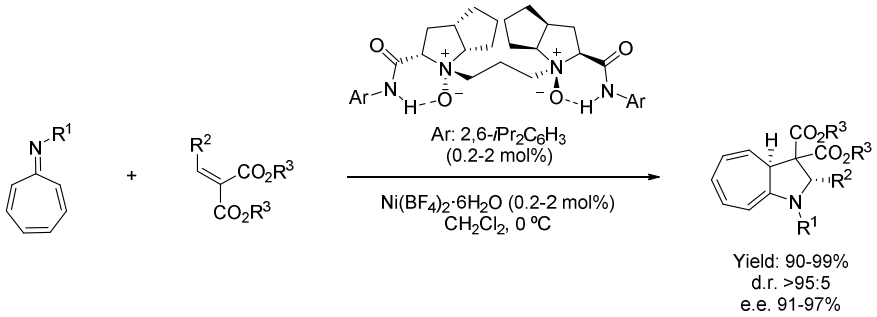


Scheme 1.28. [8+2] Cycloaddition of azaheptafulvenes with various 2π systems.

The first asymmetric [8+2] cycloaddition reaction employing azaheptafulvenes was reported by Feng and co-workers, employing a chiral *N*-*N*´-dioxide nickel(II) complex as catalyst.[57] Alkylidene malonates reacted as 2π-compounds in the transformation and cyclohepatriene-fused pyrrole derivatives were obtained in excellent diastereo- and enantioselectivities. The cycloaddition occurs through a stepwise pathway, initiated by the coordination of the bidentate alkylidene malonate, the chiral ligand and Ni(II). This intermediate adopts an octahedral

[57] Xie, M.; Liu, X.; Wu, X.; Cai, Y.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 5604.

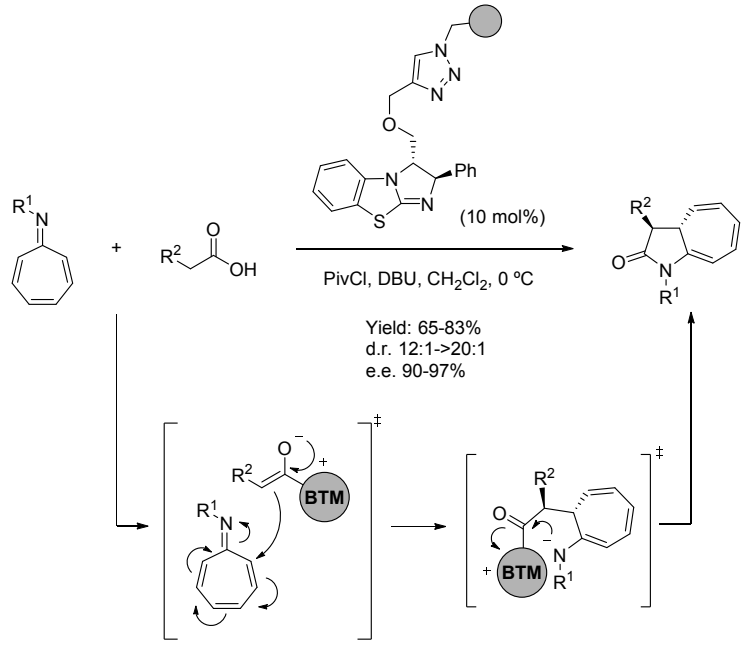
geometry shielding the *Re* face of the olefin, hence favouring the attack of the azaheptafulvene from the *Si* face (Scheme 1.29).



Scheme 1.29. Enantioselective [8+2] cycloaddition of azaheptafulvenes with alkylidene malonates.

Few years later, Pericàs and co-workers managed to develop an asymmetric [8+2] cycloaddition reaction promoted by polystyrene-supported benzotetramisole catalyst. In this case, chiral ammonium enolates, derived from activated carboxylic acids, played the role of 8π-dipolarophiles in the presence of azaheptafulvenes; obtaining the final cycloadducts in a high stereocontrol. Furthermore, the catalyst could be recycled by simple filtration at least seven times (Scheme 1.30).[58]

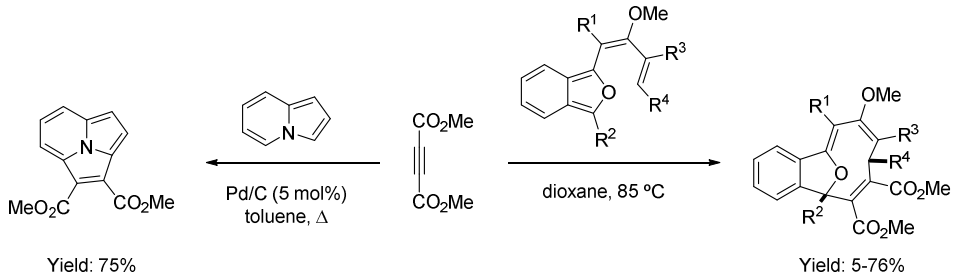
[58] Wang, S.; Rodríguez-Escrich, C.; Pericàs, M. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 15068.



Scheme 1.30. Asymmetric [8+2] cycloaddition of azaheptafulvenes with carboxylic acids promoted by immobilized isothiourea.

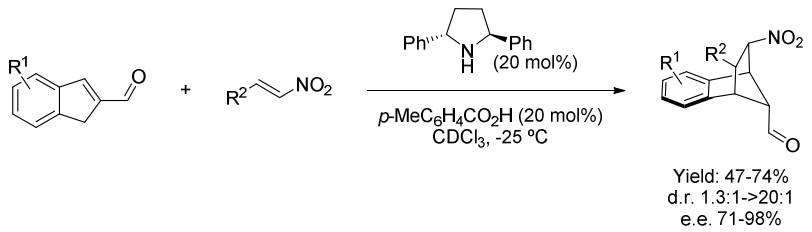
8π-Components that do not contain a cycloheptatriene in their structure can also act as 8π-systems allowing the access to other cores through the [8+2] cycloaddition reaction. In this sense, oxabridged macrocycles could be synthetised by reacting dienylisobenzofuran with dimethyl acetylene dicarboxylate in good yields.[59] Indolizines are another class of compounds investigated due to their capacity to act as 8π-components, promoting the cycloaddition in high yields in the presence of 2π-components such as dimethyl acetylene dicarboxylate (Scheme 1.31).[60]

[59] Luo, Y.; Herndon, J. W.; Cervantes-Lee, F. *J. Am. Chem. Soc.* **2003**, *125*, 12720.
[60] Galbraith, A.; Small, T.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 453.



Scheme 1.31. [8+2] Cycloaddition reaction of dienylisobenzofuranes and indolizine with dimethyl acetylene dicarboxylate.

Isobenzofulvenes have also been successfully applied, a highly stereoselctive [8+2] cycloaddition between catalytically generated amino isobenzofulvenes and nitro olefins using a secondary amine as catalyst was reported by Jørgensen´s group (Scheme 1.32).[61] Theoretical calculations suggested a stepwise mechanism where the stereochemistry of the final adduct would be determined in the first bonding-forming event. Moreover, [10+4] cycloadducts were calculated to be kinetically favoured intermediates in equilibrium with intermediates that would lead to the [8+2] adduct.



Scheme 1.32. Asymmetric [8+2] cycloaddition of indene-2-carbaldehydes and nitro olefins.

[61] Donslund, B. S.; Monleón, A.; Palazzo, T. A.; Christensen, M. L.; Dahlgaard, A.; Erickson, J. D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 1246.

1.2. Multi π-component cycloadditions

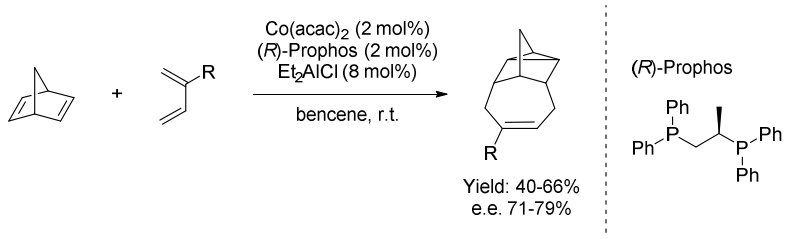
The intermolecular cycloaddition between three π-components is intrinsically more challenging than the two-component variant, because a successful interaction between three different reagents is required. Hence, the productive preparation of the 1:1:1 adduct is directly related to the ability of the transformation to avoid the formation of 1:2 adducts, to overcome competitive two π-component cycloadditions, as well as dimerization and trimerization processes. Moreover, the entropic barrier that has to be overcome for this transformation to occur is much higher than when only two π-systems participate in the reaction.

In this sense, transition metals facilitate the constructions of compounds that are generally not accessible *via* classical pericyclic reactions, often in a chemo-, regio- and stereoselective manner.[62] Different possibilities appear when more than two π-components take part in the reaction, for instance the three π-components can be located in three different molecules [n+m+p], two of them can be located at the same molecule [n+(m+p)] or [(n+m)+p], or a single molecule can bear the three of them [(n+m+p)].

One of the earliest examples of a transition metal-catalysed three π-component cycloaddition was described by Carbonaro in 1970. He reported a [4+(2+2)] cycloaddition reaction of norbornadiene with butadienes; the final adduct was obtained in poor yields when catalysing the reaction with an iron catalyst in the presence of a Lewis acid due to the formation of several side-products, however, the selectivity of the process could be dramatically increased

[62] For a selected review on three π-component high-order cycloadditions, see: Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791.

by using a cobalt catalyst.[63] Over twenty years later, Lautens and co-workers successfully performed the asymmetric version of the transformation employing a chiral cobalt complex derived from $Co(acac)_2$ and (*R*)-Prophos (Scheme 1.33).[64] Moreover, the first intramolecular cobalt-catalysed [(4+2+2)] cycloaddition reaction presented the same two compounds in the starting molecule, furnishing the final polycyclic adduct in moderate yield as a single stereoisomer.[65]



Scheme 1.33. Asymmetric [4+(2+2)] cycloaddition of norbornadiene with butadienes.

As in the first described example of a three π-component [4+2+2] cycloaddition, most of the transformations are bimolecular. In this sense, 1,3-butadienes usually react with norbornadiene[66], 1,6-enynes[67] or 1,6-diynes,[68] placing the two 2π-components in one molecule. On the other hand, the 4π-component and one of the 2π-components can be contained in one molecule such

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63 (a) Greco, A.; Carbonaro, A.; Dall´Asta, G. *J. Org. Chem.* **1970**, *35*, 271. (b) Carbonaro, A.; Cambisi, F.; Dall´Asta, G. *J. Org. Chem.* **1971**, *36*, 1443.

64 Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513.

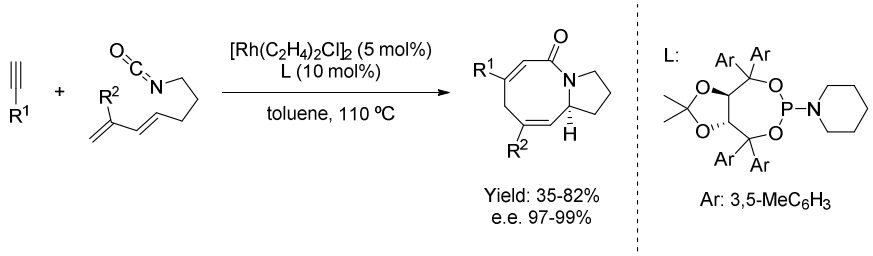
65 Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.

66 (a) ref. 56. (b) ref. 57. (c) Chen, Y.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 2060.

67 (a) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63. (b) Baik, M.-H.; Baum, E. W.; Burland, M. C.; Evans, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 1602. (c) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782.

68 Varela, J. A.; Castedo, L. Saá, C. *Org. Lett.* **2003**, *5*, 2841.

as 1,3,8-dienynes[69] or 1,3,8-trienes[70] that satisfactorily provide the [(4+2)+2] cycloadduct when reacting with alkynes. However, in the only reported highly enantioselective [(4+2)+2] cycloaddition dienyl isocyanates are the molecules containing the 4π-component and one of the 2π-components, instead of the most common 3,8-dienynes or 1,3,8-trienes. The cycloaddition leads to bicycle[6.3.0]azocine systems when employing alkynes, as the other 2π-component, under rhodium-catalysis in moderate to high yields and excellent enantiocontrol (Scheme 1.34).[71]



Scheme 1.34. Enantioselective [(4+2)+2] cycloaddition of dienyl isocyanates with alkines.

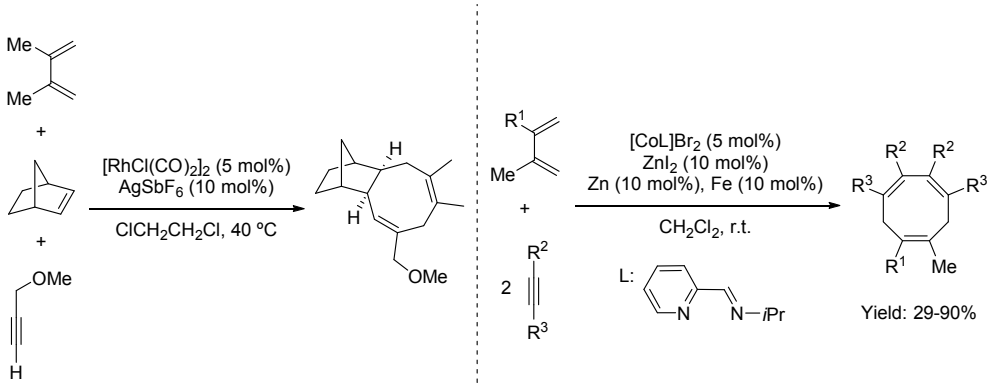
Most of the research on the field has focused on transformations that contain the three π-components in two different molecules, as this was the easiest way to avoid the competing transformations, specially the [4+2] cycloaddition and therefore, trimolecular systems have remained scarce. However, some examples can be found in the literature. In this sense, Wender and Christy described the first metal-catalysed [4+2+2] cycloaddition employing three different substrates, each of them containing one π-component. Treatment of norbornene with butadiene and propargylic ether *via* rhodium-catalysis, furnished the final cyclooctadiene in a

[69] (a) Canlas, G. M. R.; Gilbertson, S. R. *Chem. Commun.* **2014**, *50*, 5007. (b) DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. (c) Gilbertson, S. R.; BeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784.

[70] Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354.

[71] Yu, R. T.; Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13250.

moderate yield, but with a high chemo-, regio-, and diastereselectivity.[70] Few years later, the transformation between two alkynes and butadienes was reported, thereby circumventing the necessity of using a highly strained olefin.[72] In both cases eight-membered ring systems were synthetized with a high functional-group density, in an excellent regiocontrol (Scheme 1.35).



Scheme 1.35. [4+2+2] Cycloaddition between there molecules.

On the other hand, precomplexed chromium cycloheptatrienes are able to participate in formal [6+2+2] cycloadditions with two alkynes, obtaining the final polycyclic systems in moderate to high yield; the process appears to be a [6+2] cycloaddition followed by a [4+2+2] cycloaddition (Scheme 1.36).[73]

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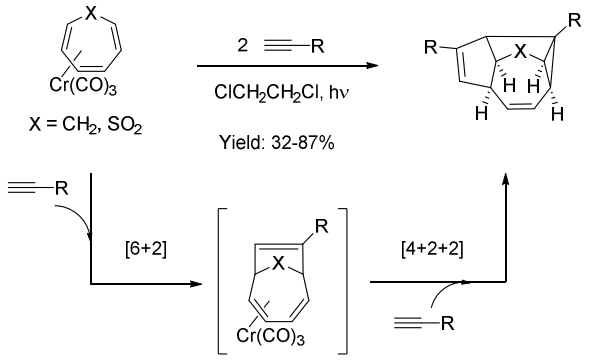
72 Hilt, G.; Janikowski, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5243.

73 (a) Rigby, J. H.; Warshakoon, N. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6094. (b) Chen, W.; Chaffee, K.; Chung, H.-J.; Sheridan, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 9980.



Scheme 1.36. [6+2+2] cycloaddition of heptatrienes with two alkynes.

More challenging four π-component cycloadditions are hard to achieve as there are many competing side-reactions, moreover the high entropic barrier that has to be overcome makes them hard to be promoted and the final cycloadduts often cannot be achieved even in low yields, as minor products of other process. Cycloaddition reactions involving four π-components were first reported by Reppe in 1948, who demonstrated the nickel-catalysed tetramerization of acetylene could furnish cyclooctatetraene.[74] Despite the evolution carried out in organic transformations, [2+2+2+2] cycloadditions still utilize four alkyne moieties and ultimately afford cyclooctatetraenes, as in the earliest example; moreover, unsymmetrical alkynes usually provide poor regio- and stereoselectivity.[75] Avoiding the competing [2+2] and [2+2+2] cycloadditions is the main challenge of the four π-component transformation, in this sense some examples were reported using nickel-catalysts where the [2+2+2+2] cycloadduct appeared in low to moderate yields.[76] Wender reported that a large load of catalyst provided the [2+2+2+2] cycloadduct selectively and also expanded the scope to unsymmetrical diynes with

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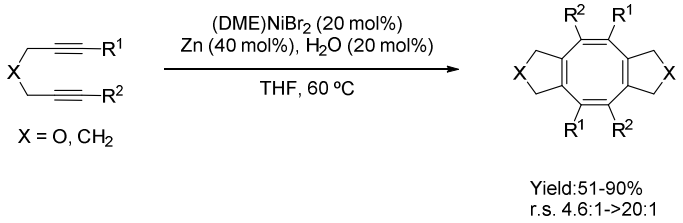
74 Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann.* **1948**, *560*, 1.

75 Diercks, R.; tom Dieck, H. *Chem. Ber.* **1985**, *118*, 428.

76 (a) Chai, Z.; Wang, H.-F.; Zhao, G. *Synlett* **2009**, 1785. (b) Wender, P. A.; Croatt, M. P.; Kühn, B. *Organometallics* **2009**, *28*, 5841.

excellent regioselectivity when one of the acetylene substituents was aromatic (Scheme 1.37).[77] More recently, a rhodium based [2+2+2+2] cycloaddition reaction has been developed with a lower catalyst load.[78]



Scheme 1.37. [2+2+2+2] cycloaddition between four alkynes.

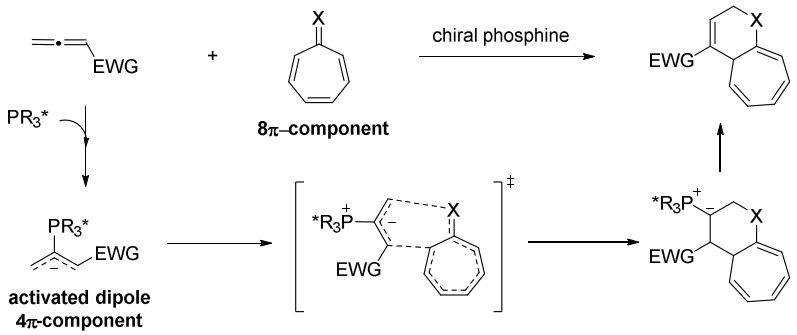
[77] (a) Wender, P. A.; Lesser, A. B.; Sirois, L. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 2736. (b) Wender, P. A.; Christy, J. P.; Lesser, A. B.; Gieseler, M. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 7687. (c) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 13402.

[78] Nasrallah, D. J.; Croatt, M. P. *Eur. J. Org. Chem.* **2014**, 3767.

2. SPECIFIC OBJETIVES AND WORK PLAN

From the literature summary presented in the introduction it can be appreciated that asymmetric high-order cycloaddition reactions remain scarce. Furthermore, reactions that occur with a high diastereo-, regio- and periselectivity are usually catalysed by transition metals and the potential that organocatalysis could have in this field has not been widely studied yet.

In this sense, we considered **developing an asymmetric organocatalytic [8+4] cycloaddition where heptafulvene derivatives would play the role of 8π-components and using 1,3-dipoles derived from allenes that could act as 4π-systems after activation by a phosphine**. We also envisioned that chiral nucleophilic phosphines would satisfactorily activate the allenes and promote the stereocontrol of the reaction as it has been previously reported for (3+2) and (4+2) annulation reactions (Scheme 2.1).[79]

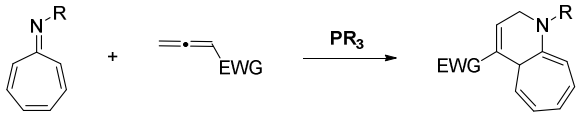


Scheme 2.1. Specific objective of the project.

[79] For a selected review on nucleophilic phosphine catalysis of allenes, see: Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

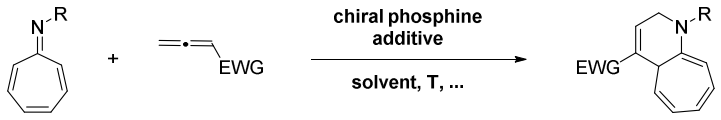
To accomplish the aforementioned objective, the subsequent work plan was followed:

1. *Proof of concept:* Structural requirements to be met by the heptafulvene will be identifiend in order to perform the [8+4] cycloaddition reaction with activated allenes. In this sense, azaheptafulvenes have been described as compounds that usually act as 8π-systems, avoiding the competing [6+n] and [4+n] cycloadditions efficiently. The capability of nucleophilic phosphines to promote the transformation will also be verified.



Scheme 2.2. Proof of concept.

2. *Optimization of the reaction conditions:* The reaction between the most suitable azaheptafulvene and electron-poor allene will be chosen as model system, with the aim of identifying the best chiral phosphine for the transformation. Once the ideal catalyst is selected, other experimental variables such as solvent, additives or temperature will be tested, in an attempt to obtain the optimal results in terms of yield and enantiocontrol (Scheme 2.3).



Scheme 2.3. Optimization of the reaction conditions.

3. RESULTS AND DISCUSSION

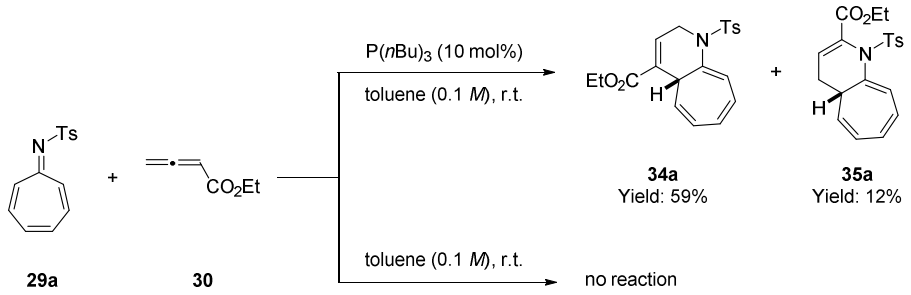
Now that the objective of the project has been defined and the work plan has been stablished, the most significant results gathered in the accomplishment of the present project will be presented in the following paragraphs.

3.1. Proof of concept

The selection of the most appropriate electron-poor allene and azaheptafulvene was decided according to literature precedents. In this sense, allenoates have been the most used allenes to promote reactions were they participate as precursors of dipole species upon activation by a nucleophilic catalyst and they subsequently react as 4π-systems.[79] On the other hand, phosphine-catalysed (3+2) annulations between allenes and imines have been extensively studied and the best results have been usually achieved when employing *N*-tosylimines.[80] Hence, *N*-tosylazaheptafulvene **29a** and ethyl 2,3-butadienoate **30a** were chosen as model substrates. The reactivity of these compounds was tested in the presence of tributylphosphine, as the high nucleophilicity of the selected phosphine would facilitate the addition of the organocatalyst to the allenoate, activating it more easily. To our delight, the [8+4] cycloaddition reaction proceeded efficiently in 4 hours rendering two regioisomeric cycloadducts **34a** and **35a** in an overall yield of 71%. (Scheme 3.1). Furthermore, the reaction did not take place in

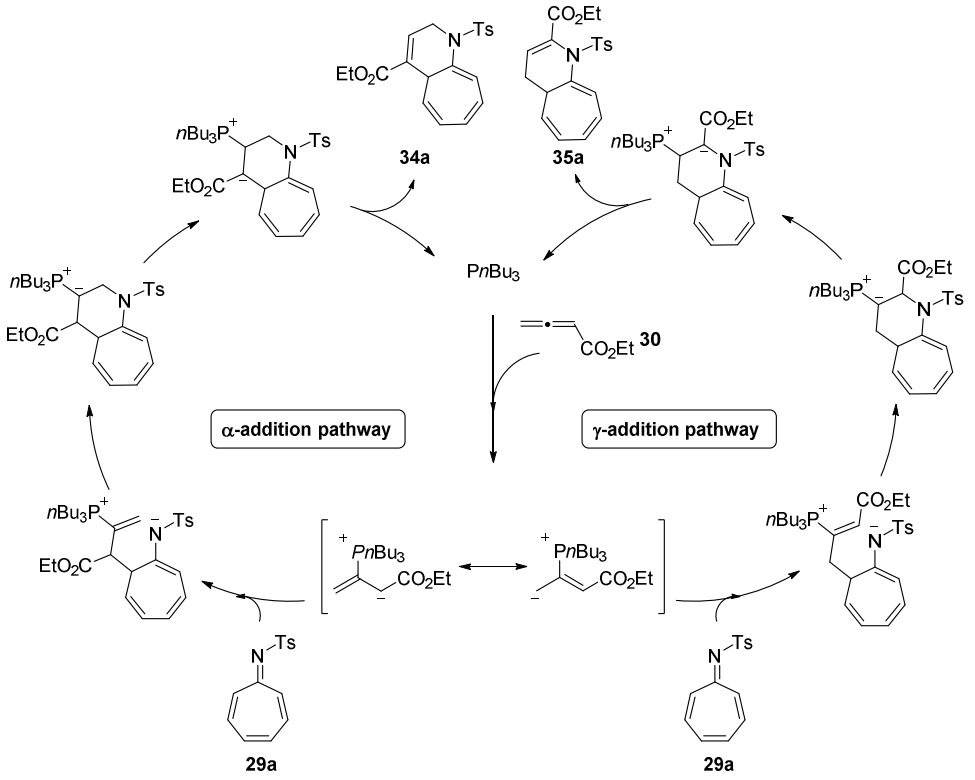
[80] For selected examples on phosphine-catalysed allene-*N*-tosylimine annulation, see: (a) Nguyen, T.-H.; Toffano, M.; Bournaud, C.; Vo-Thanh, G. *Tetrahedron Lett.* **2014**, *55*, 6377. (b) Fleury-Brégeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920. (c) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (e) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (f) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461.

the absence of catalyst demostrating that the activation of the allene with a nucleophilic phosphine is mandatory for the transformation to occur.



Scheme 3.1. Proof of concept using the reaction between *N*-tosylazaheptafulvene **29a** and 2,3-butadienoate **30**, catalysed by tributylphosphine as model system.

The formation of the two regioisomers is explained due to the fact that the zwitterionic species formed after the addition of the phosphine to the allenoate shows two resonace forms with the negative charge in α- or γ-positions, hence two reactive carbons are present the structure. It is well known that most allene-imine (3+2) annulations proceed mainly through the α-addition pathway,[80] thus, as expected, the α-addition product **34a** was generated as the major product and the γ-addition product **35a** was isolated as the minor one. The [8+4] cycloaddition starts with the activation of the allenoate **30** by the nucleophilic attack of the phosphine (see Scheme 3.2). The addition of the allene **30** to the 8π-component occurs in the C2 carbon of the heptafulevene **29a** and the second attack occurs from the negatively charged nitrogen, to the double bond of the allene, leading to a new six-membered ring. After proton transfer, the cleavage of the phosphine occurs, obtaining the two final cycloadducts **34a** and **35a**, and recovering the organocatalyst, which can restart a new catalytic cycle.

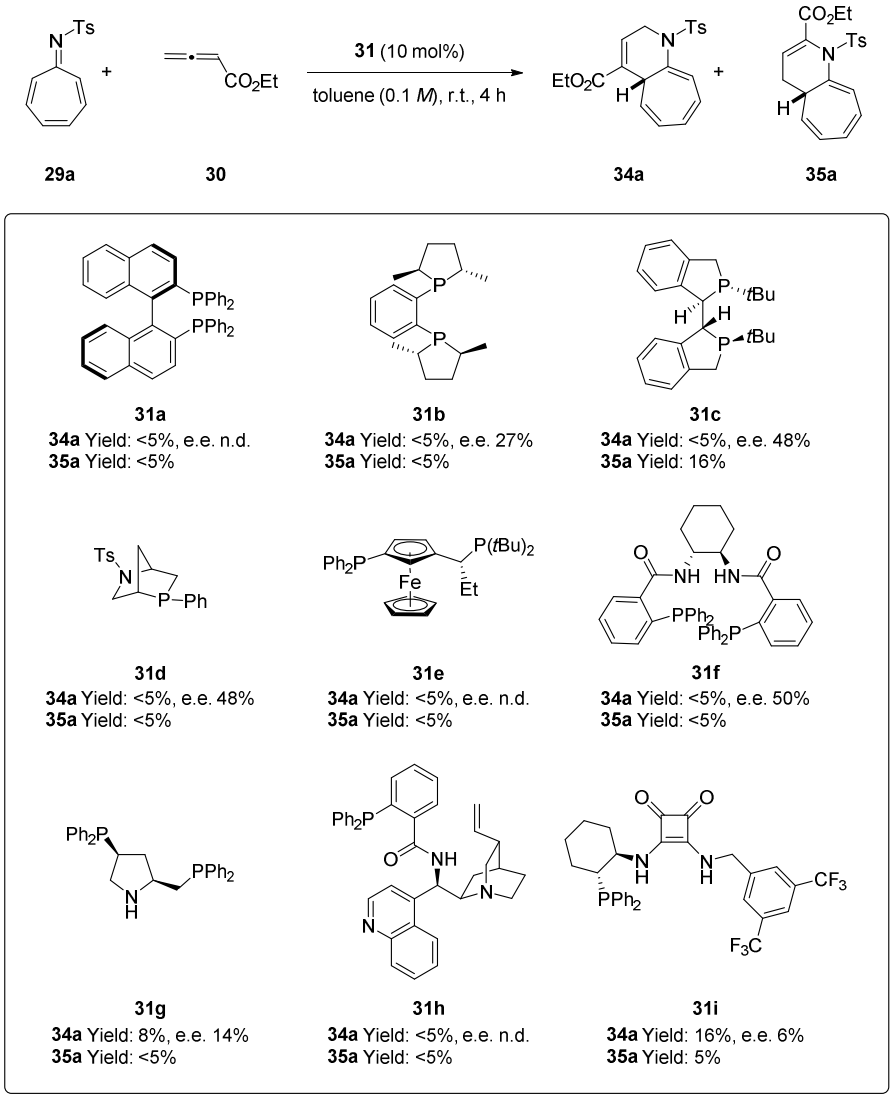


Scheme 3.2. Proposed catalytic cycle for the [8+4] cycloaddition reaction between azaheptafulvene **29a** and allenoate **30**, catalysed by tributylphosphine.

3.2. Optimization of the reaction conditions

Once the viability of the reaction had been demostrated, different types of chiral phosphines were tested in order to verify if the development of the asymmetric version of the reaction was possible (Scheme 3.3). First, chiral phosphines that have been usually used as ligands in transition metal catalysed reactions were surveyed, such as BINAP **31a**, DuPhos **31b** and DuanPhos **31c**. However, only traces of the cycloaddition product were obtained in all cases, although some degree of stereoinduction could be observed, meaning that the

[8+4] adduct could be enantioselectively obtained. More structurally rigid bridged catalyst **31d** or ferrocene derived **31e** did not improve the previous results. When carrying out the reaction with Trost ligand **31f** almost no reactivity was observed and proline derived catalyst **31g** provided the final product in low yield and almost no enantiocontrol. On the other hand, the starting materials remained untouched with cinchonidine-derived catalyst **31h** and the bifunctional chiral phosphine with a squaramide moiety **31i** provided poor results.



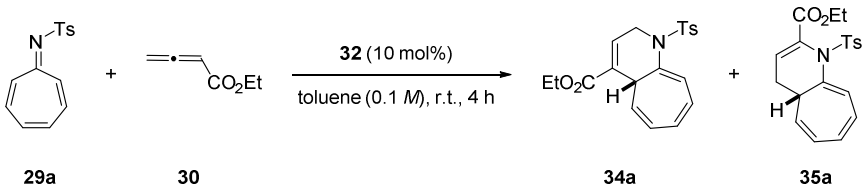
Scheme 3.3. Evaluation of a series of chiral phosphines.[81]

[81] Reactions performed in 0.05 of **29a** and **30**, using 10 mol% of catalyst **31** in 0.5 mL of toluene at r.t. for 4 h. Yield of pure product after flash chromatography. e.e. determined by HPLC analysis. n.d.: Not determined.

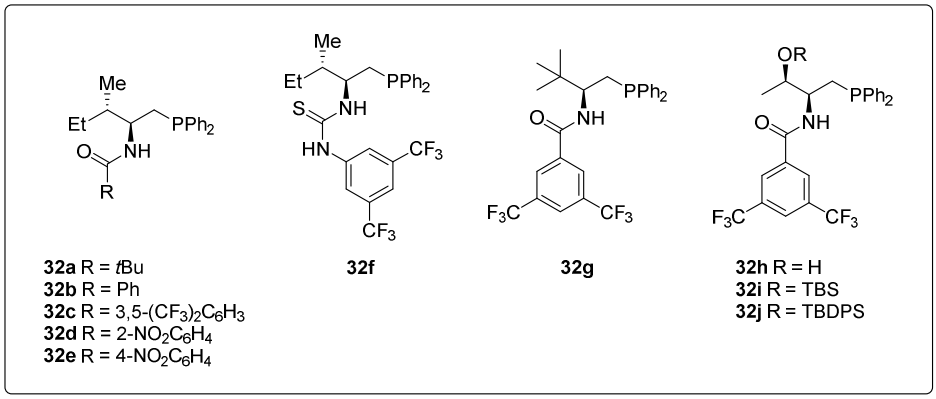
The chiral phosphines tested until the moment had showed almost no capability of promoting the reaction or had provided very poor results with respect to either conversion or stereocontrol. However, it appeared that catalysts containing hydrogen-donor substituents showed a slightly higher reactivity. With this in mind, it was decided to analyse the affect that amino acid derived phosphines could have in the cycloaddition, as they have been previously reported in other reactions involving allenes.[82] For instance, L-isoleucine derived aminophosphine was chosen as framework of the catalyst and this was modified by incorporating different substituents at the amino group. As it can be seen in Table 3.1, similar results were obtained with *N*-pivaloyl, *N*-benzoyl or *N*-aryl catalyst **32a**, **32b** and **32c** in terms of enantioselectivity, although the yield was higher with the second and third catalysts. Moving to *o*-nitrobenzoyl or *p*-nitrobenzoyl catalysts **32d** and **32e** led to a decrease in the enantiocontrol of the transformation (Table 3.1, entries 1-5). As the acidity of the NH proton could be playing an important role in the cycloaddition reaction the 3,5-bis(trifluoromethyl)phenyl phosphinothiourea **32f** was also tested, but it did not improve the results obtained with amidophosphine **32c** (Table 3.1, entry 6). Once it was decided which substituent bonded to the nitrogen would provide the best results (bis-3,5-trifluoromerhylbenzoyl group on catalyst **32c**), the effect of the volume of the functional group in position C3 was next analysed. For that, the amino acid side chain was changed moving from L-isoleucine to L-*tert*-leucine **32g**, L-threonine **32h**, *O*-*tert*-butyldimethylsilyl protected L-threonine **32i** and *O*-*tert*-butyldiphenylsilyl protected L-threonine **32j**, observing lower yields and enantiomeric excesses in all the cases (Table 3.1, entries 7-10).

[82] Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, *49*, 1369.

Table 3.1. Evaluation of a series of *N*-acyl aminophosphines.[a]



29a **30** **34a** **35a**



32a R = *t*Bu
32b R = Ph
32c R = 3,5-$(CF_3)_2C_6H_3$
32d R = 2-$NO_2C_6H_4$
32e R = 4-$NO_2C_6H_4$

32f **32g**

32h R = H
32i R = TBS
32j R = TBDPS

Entry	Catalyst	Yield 34a (%)[b]	e.e. 34a (%)[c]	Yield 35a (%)[b]
1	**32a**	48	35	23
2	**32b**	62	11	23
3	**32c**	59	39	28
4	**32d**	44	4	<5
5	**32e**	59	2	22
6	**32f**	25	20	8
7	**32g**	30	22	19
8	**32h**	34	29	17
9	**32i**	14	18	13
10	**32j**	10	35	11

[a] Reactions performed in 0.05 of **29a** and **30**, using 10 mol% of catalyst **32** in 0.5 mL of toluene at r.t. for 4 h. [b] Yield of pure product after flash chromatography. [c] Determined by HPLC analysis.

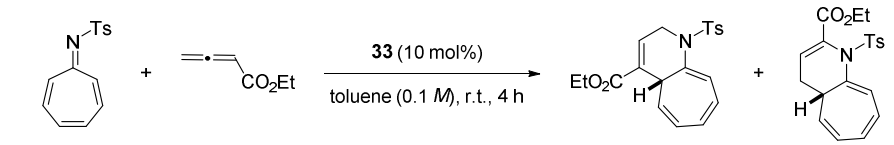
After all these experiments it is important to note that by employing amino acid derived phosphines **32a-j** the reactivity of the cycloaddition dramatically

increased by comparing them with the previously tested chiral phosphines **31a-i**. Up to this moment, catalyst **32c** provided the best results, with an overall yield of 87%, a regioisomer ratio of 2.1:1 and a 39% enantiomeric excess of the major compound.

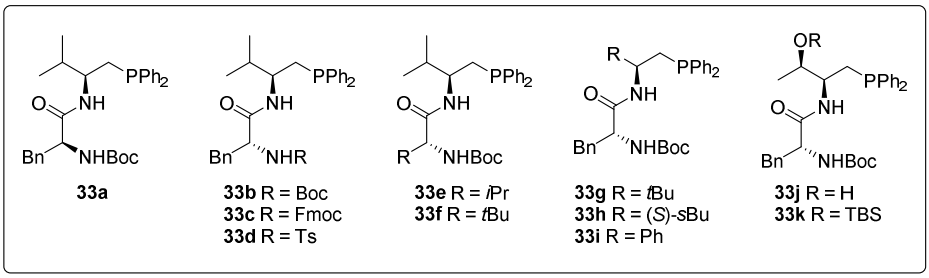
Despite the excellent yield, the regioisomer ratio and the enantioselectivity of the transformation remained quite poor, and none of the changes performed in the aminophosphine improved the results. Therefore, dipeptide-like phosphines were surveyed (see Table 3.2) in view of literature precedents that shown their good performance in other reaction[83] and for that L-Phe-L-Val derived phosphine **33a** was chosen as initial catalyst. First of all, the possible match-mismatch effect between both stereogenic centers was studied, but similar results were observed when using L-Phe-L-Val derived phosphine **33a** and D-Phe-L-Val derived phosphine **33b** (Table 3.2, entries 1-2), only observing a slightly higher yield in the second case. Next, the substituents bonded to the terminal amino group were evaluated, observing similar results when placing the fluorenylmethyloxycarbonyl (Fmoc) group **33c** and a lower enantiocontrol with the tosyl group **33d** (Table 3.2, entries 3-4). D-Val-L-Val derived phosphine **33e** and D-*tert*-Leu-L-Val derived phosphine **33f** were also surveyed but the enantiocontrol of the reaction dramatically decreased (Table 3.2, entries 5-6) showing that the benzyl group influenced the stereochemical outcome of the transformations. Finally, D-Phe-L-*tert*-Leu **33g**, D-Phe-L-Ile **33h**, D-Phe-L-Phg **33i**, D-Phe-L-Thr **33j**, as well as its *O*-*tert*-butyldimethylsilyl protected analogue **33k**, derived phosphines were evaluated (Table 3.2, entries 7-11), but without any remarkable breakthrough.

[83] Hiang, B.; Li, C.; Wang, H.; Wang, C.; Liu, L.; Zhang, J. *Org. Lett.* **2017**, *19*, 5102.

Table 3.2. Evaluation of a series of dipeptide derived chiral phosphines.[a]



29a **30** **34a** **35a**



33a

33b R = Boc
33c R = Fmoc
33d R = Ts

33e R = *i*Pr
33f R = *t*Bu

33g R = *t*Bu
33h R = (*S*)-*s*Bu
33i R = Ph

33j R = H
33k R = TBS

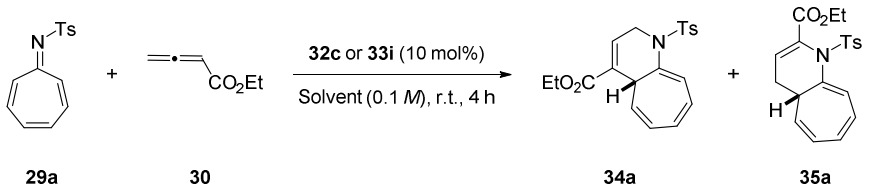
Entry	Catalyst	Yield 34a (%)[b]	e.e. 34a (%)[c]	Yield 35a (%)[b]
1	**33a**	33	35	7
2	**33b**	39	36	10
3	**33c**	37	38	12
4	**33d**	22	25	6
5	**33e**	41	17	9
6	**33f**	45	6	20
7	**33g**	36	28	29
8	**33h**	36	19	29
9	**33i**	33	41	6
10	**33j**	19	22	10
11	**33k**	53	35	26

[a] Reactions performed in 0.05 of **29a** and **30**, using 10 mol% of catalyst **33** in 0.5 mL of toluene at r.t. for 4 h. [b] Yield of pure product after flash chromatography. [c] Determined by HPLC analysis.

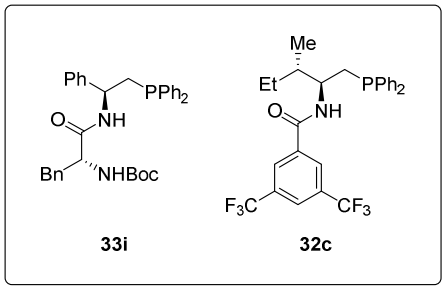
With regard to the enantioselectivity of the reaction, similar values were obtained with the best dipeptide-derived aminocatalyst **33i** and the best *N*-acyl aminophosphine **32c**, hence, we next decided to test the effect the solvents could have in the reaction (see Table 3.3) using the two catalysts that had provided the

higher e.e. values up to this moment (catalyst **34i** and **33c**). In the case of the dipeptide-derived aminocatalyst **33i** a solvent such as *meta*-xylene improved slightly the enantioselectivity of the reaction, whereas, halogenated and polar solvents provided the final product as almost racemic materials (Table 3.3, entries 2-5). On the other hand, *meta*-xylene, as well as chloroform positively influenced the enantioselectivity of the transformation when catalysing the reaction with *N*-acyl aminophosphine **32c** (Table 3.3, entries7-8) and poorer results were observed with polar THF (Table 3.3, entry 9).

Table 3.3. Evaluation of different solvents.[a]



29a **30** **34a** **35a**



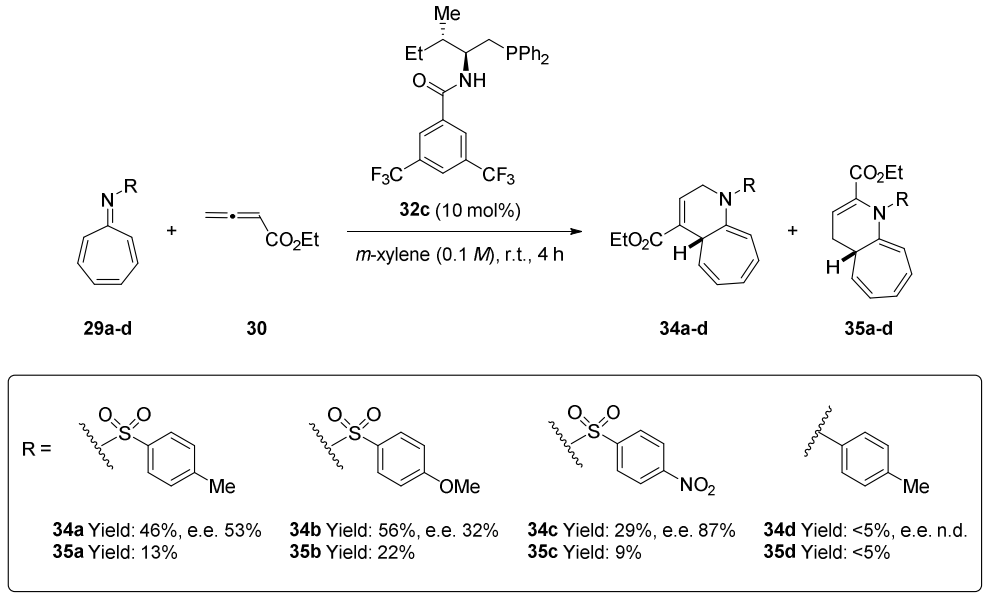
33i **32c**

Entry	Catalyst	Solvent	Yield 34a (%)[b]	e.e. 34a (%)[c]	Yield 35a (%)[b]
1	**33i**	Toluene	33	41	6
2	**33i**	*m*-Xylene	30	45	11
3	**33i**	$CHCl_3$	27	5	12
4	**33i**	THF	27	3	18
5	**33i**	EtOH	19	11	<5
6	**32c**	Toluene	59	39	28
7	**32c**	*m*-Xylene	46	53	13
8	**32c**	$CHCl_3$	29	57	22
9	**32c**	THF	31	35	43

[a] Reactions performed in 0.05 of **29a** and **30**, using 10 mol% of catalyst **32c** or **33i** in 0.5 mL of solvent at r.t. for 4 h. [b] Yield of pure product after flash chromatography. [c] Determined by HPLC analysis.

As no satisfactory improvement had been achieved by varying the chiral phosphine nor the solvents in regard of the enantiocontrol of the cycloaddition, it was thought that the chosen *N*-tosylazaheptafulvene **29a** might have not been the most appropriate one. Therefore, the reaction was carried out with azaheptafulvenes bearing different susbtituents at the nitrogen atom in order to

improve the enantiocontrol of the reaction. When methoxyphenylsulfonyl group **29b** was tested, a decrease on the enantioselectivity of the reaction was observed. However, when *N*-nosyl substituted analogue was surveyed **29c**, the final product could be isolated with an excellent enantiomeric excess of 89%. On the other hand when a neatly donor group, such as *N*-*para*-tolyl was tested **29d**, the reaction did not proceed; deducing that an azaheptafulvene susbtituted by an strongly electron-withdrawing group at the nitrogen is necessary for the reaction to happen satisfactorily (Scheme 3.4).



Scheme 3.4. Evaluation of different protecting groups in the azaheptafulvene.[84]

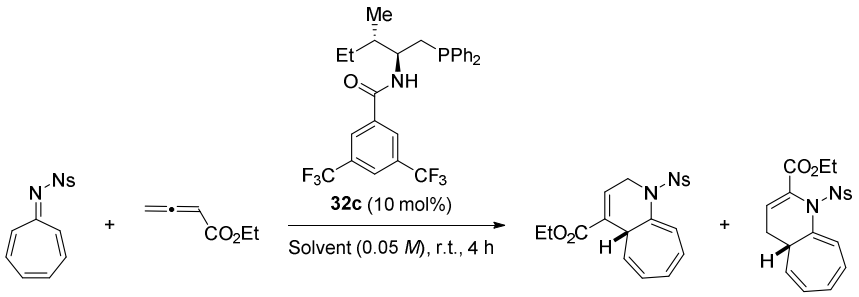
Considering that *N*-tosylazaheptafulvene **29a** and *N*-nosylazaheptafulvene **29c** behaved in a different way in terms of both yield and enantioselectivity, it was

[84] Reactions performed in 0.05 mmol of **29a-d** and **30**, using 10 mol% of catalyst **32c** in 0.5 mL of *m*-xylene at r.t. for 4 h. Yield of pure product after flash chromatography. e.e. determined by HPLC analysis. n.d.: Not determined.

decided to perform a new screening of the reaction conditions in order to increase the yield obtained with **29c**. Initially all the previously surveyed catalyst were re-evaluated with azaheptafulvene **29c**, but aminophosphine **32c** remained the best one.

Finally, a wide variety of solvents of different natures were tested (Table 3.4). Non-polar aromatic solvents affected the yield and enantiocontrol of the reaction in a similar way (Table 3.4, entries 1-3), providing moderate yields and high enantiomeric excesses, and when carrying out the reaction in halogenated solvents low yields and moderate enantioselectivities were observed (Table 3.4, entries 5-7). α,α,α-Trifluorotoluene acted as an aromatic solvent in terms of enantiocontrol and as an halogenated one according to the obtained low yield (Table 3.4, entry 4). Medium polarity solvents lowered the enantioselectivity and furnished the γ-product as the mayor cycloadduct (Table 3.4, entries 8-10) and more polar solvents increased the yield, although poor enantiomeric excesses were observed (Table 3.4, entries 11-12). Finally, the slow addition of three equivalents of the allenoate **29a** during 14 hours increased the overall yield up to 62%, maintaining the regioisomeric ratio and the enantiocontrol of the reaction (Table 3.4, entry 13).

Table 3.4. Evaluation of different solvents.[a]



Entry	Solvent	Yield 34c (%)[b]	e.e. 34c (%)[c]	Yield 35c (%)[b]
1	*m*-Xylene	19	90	8
2	Toluene	22	89	7
3	Benzene	19	87	6
4	$F_3CC_6H_5$	8	81	5
5	CH_2Cl_2	7	60	8
6	$ClCH_2CH_2Cl$	5	63	5
7	$CHCl_3$	6	72	5
8	THF	5	36	16
9	Et_2O	9	69	14
10	CH_3CN	7	16	21
11	EtOH	39	23	17
12	EtOAc	39	29	25
13[d]	Toluene	46	90	16

[a] Reactions performed in 0.05 of **29c** and **30**, using 10 mol% of catalyst **32c** in 1 mL of solvent at r.t. for 4 h. [b] Yield of pure product after flash chromatography. [c] Determined by HPLC analysis. [d] Reaction performed using 3 equiv. of **30** and performing a slow addition of it during 14h.

4. CONCLUSIONS

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

- It has been demonstrated the dipole generated upon nucleophilic addition of phosphines to allenoates can satisfactorily act as 4π-component in the presence of 8π-components such as azaheptafulvenes, undergoing high-order [8+4] cycloaddition reactions.

- Two regioisomers usually formed in the [8+4] cycloaddition and their ratio could be controlled by modifying the catalyst and the solvent.

- Asymmetric induction was possible by using chiral phosphines, obtaining an excellent enantiomeric excess of 90% with catalyst **32c** in toluene, a regioisomer ratio of 2.9:1 and a moderate yield.

- Further modifications of the reaction conditions have to be considered in order to increase the yield and the scope of the reaction has to be studied in order to demonstrate the viability of the methodology as a general tool in synthesis.

Chapter 5

5

Final Conclusions

1. CONCLUSIONS

The present work gathers a number of asymmetric reactions in which the common feature is the development of novel transformations using the organocatalytic activation of reagents that are not the typically described ones in the literature, in the presence of covalent organocatalysts. Experimental results collected during the accomplishment of this work led to the following conclusions.

Desymmetrization of *meso*-formylcyclopropanes under iminium ion activation. It has been demonstrated that the ring-opening reaction of formylcyclopropanes in the presence of an external nucleophile catalysed by a secondary amine is possible when using carboxylic acids as nucleophiles. The reaction promoted by a chiral diphenylprolinol derivative delivered γ-acyloxy aldehydes in high yields and excellent diastereo- and enantiocontrol. Adducts were subjected to various transformations in which the use of protecting groups could be avoided as the functional groups reacted selectively. Finally, mechanistic studies were carried out determining that the ring-opening reaction is a concerted but asynchronous transformation.

Total synthesis of speciosin H. The applicability of the developed ring-opening of formylcyclopropanes when using carboxylic acids as nucleophiles has been demonstrated by using this transformation as key step of the total synthesis of speciosin H. The target natural product could be prepared in an acceptable yield starting from commercially available starting materials and in a highly enantioenriched form.

Phosphine catalysed enantioselective high-order [8+4] cycloaddition. The work confirmed that the 1,3-dipoles generated upon the addition of a nucleophilic

phosphine to an electron-poor allene could react as a 4π-component in the presence of azaheptafulenes that played the role of 8π-components. The final cycloaddition adduct was obtained as a mixture of regioisomers due to the two possible resonance forms of the 1,3-dipole and when employing an amino acid derived phosphine the stereochemical outcome of the reaction could be controlled in a highly reliable manner.

Chapter 6

6

Experimental Section

1. GENERAL METHODS AND MATERIALS[1]

NMR: Monodimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 ^{o}C on a Bruker AC-300 spectrometer (300 MHz for ^{1}H, 75.5 MHz for ^{13}C, 282 MHz for ^{19}F and 121.5 MHz for ^{31}P) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals;[2] and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; p, pentucket; m, multiplet. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for nucleus assigment. Selective n.O.e., NOESY, COSY and HSQC experiments were acquired to confirm precise molecular configuration and to assist in convoluting complex multiplet signals.[3]

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

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

HRMS: High-resolution mass spectra (HRMS) were recorded on a Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI+ or ESI-).

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

HPLC: The enantiomeric excess (ee) of the products was determined by High performance liquid chromatography on a chiral stationary phase, performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel *Chiralpak AD-H*, *AS-H*, *AZ-3*, *IC* and *Chiralcel OZ-3* columns were used; specific conditions are indicated for each case.

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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.

Optical rotations ($[\alpha]_D^{20}$) were measured at 20 °C on a Jasco P-2000 polarimeter with a sodium lamp at 589 nm and a path 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 120 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing miscroscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone N inert oil and transferred to the diffractometer.

Miscellaneous: Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[4] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 °C, and allowed to cool under a dehumidified atmosphere.[5] Reactions at reduced temperatures were carried out using Isotemp refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation, phosphomolybdic acid, potassium permanganate or *p*-anisaldehyde dips.[6] For flash chromatography Merck 60, 230-400 mesh silica gel was used.[7] For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used.

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4 Armarego, W. L. F.; Chai, C. L. L. *Purifications of Laboratory Chemicals*, 7th ed., Elsevier: Oxford, 2012.

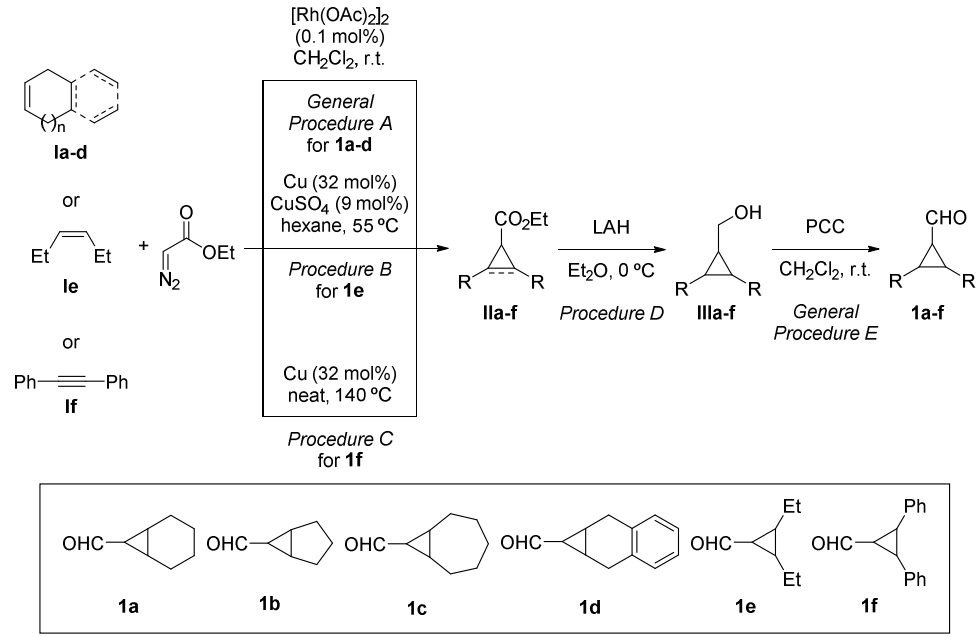
5 Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, 1975.

6 Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlin, 1969.

7 Still, W. C.; Kann, H. ; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.

2. DESYMMETRIZATION OF *MESO*-FORMYLCYCLOPROPANES UNDER IMINIUM ION ACTIVATION

2.1 Standard procedures *A*-*E* for the preparation of formylcyclopropanes 1a-f



Scheme 2.1. General overview of the synthesis of formylcyclopropanes **1a-f**.

Synthesis of alkenes **Ia-e** and alkyne **If.** Alkenes and alkyne **Ia-f** were obtained from commercial sources.

General Procedure A for the synthesis of cyclopropanecarboxylates **IIa-d.** Products **IIa-d** were prepared following the procedure described in the literature[8] as follows: A solution of the corresponding cycloalkene (30.4 mmol, 1 equiv.) and

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8 (a) Alper, P. B.; Chianelli, D.; Mutnick, D.; Rucker, P. V.; Tully, D. C. *Compositions and methods for modulating fxr.* (Irm Llc) WO2012087519, Jun 28, 2012. (b) Ponsford, R. J.; Stachulski, A. V. *Preparation of 6ß-[2-(2-aminothiazol-4-yl)acrylamido]penicillanates*. (Beecham Group PLC, UK) EP 421752, Apr 10, 1991.

rhodium(II)acetate dimmer (0.03 mmol, 0.001 equiv.) in dry CH_2Cl_2 (10 mL, 3 *M*) was treated, under inert atmosphere, with dropwise addition of a solution of ethyl diazoacetate (30.4 mmol, 1 equiv.) in dry CH_2Cl_2 (10 mL, 3 *M*) over 5 h (33 µL/min) at room temperature. The reaction was stirred for another 30 minutes and was then passed through a basic alumina plug (CH_2Cl_2 as eluant) to remove any catalyst. The solution was concentrated *in vacuo* and the obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford the corresponding ethyl cyclopropanecarboxylate **IIa-d**.

Procedure B for the synthesis of cyclopropanecarboxylate **IIe**. See below.

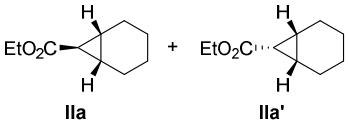
Procedure C for the synthesis of cyclopropenecarboxylate **IIf**. See below.

General Procedure D for the synthesis of cyclopropanemethanol **IIIa-e**. A solution of the corresponding ethyl cyclopropanecarboxylate **IIa-e** (6.5 mmol, 1 equiv.) in dry Et_2O (5 mL, 1.3 *M*) was added dropwise, under inert atmosphere, over a solution of lithium aluminum hydride (8.4 mmol, 1.3 equiv.) in dry Et_2O (15 mL, 0.5 *M*) at 0 °C. After stirring for 1 h, the reaction was quenched with the slow addition of H_2O (15 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding cyclopropanemethanol **IIIa-e**.

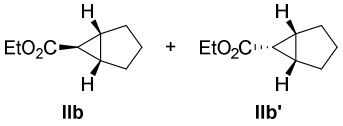
Procedure D for the synthesis of cyclopropanemethanol **IIIf**. See below.

General Procedure E for the synthesis of formylcyclopropanes **1a-f**. The corresponding cyclopropylmethanol **IIIa-f** (1.6 mmol, 1 equiv.) in dry CH_2Cl_2 (1 mL, 1.6 *M*) was added in one portion, under inert atmosphere, to a stirred solution of pyridinium chlorochromate (3 mmol, 1.9 equiv.) in dry CH_2Cl_2 (3 mL, 1 *M*) at room temperature. After stirring for 1 h, the reaction mixture was taken up in Et_2O (10 mL), filtered through a silica gel pad (Et_2O as eluant) and concentrated *in vacuo*. The corresponding formylcycplopropanes **1a-f** were obtained without further purification.

*2.1.1. Preparation and characterization of cyclopropanecarboxylates **IIa-e** and cyclopropenecarboxylate **IIf***



Ethyl (1*R*,6*S*,7*r*)-bicyclo[4.1.0]heptane-7-carboxylate (**IIa**) and Ethyl (1*R*,6*S*,7*s*)-bicyclo[4.1.0]heptane-7-carboxylate (**IIa'**).[9] Following the *General Procedure A*, **IIa** and **IIa'** (3.99 g, 23.7 mmol) were isolated as a colorless oil, starting from cyclohexene (3.1 mL, 30.4 mmol) and ethyl diazoacetate (3.2 mL, 30.4 mmol) in the presence of rhodium(II)acetate dimmer (13.4 mg, 0.03 mmol). Yield: 78%. d.r.: 4:1. Data for **IIa**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 1.87-1.72 (m, 2H, C_1-H, C_6-H), 1.67-1.51 (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 1.51-1.43 (m, 2H, C_3-H_aH_b, C_4-H_aH_b), 1.26 (t, *J* = 4.3 Hz, 1H, C_7-H), 1.22-0.98 (m, 7H, CH_3, C_2-H_aH_b, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.48 (COO), 59.92 (CH_3CH_2), 25.49 (C_7), 22.60 (C_2, C_5), 21.84 (C_1, C_6), 20.84 (C_3, C_4), 14.13 (CH_3). Data for **IIa'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 1.87-1.72 (m, 2H, C_1-H, C_6-H), 1.68-1.55 (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 1.51-1.27 (m, 5H, C_3-H_2, C_4-H_2, C_7-H), 1.26-1.13 (m, 5H, CH_3, C_2-H_aH_b, C_5-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.87 (COO), 59.71 (CH_3CH_2), 22.03 (C_7), 21.22 (C_2, C_5), 18.54 (C_3, C_4), 16.33 (C_1, C_6), 14.38 (CH_3).



Ethyl (1*R*,5*S*,6*r*)-bicyclo[3.1.0]hexane-6-carboxylate (**IIb**) and Ethyl (1*R*,5*S*,6*s*)-bicyclo[3.1.0]hexane-6-carboxylate (**IIb'**).[10] Following the *General Procedure A*, **IIb** and **IIb'** (3.09 g, 20.1 mmol) were isolated as an inseparable mixture of diastereoisomers as a yellow oil, starting from cyclopentene (2.7 mL, 30.4 mmol) and ethyl diazoacetate (3.2 mL, 30.4 mmol) in the presence of rhodium(II)acetate dimmer (13.4 mg, 0.03 mmol). Yield: 66%. d.r.: n.d. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09-3.97 (m, 2H, CH_3CH_2), 1.89-1.46 (m, 7H, C_1-H, C_2-H_2, C_3-H_aH_b, C_4-H_2, C_5-H), 1.31 (t, *J* = 2.8 Hz, 1H, C_6-H), 1.23-1.13 (m, 3H, CH_3), 1.10-0.92 (m, 1H, C_3-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 174.01 (COO), 171.60* (COO), 60.06 (CH_3CH_2), 28.56

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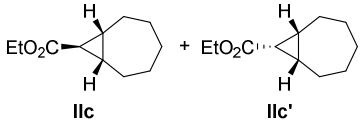
[9] MacInnes, I.; Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *J. Chem. Soc., Perkin Trans. I.* **1983**, 2771.

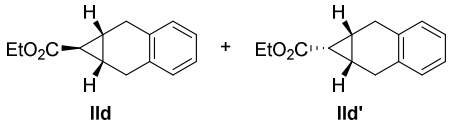
[10] Barret, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260.

(C_1, C_5), 27.21 (C_2, C_4), 25.80* (C_2, C_4), 25.11* (C_1, C_5), 23.80* (C_3), 23.60* (C_6), 21.29 (C_6), 20.19 (C_3), 14.26 (CH_3), 14.22* (CH_3).



IIc **IIc'**

Ethyl (1*R*,7*S*,8*r*)-bicyclo[5.1.0]octane-8-carboxylate (**IIc**) and Ethyl (1*R*,7*S*,8*s*)-bicyclo[5.1.0]octane-8-carboxylate (**IIc'**).[11] Following the *General Procedure A*, **IIc** and **IIc´** (1.66 g, 9.12 mmol) were isolated as a colorless oil, starting from cycloheptene (3.5 mL, 30.4 mmol) and ethyl diazoacetate (3.2 mL, 30.4 mmol) in the presence of rhodium(II)acetate dimmer (13.4 mg, 0.03 mmol). Yield: 30%. d.r.: n.d. Data for **IIc**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 2.24-2.09 (m, 2H, C_1-H, C_7-H), 1.86-1.74 (m, 1H, C_8-H), 1.74-1.60 (m, 2H, C_3-H_aH_b, C_5-H_aH_b), 1.60-1.48 (m, 2H, C_3-H_aH_b, C_5-H_aH_b), 1.46-1.30 (m, 3H, C_2-H_aH_b, C_4-H_aH_b, C_6-H_aH_b), 1.29-1.00 (m, 6H, CH_3, C_2-H_aH_b, C_4-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.27 (COO), 60.32 (CH_3CH_2), 32.52 (C_4), 29.90 (C_8), 29.57 (C_2, C_6), 28.82 (C_3, C_5), 27.96 (C_1, C_7), 14.44 (CH_3). Data for **IIc'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 1.97-1.75 (m, 7H, C_1-H, C_2-H_aH_b, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b, C_7-H), 1.69 (t, *J* = 8.5 Hz, 1H, C_8-H), 1.49-1.35 (m, 2H, C_3-H_aH_b, C_5-H_aH_b), 1.35-1.18 (m, 6H, CH_3, C_2-H_aH_b, C_4-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.27 (COO), 59.58 (CH_3CH_2), 32.18 (C_4), 29.21 (C_2, C_6), 25.48 (C_1, C_7), 23.72 (C_8), 22.65 (C_3, C_5), 14.26 (CH_3).



IId **IId'**

Ethyl (1*r*,1a*R*,7a*S*)-1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carboxylate (**IId**) and Ethyl (1*s*,1a*R*,7a*S*)-1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carboxylate (**IId'**).[12] Following the *General Procedure A*, **IId** and **IId'** (2.63 g, 12.16 mmol) were isolated as an inseparable mixture of diastereoisomers as a colorless oil, starting from 1,4-dihydronaphthalene (3.9 mL, 30.4 mmol) and ethyl diazoacetate (3.2 mL, 30.4 mmol) in the presence of rhodium(II)acetate dimmer (13.4 mg, 0.03 mmol). Yield: 40%. d.r.: 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.22-6.97 (m, 4H, C_{arom}-H), 4.11 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 3.78* (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 3.21-3.00 (m, 4H, C_2-H_2, C_7-H_2), 2.05-1.94 (m, 2H, C_{1a}-H, C_{7a}-H), 1.79-1.67 (m, 1H, C_1-H), 1.55-1.46* (m, 2H, C_{1a}-H, C_{7a}-H), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3), 1.10* (t, *J* = 7.1 Hz, 3H, CH_3).

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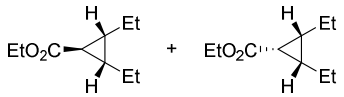
11 Azzouzi-Zriba, K.; Delpon-Bonnet, D.; Crousse, B. *J. Fluorine Chem.* **2011**, *132*, 811.

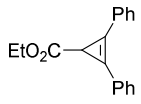
12 Cordi, A. A.; Berque-Bestel, I.; Persigand, T.; Lacoste, J. M.; Newman-Tancredi, A.; Audinol, V.; Millan, M. J. *J. Med. Chem.* **2001**, *44*, 787.

^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 174.30 (COO), 170.89* (COO), 135.68* (C_{2a}, C_{6a}), 133.58 (C_{2a}, C_{6a}), 128.96 (C_{arom}-H), 128.51* (C_{arom}-H), 126.51 (C_{arom}-H), 125.75* (C_{arom}-H), 60.32 (CH_3CH_2), 59.93* (CH_3CH_2), 28.25 (C_2, C_7), 25.01* (C_2, C_7), 22.17 (C_{1a}, C_{7a}), 21.00* (C_1), 18.80 (C_1), 16.88* (C_{1a}, C_{7a}), 14.29 (CH_3), 14.07* (CH_3).



IIe **IIe'**

Ethyl (1*r*,2*R*,3*S*)-2,3-diethylcyclopropane-1-carboxylate (**IIe**) and Ethyl (1*s*,2*R*,3*S*)-2,3-diethylcyclopropane-1-carboxylate (**IIe'**).[13] The product was synthesized according to a literature procedure[9] as follows: To a solution of *cis*-hex-3-ene (1.5 mL, 11.9 mmol) in dry hexane (12 mL, 1 *M*) was added dry cooper (232 mg, 3.65 mmol) and anhydrous cooper sulphate (177 mg, 1.11 mmol). The mixture was heated up to 55 °C and ethyl diazoacetate (1.2 mL, 11.9 mmol) was added over 4 h (5 µL/min). The reaction was stirred for another 1 h, filtered and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford the corresponding ethyl 2,3-diethylcyclopropane-1-carboxylate **IIe** and **IIe'** (404.9 mg, 2.38 mmol) as a colorless oil. Yield: 20%. d.r.: 2:1. Data for **IIe**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 1.47-1.24 (m, 6H, $CH_3CH_2C_2$, $CH_3CH_2C_3$, C_2-H, C_3-H), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 1.05-0.90 (m, 7H, C_1-H, $CH_3CH_2C_2$, $CH_3CH_2C_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.71 (COO), 60.14 (CH_3CH_2O), 29.85 (C_2, C_3), 26.53 (C_1), 20.62 ($CH_3CH_2C_2$, $CH_3CH_2C_3$), 14.28 (CH_3CH_2O), 13.93 ($CH_3CH_2C_2$, $CH_3CH_2C_3$). Data for **IIe'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 1.70-1.52 (m, 5H, C_1-H, $CH_3CH_2C_2$, $CH_3CH_2C_3$), 1.29-1.15 (m, 5H, CH_3CH_2O, C_2-H, C_3-H), 0.89 (t, *J* = 7.4 Hz, 6H, $CH_3CH_2C_2$, $CH_3CH_2C_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.22 (COO), 59.65 (CH_3CH_2O), 27.23 (C_2, C_3), 20.07 (C_1), 15.69 ($CH_3CH_2C_2$, $CH_3CH_2C_3$), 14.39 (CH_3CH_2O), 14.07 ($CH_3CH_2C_2$, $CH_3CH_2C_3$).



IIf

Ethyl 2,3-diphenylcycloprop-2-ene-1-carboxylate (**IIf**).[14] The product was synthesized following a literature procedure[8b,15] as follows: A mixture of diphenylacetylene (2 g, 11.2 mmol) with cooper (126.0 mg, 2.0 mmol) was heated at 140 °C with stirring. Ethyl diazoacetate (0.65 mL, 6.2 mmol) was added dropwise over 2.5 h and the reaction was continued until

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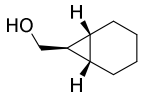
13 Zhu, Z.; Espenson, J. H. *J. Am. Chem, Soc.* **1996**, *118*, 9901.

14 Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413.

15 (a) Breslow, R.; Winter, R.; Battiste, M. *J. Org. Chem.* **1959**, *24*, 415. (b) Breslow, R.; Lockhart, J.; Small, A. *J. Am. Chem.* **1962**, *84*, 2793.

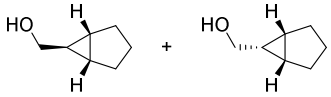
N_2 evolution had ceased. The reaction was cooled down to room temperature and then, taken up in Et_2O (10 mL), filtered and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 8:2) to afford the corresponding ethyl cyclopropenecarboxylate **IIf** (540.8 mg, 2.05 mmol) as a yellow solid. Yield: 33%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 4H, C_{arom}-H), 7.53-7.45 (m, 4H, C_{arom}-H), 7.44-7.36 (m, 2H, C_{arom}-H), 4.21 (q, *J* = 7.1 Hz, 2H, CH_2), 2.86 (s, 1H, C_1-H), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.92 (COO), 130.01 (C_{arom}-H), 129.37 (C_{arom}-H), 128.95 (C_{arom}-H), 127.27 (C_{arom}-C), 107.75 (C_2, C_3), 60.46 (CH_2), 21.81 (C_1), 14.50 (CH_3).

*2.1.2. Preparation and characterization of cyclopropanemethanols **IIIa-f***



IIIa

((1*R*,6*S*,7*r*)-Bicyclo[4.1.0]heptan-7-yl)methanol (**IIIa**).[16] Following the *General Procedure D*, **IIIa** (443.0 mg, 3.51 mmol) was isolated as a colorless oil, starting from ethyl (1*R*,6*S*,7*r*)-bicyclo[4.1.0]heptane-7-carboxylate **IIa** (1.09 g, 6.5 mmol) in the presence of lithium aluminum hydride (318.8 mg, 8.4 mmol). Yield: 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28 (d, *J* = 6.4 Hz, 2H, C*H*$_2$OH), 3.15 (s, 1H, OH), 1.83-1.66 (m, 2H, C_2-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$), 1.60-1.45 (m, 2H, C_3-*H*$_a$H$_b$, C_4-*H*$_a$H$_b$), 1.20-0.96 (m, 4H, C_2-H$_a$*H*$_b$, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$), 0.73-0.58 (m, 3H, C_1-H, C_6-H, C_7-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.84 (CH_2OH), 25.93 (C_7), 23.31 (C_2, C_5), 21.41 (C_3, C_4), 15.08 (C_1, C_6).

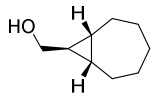


IIIb **IIIb'**

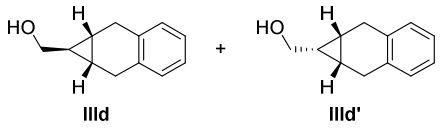
((1*R*,5*S*,6*r*))-Bicyclo[3.1.0]hexan-6-yl)methanol (**IIIb**) and ((1*R*,5*S*,6*s*)-Bicyclo[3.1.0]hexan-6-yl)methanol (**IIIb'**).[8b] Following the *General Procedure D*, **IIIb** and **IIIb'** (510.4 mg, 4.55 mmol) were isolated as an inseparable mixture of diastereoisomers as a yellow oil, starting from the mixture of ethyl bicyclo[3.1.0]hexane-6-carboxylate **IIb** and **IIb'** (1.0 g, 6.5 mmol) in the presence of lithium aluminum hydride (318.8 mg, 8.4 mmol). Yield: 70%. d.r.: 3:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 3.65* (d, *J* = 7.6 Hz, 2H, C*H*$_2$OH), 3.41 (d, *J* = 7.2 Hz, 2H, C*H*$_2$OH), 1.97-0.84 (m, 9H, C_1-H, C_2-H_2, C_3-H_2, C_4-H_2, C_5-H, C_6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 66.15 (CH_2OH), 60.16* (CH_2OH), 27.36 (C_2, C_4),

[16] MacInnes, I.; Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *J. Chem. Soc., Perkin Trans. I.* **1983**, 2771.

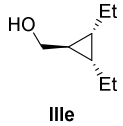
26.92* (C_3), 25.58* (C_2, C_4), 23.99* (C_6), 23.21* (C_1, C_5), 22.65 (C_1, C_5), 21.75 (C_6), 21.41 (C_3).


IIIc

((1*R*,7*S*,8*r*)-Bicyclo[5.1.0]octan-8-yl)methanol (**IIIc**).[17] Following the *General Procedure D*, **IIIc** (601.6 mg, 4.29 mmol) was isolated as a colorless oil, starting from ethyl (1*R*,7*S*,8*r*)-bicyclo[5.1.0]octane-8-carboxylate **IIc** (1.2 g, 6.5 mmol) in the presence of lithium aluminum hydride (318.8 mg, 8.4 mmol). Yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (d, *J* = 7.0 Hz, 2H, C*H*$_2$OH), 2.20-2.05 (m, 2H, C_3-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$), 1.85 (s, 1H, OH), 1.83-1.73 (m, 1H, C_4-*H*$_a$H$_b$), 1.73-1.58 (m, 2H, C_3-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$), 1.39-1.22 (m, 2H, C_2-*H*$_a$H$_b$, C_6-*H*$_a$H$_b$), 1.22-1.08 (m, 1H, C_4-H$_a$*H*$_b$), 1.05-0.88 (m, 2H, C_1-H, C_7-H), 0.88-0.78 (m, 1H, C_8-H), 0.78-0.64 (m, 2H, C_2-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 66.81 (CH_2OH), 32.71 (C_4), 31.51 (C_8), 30.42 (C_2, C_6), 29.74 (C_3, C_5), 22.36 (C_1, C_7).


IIId **IIId'**

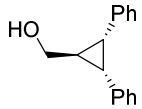
((1*r*,1a*R*,7a*S*)-1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-yl)methanol (**IIId**) and ((1*s*,1a*R*,7a*S*)-1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-yl)methanol (**IIId'**). Following the *General Procedure D*, **IIId** and **IIId'** (1.06 g, 6.11 mmol) were isolated as an inseparable mixture of diastereoisomers as a colorless oil, starting from the mixture of ethyl 1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carboxylate **IId** and **IId'** (1.4 g, 6.5 mmol) in the presence of lithium aluminum hydride (318.8 mg, 8.4 mmol). Yield: 94%. d.r.: 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.19-6.96 (m, 4H, C_{arom}-H), 3.49 (d, *J* = 7.0 Hz, 2H, C*H*$_2$OH), 3.44* (d, *J* = 7.5 Hz, 2H, C*H*$_2$OH), 3.28-2.79 (m, 4H, C_2-H$_2$, C_7-H$_2$), 1.92 (s, 1H, OH), 1.46-1.35* (m, 2H, C_{1a}-H, C_{7a}-H), 1.25-1.12 (m, 1H, C_1-H), 0.98-0.85 (m, 2H, C_{1a}-H, C_{7a}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 135.86* (C_{2a}, C_{6a}), 135.04 (C_{2a}, C_{6a}), 128.90 (C_{arom}-H), 128.55* (C_{arom}-H), 126.15 (C_{arom}-H), 125.73* (C_{arom}-H), 65.92 (CH_2OH), 59.03* (CH_2OH), 29.01 (C_2, C_7), 24.99* (C_2, C_7), 21.21* (C_1), 18.75 (C_1), 15.94 (C_{1a}, C_{7a}), 12.72* (C_{1a}, C_{7a}). IR (ATR): 3379 (O-H st) cm^{-1}.


IIIe

((1r,2R,3S)-2,3-Diethylcyclopropyl)methanol (IIIe).[9] Following the General Procedure D, IIIe (120.5 mg, 0.94 mmol) was isolated as a colorless oil, starting from ethyl (1r,2R,3S)-2,3-diethylcyclopropane-1-

[17] Kirmse, W.; Pook, K. H. *Chem. Ber.* **1965**, *98*, 4022.

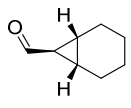
carboxylate IIe (400 mg, 2.35 mmol) in the presence of lithium aluminum hydride (115.9 mg, 3.06 mmol). Yield: 40%. 1H NMR (300 MHz, CDCl3) δ 3.35 (d, J = 7.0 Hz, 2H, CH2OH), 2.30 (s, 1H, OH), 1.33 (dq, J = 13.9, 6.9 Hz, 2H, CH3CHaHbC2, CH3CHaHbC3), 1.17 (dq, J = 14.2, 7.2 Hz, 2H, CH3CHaHbC2, CH3CHaHbC3), 0.91 (t, J = 7.4 Hz, 6H, CH3CH2C2, CH3CH2C3), 0.59-0.47 (m, 2H, C2-H, C3-H), 0.47-0.34 (m, 1H, C1-H). 13C NMR (75.5 MHz, CDCl3) δ 67.01 (CH2OH), 27.42 (C1), 23.90 (C2, C3), 21.01 (CH3CH2C2, CH3CH2C3), 14.39 (CH3CH2C2, CH3CH2C3).



IIIf

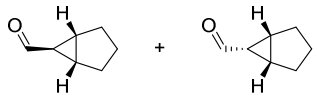
((1*r*,2*R*,3*S*)-2,3-Diphenylcyclopropyl)methanol (**IIIf**).[14] Dry Et_2O (15 mL, 0.1 *M*) was slowly added over lithium aluminum hydride (368.1 mg, 9.7 mmol) and then the mixture was stirred for 1 h. To this solution was added in small portions the ethyl cyclopropenecarboxylate **IIf** (396.5 mg, 1.5 mmol) over 2 h. After stirring for another 1 h, the reaction was quenched with the slow addition of H_2O (25 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 8:2 to 7:3) to afford the corresponding cyclopropylmethanol **IIIf** (178.3 mg, 0.80 mmol) as a white solid. Yield: 53%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.03 (m, 6H, C_{arom}-H), 7.03-6.89 (m, 4H, C_{arom}-H), 3.85 (d, *J* = 6.5 Hz, 2H, CH_2), 2.42 (d, *J* = 5.6 Hz, 2H, C_2-H, C_3-H), 2.20-2.06 (m, 1H, C_1-H), 1.86 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.45 (C_{arom}-C), 129.05 (C_{arom}-H), 127.90 (C_{arom}-H), 125.97 (C_{arom}-H), 66.36 (CH_2), 29.69 (C_2, C_3), 27.82 (C_1).

*2.1.3. Preparation and characterization of formylcyclopropanes **1a-f***

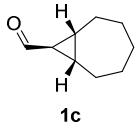


1a

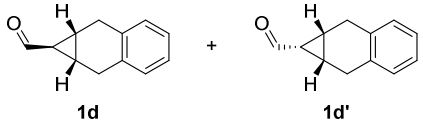
(1*R*,6*S*,7*r*)-Bicyclo[4.1.0]heptane-7-carbaldehyde (**1a**).9 Following the *General Procedure E*, **1a** (149.0 mg, 1.2 mmol) was isolated as a yellow oil, starting from ((1*R*,6*S*,7*r*)-bicyclo[4.1.0]heptan-7-yl)methanol **IIIa** (201.9 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, *J* = 5.3 Hz, 1H, CHO), 2.05-1.86 (m, 2H, C_2-$H_a$$H_b$, C_5-$H_a$$H_b$), 1.82-1.60 (m, 5H, C_1-H, C_3-$H_a$$H_b$, C_4-$H_a$$H_b$, C_6-H, C_7-H), 1.39-1.12 (m, 4H, C_2-$H_a$$H_b$, C_3-$H_a$$H_b$, C_4-$H_a$$H_b$, C_5-$H_a$$H_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.61 (CHO), 36.66 (C_7), 22.66 (C_2, C_5), 22.39 (C_1, C_6), 21.00 (C_3, C_4).



((1*R*,5*S*,6*r*))-Bicyclo[3.1.0]hexan-6-yl)methanol (**1b**) and ((1*R*,5*S*,6*s*)-Bicyclo[3.1.0]hexan-6-yl)methanol (**1b'**).[8b] Following the *General Procedure E*, **1b** and **1b'** (107.5 mg, 0.98 mmol) were isolated as an inseparable mixture of diastereoisomers as a yellow oil, starting from the mixture of (bicyclo[3.1.0]hexan-6-yl)methanol **IIIb** and **IIIb'** (179.4 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 61%. d.r.: 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 9.46* (d, *J* = 6.5 Hz, 1H, CHO), 9.09 (d, *J* = 5.3 Hz, 1H, CHO), 2.19-0.99 (m, 9H, C_1-H, C_2-H_2, C_3-H_2, C_4-H_2, C_5-H, C_6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.83* (CHO), 200.83 (CHO), 33.92* (C_6), 32.03 (C_6), 30.59* (C_1, C_5), 28.69 (C_1, C_5), 27.14 (C_2, C_4), 26.82* (C_2, C_4), 24.49* (C_3), 20.12 (C_3).

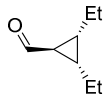


(1*R*,7*S*,8*r*)-Bicyclo[5.1.0]octane-8-carbaldehyde (**1c**).[17] Following the *General Procedure E*, **1c** (152.6 mg, 1.1 mmol) was isolated as a colorless oil, starting from ((1*R*,6*S*,8*r*)-bicyclo[5.1.0]heptan-8-yl)methanol **IIIc** (224.4 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 69%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, *J* = 4.8 Hz, 1H, CHO), 2.21-2.04 (m, 2H, C_1-H, C_7-H), 1.81-1.57 (m, 6H, C_3-H_2, C_4-$H_a$$H_b$, C_5-H_2, C_8-H), 1.44-1.05 (m, 5H, C_2-H_2, C_4-$H_a$$H_b$, C_6-H_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.75 (CHO), 40.35 (C_8), 32.25 (C_4), 29.10 (C_2, C_6), 28.49 (C_3, C_5), 27.86 (C_1, C_7).



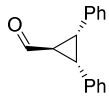
(1*r*,1a*R*,7a*S*)1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carbaldehyde (**1d**) and (1*s*,1a*R*,7a*S*)1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-carbaldehyde (**1d'**).12 Following the *General Procedure E*, **1d** and **1d'** (173.6 mg, 1.01 mmol) were isolated as an inseparable mixture of diastereoisomers as a colorless oil, starting from the mixture of 1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1-yl)methanol **IIId** and **IIId'** (278.8 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 63%. d.r.: 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 9.31 (d, *J* = 4.6 Hz, 1H, CHO), 8.94* (d, *J* = 6.5 Hz, 1H, CHO), 7.20-6.99 (m, 4H, C_{arom}-H), 3.54-2.95 (m, 4H, C_2-H_2, C_7-H_2), 2.16-2.09 (m, 2H, C_{1a}-H, C_{7a}-H), 2.07-1,99* (m, 2H, C_{1a}-H, C_{7a}-H), 1.95-1.84* (m, 1H, C_1-H), 1.83-1.77 (m, 1H, C_1-H). ^{13}C NMR (75.5 MHz, $CDCl_3$)

(* indicates minor diastereoisomer resonances) δ 201.05 (CHO), 200.69* (CHO), 134.18* (C_{2a}, C_{6a}), 133.12 (C_{2a}, C_{6a}), 128.93 (C_{arom}-H), 128.57* (C_{arom}-H), 126.64 (C_{arom}-H), 126.51* (C_{arom}-H), 33.34* (C_1), 29.25 (C_1), 27.97 (C_2, C_7), 25.82* (C_2, C_7), 22.99 (C_{1a}, C_{7a}), 21.59* (C_{1a}, C_{7a}).



1e

(1*r*,2*R*,3*S*)-2,3-Diethylcyclopropane-1-carbaldehyde (**1e**).[18] Following the *General Procedure E*, **1e** (71.9 mg, 0.57 mmol) was isolated as a colorless oil, starting from ((1*r*,2*R*,3*S*)-2,3-diethylcyclopropyl)methanol **IIIe** (100 mg, 0.78 mmol) in the presence of pyridinium chlorochromate (319.4 mg, 1.48 mmol). Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, *J* = 5.3 Hz, 1H, CHO), 1.60-1.44 (m, 4H, $CH_3CH_2C_2$, $CH_3CH_2C_3$), 1.43-1.27 (m, 3H, C_1-H, C_2-H, C_3-H), 0.99 (t, *J* = 7.1 Hz, 6H, $CH_3CH_2C_2$, $CH_3CH_2C_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.13 (CHO), 37.44 (C_1), 30.08 (C_2, C_3), 20.32 ($CH_3CH_2C_2$, $CH_3CH_2C_3$), 13.81 ($CH_3CH_2C_2$, $CH_3CH_2C_3$).



1f

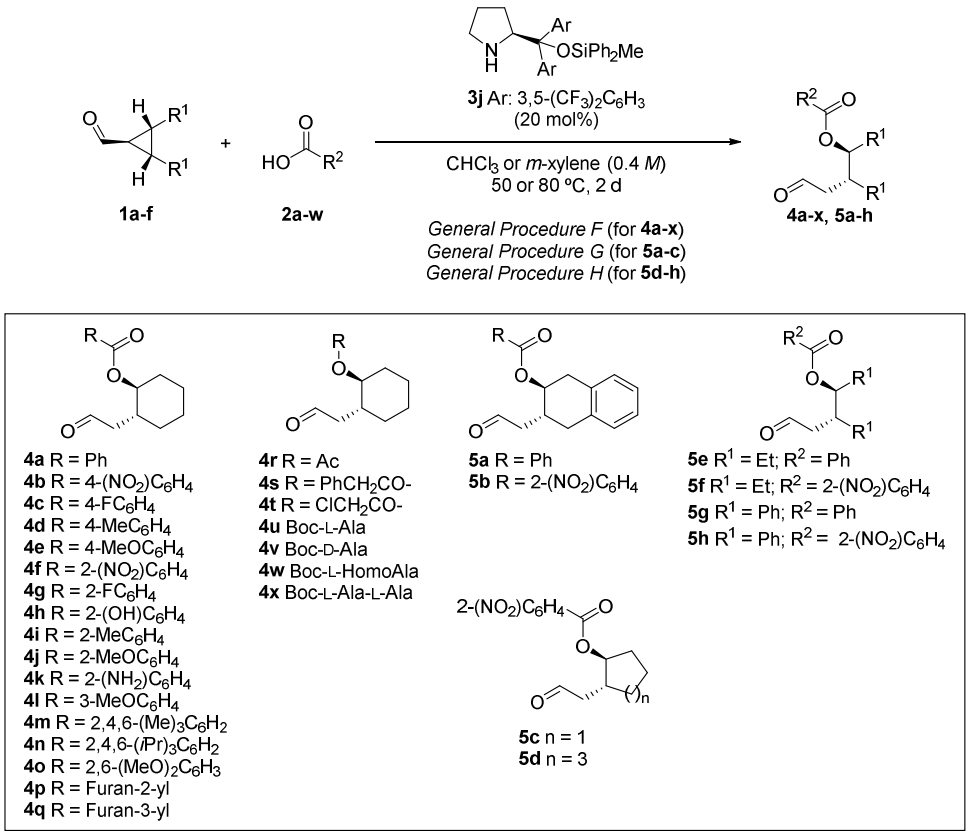
(1*r*,2*R*,3*S*)-2,3-Diphenylcyclopropane-1-carbaldehyde (**1f**).[19] Following the *General Procedure E*, **1f** (302.3 mg, 1.36 mmol) was isolated as a grey solid, starting from ((1*r*,2*R*,3*S*)-2,3-diphenylcyclopropyl)methanol **IIIf** (390.9 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, *J* = 4.1 Hz, 1H, CHO), 7.21-7.13 (m, 6H, C_{arom}-H), 7.04-6.90 (m, 4H, C_{arom}-H), 3.21 (d, *J* = 5.1 Hz, 2H, C_2-H, C_3-H), 2.86 (q, *J* = 4.6 Hz, 1H, C_1-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.68 (CHO), 134.87 (C_{arom}-C), 128.95 (C_{arom}-H), 128.13 (C_{arom}-H), 126.80 (C_{arom}-H), 36.80 (C_1), 33.46 (C_2, C_3).

[18] Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8391.

[19] Ryland, B. L.; MacCann, S. D.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 12166.

2.2. Synthesis of γ-acycloxy aldehydes 4a-x and 5a-j

*2.2.1. Preparation and characterization of aldehydes **4a-x** and **5a-h***



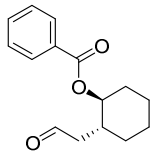
Scheme 2.2. General overview of the synthesis of products **4a-x** and **5a-h**.

General Procedure F for the synthesis of γ-acyloxy-substituted aldehydes **4a-x**. The corresponding carboxylic acid **2a-t** (0.75 mmol, 3 equiv.) or amino acid **2u-w** (0.375 mmol, 1.5 equiv.) was added to a solution of (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((methyldiphenylsilyl)oxy)methyl)pyrrolidine **3j** (0.05 mmol, 20 mol%) and formylcyclopropane **1a** (0.25 mmol, 1 equiv.) in $CHCl_3$ (625 μL, 0.4 *M*) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at 50 °C for 2 days. Then the solvent was evaporated *in vacuo*,

the crude diluted in Et_2O (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 7:3) to afford the corresponding aldehydes **4a-x**. Racemic standards for HPLC separation of stereoisomers were prepared using racemic mixture of enantiomers of catalyst **3g**.

General Procedure G for the synthesis of γ-acyloxy-substituted aldehydes **5a-c**. A solution of (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((methyldiphenylsilyl)oxy)-methyl)pyrrolidine **3j** (0.05 mmol, 20 mol%) and formylcyclopropane **1b** or **1d** (0.25 mmol, 1 equiv.) in *m*-xylene (625 µL, 0.4 *M*) was heated overnight at 80 °C in an ordinary vial equipped with a magnetic stirring bar. At this point, the diastereoselectivity of the starting material could be measured observing a d.r. (*trans*/*cis*) 8:1 and 18:1 for aldehydes **1b** and **1d**, respectively. Then, the corresponding carboxylic acid **2a** or **2f** (0.75 mmol, 3 equiv.) was added and the reaction mixture was stirred at 80 °C for further 2 days. Then the solvent was evaporated *in vacuo*, the crude diluted in Et_2O (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 7:3) to afford the corresponding aldehydes **5a-c**. Racemic standards for HPLC separation of stereoisomers were prepared using racemic mixture of enantiomers of catalyst **3g**.

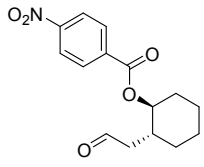
General Procedure H for the synthesis of γ-acyloxy-substituted aldehydes **5d-h**. The reaction was performed following the *General Procedure G* but using *m*-xylene as solvent and carrying out the reaction at 80 °C.



4a

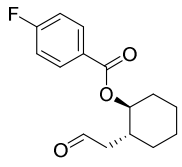
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl benzoate (**4a**). Following the *General Procedure F*, **4a** (45.6 mg, 0.19 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and benzoic acid **2a** (91.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1H, CHO), 8.05-7.97 (m, 2H, C_{arom}-H), 7.60-7.51 (m, 1H, C_{arom}-H), 7.48-7.38 (m, 2H, C_{arom}-H), 4.76 (td, *J* = 9.8, 4.5 Hz, 1H, C_1-H), 2.66-2.56 (m, 1H, C*H*$_a$H$_b$CHO), 2.38-2.21 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.21-2.10 (m, 1H, C_6-*H*$_a$H$_b$), 1.92 (dt, *J* = 13.0, 2.7 Hz, 1H, C_3-*H*$_a$H$_b$), 1.87-1.77 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-

1.67 (m, 1H, C_4-H_aH_b), 1.49-1.11 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.79 (CHO), 166.13 (COO), 133.13 (C_{arom}-H), 130.35 (C_{arom}-C), 129.71 (C_{arom}-H), 128.52 (C_{arom}-H), 77.14 (C_1), 47.58 (CH_2CHO), 37.55 (C_2), 31.94 (C_6), 31.67 (C_3), 25.20 (C_4), 24.57 (C_5). IR (ATR): 1695 (C=O st) cm^{-1}. MS (EI) m/z (%): 124 (15), 123 (18), 105 (100, $PhCO^+$), 96 (26), 83 (17), 81 (23), 80 (16), 77 (40), 67 (18), 51 (19). HRMS: Calculated for $[C_{15}H_{19}O_3]^+$: 247.1334 [$(M+H)^+$]; found: 247.1348. The ee (92%) was determined on compound **6a**. $[\alpha]_D^{20}$: +57.7 (*c* = 1.0, CH_2Cl_2).



4b

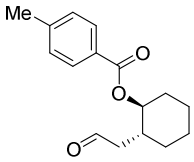
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 4-nitrobenzoate (**4b**). Following the *General Procedure F*, **4b** (58.3 mg, 0.20 mmol) was isolated as a yellow oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 4-nitrobenzoic acid **2b** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.7 Hz, 1H, CHO), 8.27 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 8.16 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 4.79 (td, *J* = 9.9, 4.3 Hz, 1H, C_1-H), 2.64-2.51 (m, 1H, CH_aH_bCHO), 2.39-2.26 (m, 2H, C_2-H, CH_aH_bCHO), 2.21-2.11 (m, 1H, C_6-H_aH_b), 2.00-1.86 (m, 1H, C_3-H_aH_b), 1.89-1.79 (m, 1H, C_5-H_aH_b), 1.79-1.68 (m, 1H, C_4-H_aH_b), 1.51-1.17 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.28 (CHO), 164.15 (COO), 150.59 (C_{arom}-N), 135.64 (C_{arom}-C), 130.77 (C_{arom}-H), 123.61 (C_{arom}-H), 78.44 (C_1), 47.64 (CH_2CHO), 37.24 (C_2), 31.77 (C_6), 31.61 (C_3), 25.05 (C_4), 24.44 (C_5). IR (ATR): 1716 (C=O st), 1605 (NO_2 st), 1523 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 207 (25), 151 (26), 150 (100, 4-$NO_2C_6H_4CO^+$), 124 (19), 104 (34), 96 (21), 95 (23), 92 (15), 83 (18), 82 (19), 81 (56), 80 (23), 79 (20), 77 (18), 67 (33). HRMS: Calculated for $[C_{15}H_{16}NO_5]^-$: 290.1028 [$(M-H)^-$]; found: 290.1038. The ee (86%) was determined on compound **6b**. $[\alpha]_D^{20}$: +27.8 (*c* = 1.0, CH_2Cl_2).



4c

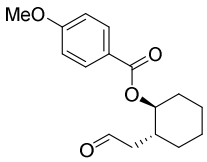
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 4-fluorobenzoate (**4c**). Following the *General Procedure F*, **4c** (50.2 mg, 0.19 mmol) was isolated as a white solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 4-fluorobenzoic acid **2c** (105.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H, CHO), 8.11-7.92 (m, 2H, C_{arom}-H), 7.20-7.02 (m, 2H, C_{arom}-H), 4.74 (td, *J* = 9.9, 4.5 Hz, 1H, C_1-H), 2.67-2.50 (m, 1H, CH_aH_bCHO), 2.37-2.23 (m, 2H, C_2-H, CH_aH_bCHO), 2.22-2.09 (m, 1H, C_6-H_aH_b), 1.92 (dt, *J* = 12.7, 3.0 Hz, 1H, C_3-H_aH_b), 1.86-1.77 (m, 1H, C_5-H_aH_b), 1.77-1.67 (m, 1H, C_4-H_aH_b), 1.50-1.15 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 201.67 (CHO), 165.94 (d, $^1J_{CF}$ = 254.2 Hz, C_{arom}-F), 165.18 (COO), 132.27 (d, $^3J_{CF}$ = 9.3 Hz, C_{arom}-H), 126.59 (d, $^4J_{CF}$ = 2.8 Hz, *C*$_{arom}$-C), 115.69 (d, $^2J_{CF}$ = 22.0 Hz, C_{arom}-H), 77.41 (C_1), 47.67 (*C*H_2CHO), 37.53 (C_2), 31.96 (C_6), 31.71 (C_3), 25.20 (C_4), 24.57 (C_5). ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.61. IR (ATR): 1713 (C=O st), 1702 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (100, 4-$FC_6H_4CO^+$), 96 (20), 95 (21), 83 (22), 81 (15). HRMS: Calculated for $[C_{15}H_{18}O_3F]^+$: 265.1240 [$(M+H)^+$]; found: 265.1255. M.p. (petroleum ether/EtOAc): 106-109 °C. The ee (91%) was determined on compound **6c**. $[\alpha]_D^{20}$: +30.9 (*c* = 1.0, CH_2Cl_2).



4d

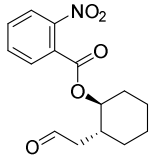
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 4-methylbenzoate (**4d**). Following the *General Procedure F*, **4d** (29.3 mg, 0.11 mmol) was isolated as a white solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 4-methylbenzoic acid **2d** (102.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 45%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.8 Hz, 1H, CHO), 7.89 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 7.22 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 4.73 (td, *J* = 9.9, 4.4 Hz, 1H, C_1-H), 2.66-2.52 (m, 1H, C*H*$_a$H$_b$CHO), 2.39 (s, 3H, CH_3), 2.33-2.21 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.20-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 1.96-1.86 (m, 1H, C_3-*H*$_a$H$_b$), 1.86-1.77 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-1.66 (m, 1H, C_4-*H*$_a$H$_b$), 1.47-1.14 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.84 (CHO), 166.18 (COO), 143.81 (C_{arom}-CH_3), 129.73 (C_{arom}-H), 129.22 (C_{arom}-H), 127.59 (*C*$_{arom}$-CO), 76.89 (C_1), 47.60 (*C*H_2CHO), 37.60 (C_2), 31.95 (C_6), 31.67 (C_3), 25.21 (C_4), 24.56 (C_5), 21.74 (CH_3). IR (ATR): 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 137 (25), 136 (17), 119 (100, 4-$MeC_6H_4CO^+$), 96 (47), 95 (20), 91 (69), 83 (19), 81 (32), 79 (20), 67 (22). HRMS: Calculated for $[C_{16}H_{21}O_3]^+$: 261.1491 [$(M+H)^+$]; found: 261.1498. M.p. (petroleum ether/EtOAc): 28-30 °C. The ee (93%) was determined on compound **6d**. $[\alpha]_D^{20}$: +50.3 (*c* = 1.0, CH_2Cl_2).



4e

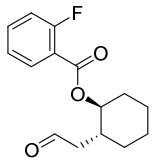
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 4-methoxybenzoate (**4e**). Following the *General Procedure F*, **4e** (12.4 mg, 0.05 mmol) was isolated as a yellow oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 4-methoxybenzoic acid **2e** (114.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 18%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.8 Hz, 1H, CHO), 7.95 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.9 Hz, 2H, C_{arom}-H), 4.72 (td, *J* = 9.9, 4.4 Hz, 1H, C_1-H), 3.85 (s, 3H, CH_3), 2.70-2.48 (m, 1H, C*H*$_a$H$_b$CHO), 2.40-2.21 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.20-2.07 (m, 1H, C_6-*H*$_a$H$_b$), 1.91 (dt, *J* = 12.9, 2.7 Hz, 1H, C_3-

H_aH_b), 1.86-1.77 (m, 1H, C_5-H_aH_b), 1.76-1.65 (m, 1H, C_4-H_aH_b), 1.51-1.11 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.71 (CHO), 165.70 (COO), 163.39 (C_{arom}-O), 131.58 (C_{arom}-H), 122.59 (C_{arom}-C), 113.61 (C_{arom}-H), 76.63 (C_1), 55.40 (CH_3), 47.50 (CH_2CHO), 37.51 (C_2), 31.86 (C_6), 31.57 (C_3), 25.09 (C_4), 24.47 (C_5). IR (ATR): 1709 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (20), 153 (31), 152 (100), 135 (92, 4-$MeOC_6H_4CO^+$), 83 (17), 81 (20), 77 (25). HRMS: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[(M+H)^+]$; found: 277.1446. The ee (92%) was determined on compound **6e**. $[\alpha]_D^{20}$: +3.8 (*c* = 0.8, CH_2Cl_2).



4f

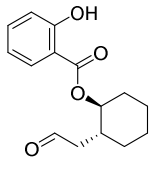
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-nitrobenzoate (**4f**). Following the *General Procedure F*, **4f** (87.0 mg, 0.20 mmol) was isolated as an orange solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, *J* = 2.0 Hz, 1H, CHO), 7.90 (d, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.70-7.64 (m, 2H, C_{arom}-H), 7.65-7.57 (m, 1H, C_{arom}-H), 4.76 (td, *J* = 10.1, 4.5 Hz, 1H, C_1-H), 2.60 (ddd, *J* = 16.5, 5.1, 2.2 Hz, 1H, CH_aH_bCHO), 2.36-2.10 (m, 3H, C_2-H, C_6-H_aH_b, CH_aH_bCHO), 1.95-1.75 (m, 2H, C_3-H_aH_b, C_5-H_aH_b), 1.72-1.62 (m, 1H, C_4-H_aH_b), 1.46-1.09 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.71 (CHO), 165.10 (COO), 147.80 (C_{arom}-N), 133.18 (C_{arom}-H), 131.68 (C_{arom}-H), 129.74 (C_{arom}-H), 128.07 (C_{arom}-C), 123.96 (C_{arom}-H), 78.94 (C_1), 47.51 (CH_2CHO), 36.99 (C_2), 31.60 (C_6), 31.13 (C_3), 24.98 (C_4), 24.39 (C_5). IR (ATR): 1720 (C=O st), 1533 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 151 (100), 150 (53, 2-$NO_2C_6H_4CO^+$), 124 (22), 121 (44), 96 (18), 95 (36), 93 (20), 81 (71), 80 (29), 79 (34), 77 (21), 76 (28), 67 (44), 65 (21). HRMS: Calculated for $[C_{15}H_{18}NO_5]^+$: 292.1185 $[(M+H)^+]$; found: 292.1189. M.p. (petroleum ether/EtOAc): 44-45 °C. The ee (92%) was determined on compound **6f**. $[\alpha]_D^{20}$: +27.8 (*c* = 1.0, CH_2Cl_2).



4g

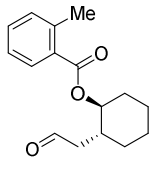
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-fluorobenzoate (**4g**). Following the *General Procedure F*, **4g** (49.6 mg, 0.19 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-fluorobenzoic acid **2g** (105.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.0 Hz, 1H, CHO), 7.88 (td, *J* = 7.6, 1.9 Hz, 1H, C_{arom}-H), 7.56-7.44 (m, 1H, C_{arom}-H), 7.23-7.05 (m, 2H, C_{arom}-H), 4.76 (td, *J* = 9.8, 4.4 Hz, 1H, C_1-H), 2.71-2.57 (m, 1H, CH_aH_bCHO), 2.35-2.23 (m, 2H, C_2-H, CH_aH_bCHO), 2.23-2.14 (m, 1H, C_6-H_aH_b), 1.98-1.86 (m, 1H, C_3-H_aH_b), 1.86-1.76 (m,

1H, C_5-H_aH_b), 1.76-1.65 (m, 1H, C_4-H_aH_b), 1.51-1.10 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.85 (CHO), 164.07 (d, $^3J_{CF}$ = 3.5 Hz, COO), 162.02 (d, $^1J_{CF}$ = 259.7 Hz, C_{arom}-F), 134.59 (d, $^3J_{CF}$ = 9.0 Hz, C_{arom}-H), 132.17 (C_{arom}-H), 124.10 (d, $^3J_{CF}$ = 3.9 Hz, C_{arom}-H), 118.98 (d, $^2J_{CF}$ = 9.9 Hz, C_{arom}-C), 117.10 (d, $^2J_{CF}$ = 22.5 Hz, C_{arom}-H), 77.57 (C_1), 47.48 (CH_2CHO), 37.33 (C_2), 31.81 (C_6), 31.53 (C_3), 25.11 (C_4), 24.50 (C_5). ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.22. IR (ATR): 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 141 (21), 123 (100, 2-$FC_6H_4CO^+$), 96 (17), 95 (33), 81 (21), 67 (15). HRMS: Calculated for $[C_{15}H_{18}O_3F]^+$: 265.1240 [$(M+H)^+$]; found: 265.1245. The ee (95%) was determined on compound **6g**. $[\alpha]_D^{20}$: +39.2 (*c* = 1.0, CH_2Cl_2).



4h

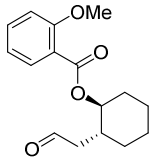
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-hydroxybenzoate (**4h**). Following the *General Procedure F*, **4h** (51.8 mg, 0.20 mmol) was isolated as a white solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-hydroxybenzoic acid **2h** (103.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.79 (s, 1H, OH), 9.75 (t, *J* = 1.7 Hz, 1H, CHO), 7.77 (dd, *J* = 8.0, 1.7 Hz, 1H, C_{arom}-H), 7.51-7.40 (m, 1H, C_{arom}-H), 6.97 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.94-6.82 (m, 1H, C_{arom}-H), 4.78 (td, *J* = 9.9, 4.2 Hz, 1H, C_1-H), 2.67-2.53 (m, 1H, CH_aH_bCHO), 2.39-2.23 (m, 2H, C_2-H, CH_aH_bCHO), 2.22-2.12 (m, 1H, C_6-H_aH_b), 1.99-1.88 (m, 1H, C_3-H_aH_b), 1.88-1.79 (m, 1H, C_5-H_aH_b), 1.79-1.66 (m, 1H, C_4-H_aH_b), 1.52-1.16 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.38 (CHO), 169.79 (COO), 161.92 (C_{arom}-O), 135.90 (C_{arom}-H), 129.87 (C_{arom}-H), 119.31 (C_{arom}-H), 117.73 (C_{arom}-H), 112.51 (C_{arom}-C), 77.76 (C_1), 47.42 (CH_2CHO), 37.24 (C_2), 31.79 (C_6), 31.53 (C_3), 25.05 (C_4), 24.47 (C_5). IR (ATR): 3141 (OH st), 1670 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (26), 138 (31), 125 (68), 121 (59, 2-$OHC_6H_4CO^+$), 120 (100, $C_7H_4O_2^{2+}$), 107 (22), 95 (29), 92 (18), 85 (21), 83 (36), 81 (88), 80 (24), 79 (40), 67 (22), 65 (15), 55 (22). HRMS: Calculated for $[C_{15}H_{18}O_4Na]^+$: 285.1103 [$(M+Na)^+$]; found: 285.1115. M.p. (petroleum ether/EtOAc): 95-97 °C. The ee (95%) was determined on compound **6h**. $[\alpha]_D^{20}$: +43.1 (*c* = 1.0, CH_2Cl_2).



4i

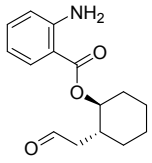
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-methylbenzoate (**4i**). Following the *General Procedure F*, **4i** (28.6 mg, 0.11 mmol) was isolated as a light blue oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-methylbenzoic acid **2i** (102.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 44%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.86 (dd, *J* = 8.1, 1.5 Hz, 1H, C_{arom}-H), 7.39 (td, *J* = 7.4, 1.5 Hz, 1H, C_{arom}-H), 7.30-7.18 (m, 2H, C_{arom}-H),

4.76 (td, *J* = 9.9, 4.4 Hz, 1H, C_1-H), 2.67-2.56 (m, 4H, CH_3, C*H*$_a$H$_b$CHO), 2.36-2.24 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.22-2.12 (m, 1H, C_6-*H*$_a$H$_b$), 1.99-1.88 (m, 1H, C_3-*H*$_a$H$_b$), 1.87-1.78 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-1.63 (m, 1H, C_4-*H*$_a$H$_b$), 1.50-1.15 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.81 (CHO), 167.10 (COO), 140.35 (*C*$_{arom}$-CH_3), 132.12 (C_{arom}-H), 131.87 (C_{arom}-H), 130.49 (C_{arom}-H), 129.74 (*C*$_{arom}$-CO), 125.87 (C_{arom}-H), 76.64 (C_1), 47.51 (*C*H_2CHO), 37.47 (C_2), 32.02 (C_6), 31.61 (C_3), 25.16 (C_4), 24.58 (C_5), 21.92 (CH_3). IR (ATR): 1713 (C=O st), 1702 (C=O st) cm^{-1}. MS (EI) m/z (%): 136 (33), 125 (71), 124 (16), 119 (100, 2-Me$C_6H_4CO^+$), 118 (70), 107 (18), 96 (24), 95 (32), 91 (98), 90 (15), 85 (17), 83 (30), 82 (15), 81 (81), 80 (28), 79 (38), 77 (26), 67 (41), 65 (27), 55 (23), 53 (21), 51 (15). HRMS: Calculated for $[C_{16}H_{20}O_3Na]^+$: 283.1310 [(M+Na)$^+$]; found: 283.1316. The ee (93%) was determined on compound **6i**. $[\alpha]_D^{20}$: +50.9 (*c* = 1.0, CH_2Cl_2).



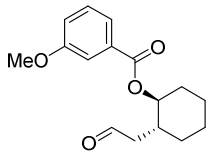
4j

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-methoxybenzoate (**4j**). Following the *General Procedure F*, **4j** (22.8 mg, 0.08 mmol) was isolated as a white solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-methoxybenzoic acid **2j** (114.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 33%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.6 Hz, 1H, CHO), 7.72 (dd, *J* = 8.0, 1.8 Hz, 1H, C_{arom}-H), 7.45 (td, *J* = 7.9, 1.8 Hz, 1H, C_{arom}-H), 7.02-6.92 (m, 2H, C_{arom}-H), 4.75 (td, *J* = 9.9, 4.5 Hz, 1H, C_1-H), 3.87 (s, 3H, CH_3), 2.79-2.65 (m, 1H, C*H*$_a$H$_b$CHO), 2.34-2.13 (m, 3H, C_2-H, C_6-*H*$_a$H$_b$, CH$_a$*H*$_b$CHO), 1.92 (dt, *J* = 13.0, 2.8 Hz, 1H, C_3-*H*$_a$H$_b$), 1.86-1.76 (m, 1H, C_5-*H*$_a$H$_b$), 1.76-1.64 (m, 1H, C_4-*H*$_a$H$_b$), 1.48-1.10 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.20 (CHO), 166.03 (COO), 159.14 (C_{arom}-O), 135.55 (C_{arom}-H), 131.48 (C_{arom}-H), 120.54 (*C*$_{arom}$-C), 120.30 (C_{arom}-H), 112.13 (C_{arom}-H), 76.78 (C_1), 55.98 (CH_3), 47.40 (*C*H_2CHO), 37.49 (C_2), 31.92 (C_6), 31.60 (C_3), 25.20 (C_4), 24.58 (C_5). IR (ATR): 1695 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (28), 153 (28), 152 (17), 135 (100, 2-Me$OC_6H_4CO^+$), 123 (17), 85 (25), 83 (32), 81 (15), 77 (20). HRMS: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 [(M+H)$^+$]; found: 277.1447. M.p. (petroleum ether/EtOAc): 69-75 ^{o}C. The ee (91%) was determined on compound **6j**. $[\alpha]_D^{20}$: +56.7 (*c* = 0.9, CH_2Cl_2).



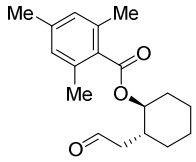
4k

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-aminobenzoate (**4k**). Following the *General Procedure F*, **4k** (6.5 mg, 0.03 mmol) was isolated as a yellow oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-aminobenzoic acid **2k** (102.9 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 10%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1H, CHO), 7.85-7.72 (m, 1H, C_{arom}-H), 7.35-7.19 (m, 1H, C_{arom}-H), 6.73-6.58 (m, 2H, C_{arom}-H), 5.73 (s, 2H, NH_2), 4.72 (td, *J* = 9.9, 4.5 Hz, 1H, C_1-H), 2.71-2.54 (m, 1H, C*H*$_a$H$_b$CHO), 2.35-2.21 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.20-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 1.99-1.87 (m, 1H, C_3-*H*$_a$H$_b$), 1.87-1.77 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-1.65 (m, 1H, C_4-*H*$_a$H$_b$), 1.47-1.17 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.91 (CHO), 167.67 (COO), 150.81 (C_{arom}-N), 134.33 (C_{arom}-H), 131.20 (C_{arom}-H), 116.87 (C_{arom}-H), 116.45 (C_{arom}-H), 110.85 (*C*$_{arom}$-C), 76.26 (C_1), 47.55 (*C*H$_2$CHO), 37.57 (C_2), 32.08 (C_6), 31.67 (C_3), 25.23 (C_4), 24.62 (C_5). IR (ATR): 3483 (NH_2 st), 3350 (NH_2 st), 1681 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (48), 137 (100, 2-$NH_3C_6H_4COO^{2+}$), 120 (27, 2-$NH_2C_6H_4CO^+$), 119 (97), 92 (15), 85 (34), 83 (58), 81 (25). HRMS: Calculated for $[C_{15}H_{20}NO_3]^+$: 262.1443 [(M+H)$^+$]; found: 262.1455. The ee (74%) was determined on compound **6k**. $[\alpha]_D^{20}$: +23.1 (*c* = 0.4, CH_2Cl_2).



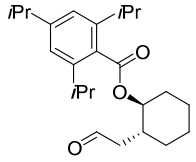
4l

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 3-methoxybenzoate (**4l**). Following the *General Procedure F*, **4l** (49.7 mg, 0.18 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 3-methoxybenzoic acid **2l** (114.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 1H, CHO), 7.59 (d, *J* = 8.0 Hz, 1H, C_{arom}-H), 7.55-7.49 (m, 1H, C_{arom}-H), 7.34 (t, *J* = 8.0 Hz, 1H, C_{arom}-H), 7.10 (dd, *J* = 8.2, 2.6 Hz, 1H, C_{arom}-H), 4.74 (td, *J* = 9.9, 4.5 Hz, 1H, C_1-H), 3.85 (s, 3H, CH_3), 2.68-2.53 (m, 1H, C*H*$_a$H$_b$CHO), 2.38-2.22 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.22-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 2.00-1.87 (m, 1H, C_3-*H*$_a$H$_b$), 1.86-1.78 (m, 1H, C_5-*H*$_a$H$_b$), 1.76-1.67 (m, 1H, C_4-*H*$_a$H$_b$), 1.51-1.13 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.76 (CHO), 166.00 (COO), 159.72 (C_{arom}-O), 131.67 (*C*$_{arom}$-C), 129.56 (C_{arom}-H), 122.09 (C_{arom}-H), 119.58 (C_{arom}-H), 114.29 (C_{arom}-H), 77.32 (C_1), 55.59 (CH_3), 47.63 (*C*H$_2$CHO), 37.56 (C_2), 31.92 (C_6), 31.70 (C_3), 25.22 (C_4), 24.58 (C_5). IR (ATR): 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (18), 152 (93), 135 (100, 3-$MeOC_6H_4CO^+$), 81 (25), 79 (31), 77 (23). HRMS: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 [(M+H)$^+$]; found: 277.1443. The ee (92%) was determined on compound **6l**. $[\alpha]_D^{20}$: +21.6 (*c* = 1.0, CH_2Cl_2).



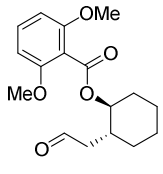
4m

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2,4,6-trimethylbenzoate (**4m**). Following the *General Procedure F*, **4m** (53.4 mg, 0.19 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2,4,6-trimethylbenzoic acid **2m** (123.2 mg, 0.75 mmol) in the presence of catalyst **3j**(36.1 mg, 0.05 mmol). Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, *J* = 2.0 Hz, 1H, CHO), 6.85 (s, 2H, C_{arom}-H), 4.78 (td, *J* = 10.0, 4.2 Hz, 1H, C_1-H), 2.73-2.59 (m, 1H, C*H*$_a$H$_b$CHO), 2.36-2.12 (m, 12H, C_2-H, C_6-*H*$_a$H$_b$, CH$_a$*H*$_b$CHO, CH_3 × 3), 1.92 (dt, *J* = 12.9, 2.8 Hz, 1H, C_3-*H*$_a$H$_b$), 1.87-1.77 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-1.66 (m, 1H, C_4-*H*$_a$H$_b$), 1.53-1.09 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.77 (CHO), 169.94 (COO), 139.40 (*C*$_{arom}$-CH_3), 134.78 (*C*$_{arom}$-CH_3), 131.24 (*C*$_{arom}$-CO), 128.57 (C_{arom}-H), 77.09 (C_1), 47.15 (*C*H$_2$CHO), 37.15 (C_2), 31.96 (C_6), 31.46 (C_3), 25.12 (C_4), 24.59 (C_5), 21.24 (CH_3), 19.91 (CH3 x 2). IR (ATR): 1716 (C=O st) cm^{-1}. MS (EI) m/z (%):164 (35), 147 (96, 2,4,6-(Me)$_3$C$_6$H$_4$CO$^+$), 146 (100), 125 (22), 119 (27), 91 (19), 81 (43), 79 (21), 77 (21), 67 (16). HRMS: Calculated for [$C_{18}H_{25}O_3$]$^+$: 289.1804 [(M+H)$^+$]; found: 289.1804. The ee (93%) was determined on compound **6m**. [α]$_D^{20}$: +25.8 (*c* = 1.0, CH_2Cl_2).



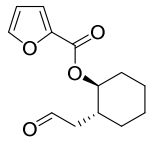
4n

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2,4,6-triisopropylbenzoate (**4n**)**.** Following the *General Procedure F*, **4n** (78.2 mg, 0.21 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2,4,6-triisopropylbenzoic acid **2n** (186.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74-9.71 (m, 1H, CHO), 7.01 (s, 2H, C_{arom}-H), 4.78 (td, *J* = 10.2, 4.3 Hz, 1H, C_1-H), 2.96-2.79 (m, 3H, C*H*(CH$_3$)$_2$ × 3), 2.70 (dd, *J* = 16.5, 3.1 Hz, 1H, C*H*$_a$H$_b$CHO), 2.40-2.25 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.24-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 1.99-1.87 (m, 1H, C_3-*H*$_a$H$_b$), 1.87-1.77 (m, 1H, C_5-*H*$_a$H$_b$), 1.77-1.66 (m, 1H, C_4-*H*$_a$H$_b$), 1.51-1.18 (m, 22H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH_3 × 6). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.65 (CHO), 170.58 (COO), 150.30 (*C*$_{arom}$-CH), 144.67 (*C*$_{arom}$-CH), 130.52 (*C*$_{arom}$-CO), 121.04 (C_{arom}-H), 77.12 (C_1), 46.88 (*C*H$_2$CHO), 36.92 (C_2), 34.54 (*C*H(CH$_3$)$_2$), 31.71 (C_6), 31.61 (*C*H(CH$_3$)$_2$ x 2), 31.37 (C_3), 25.04 (C_4), 24.60 (CH_3), 24.57 (C_5), 24.17 (CH_3), 24.08 (CH_3), 24.06 (CH_3). IR (ATR): 1716 (C=O st), 1695 (C=O) cm^{-1}. MS (EI) m/z (%): 281 (25), 252 (18), 248 (20), 247 (42), 233 (63), 231 (90, 2,4,6-(*i*Pr)$_3$C$_6$H$_4$CO$^+$), 230 (78), 229 (17), 207 (74), 205 (16), 125 (100), 107 (44), 85 (41), 83 (67), 81 (52), 79 (16). HRMS: Calculated for [$C_{24}H_{36}O_3Na$]$^+$: 395.2562 [(M+Na)$^+$]; found: 395.2553. The ee (91%) was determined on compound **6n**. [α]$_D^{20}$: -5.0 (*c* = 1.0, CH_2Cl_2).



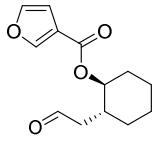
4o

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2,6-dimethoxybenzoate (**4o**). Following the *General Procedure F*, **4o** (62.0 mg, 0.20 mmol) was isolated as a white solid, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2,6-dimethoxybenzoic acid **2o** (136.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (dd, *J* = 2.6, 1.3 Hz, 1H, CHO), 7.27 (t, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.55 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 4.81 (td, *J* = 10.3, 4.4 Hz, 1H, C_1-H), 3.79 (s, 6H, CH_3 × 2), 2.86 (ddd, *J* = 16.7, 3.7, 1.3 Hz, 1H, C*H*$_a$H$_b$CHO), 2.36-2.08 (m, 3H, C_2-H, C_6-*H*$_a$H$_b$, CH$_a$*H*$_b$CHO), 1.95-1.85 (m, 1H, C_3-*H*$_a$H$_b$), 1.86-1.76 (m, 1H, C_5-*H*$_a$H$_b$), 1.76-1.63 (m, 1H, C_4-*H*$_a$H$_b$), 1.49-1.06 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.59 (CHO), 166.31 (COO), 157.21 (C_{arom}-O), 131.10 (C_{arom}-H), 113.54 (*C*$_{arom}$-C), 104.08 (C_{arom}-H), 76.95 (C_1), 56.03 (CH_3 x 2), 46.97 (*C*H$_2$CHO), 37.50 (C_2), 32.01 (C_6), 31.63 (C_3), 25.27 (C_4), 24.68 (C_5). IR (ATR): 1720 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (23), 183 (22), 182 (17), 165 (100, 2,6-(MeO)$_2$C$_6$H$_4$CO$^+$), 83 (21). HRMS: Calculated for [$C_{15}H_{23}O_5$]$^+$: 307.1546 [(M+H)$^+$]; found: 307.1550. M.p. (petroleum ether/EtOAc): 86-87 °C. The ee (89%) was determined on compound **6o**. [α]$_D^{20}$: -45.1 (*c* = 1.0, CH_2Cl_2).



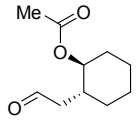
4p

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl furan-2-carboxylate (**4p**). Following the *General Procedure F*, **4p** (33.7 mg, 0.14 mmol) was isolated as a yellow oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 2-furoic acid **2p** (84.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.56 (dd, *J* = 1.7, 0.8 Hz, 1H, C_{arom}-H), 7.13 (dd, *J* = 3.5, 0.8 Hz, 1H, C_{arom}-H), 6.49 (dd, *J* = 3.5, 1.7 Hz, 1H, C_{arom}-H), 4.70 (td, *J* = 10.0, 4.5 Hz, 1H, C_1-H), 2.64-2.51 (m, 1H, C*H*$_a$H$_b$CHO), 2.34-2.20 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.20-2.10 (m, 1H, C_6-*H*$_a$H$_b$), 1.96-1.84 (m, 1H, C_3-*H*$_a$H$_b$), 1.84-1.76 (m, 1H, C_5-*H*$_a$H$_b$), 1.76-1.64 (m, 1H, C_4-*H*$_a$H$_b$), 1.48-1.09 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.71 (CHO), 158.30 (COO), 146.53 (C_{arom}-H), 144.70 (*C*$_{arom}$-C), 118.16 (C_{arom}-H), 111.98 (C_{arom}-H), 77.37 (C_1), 47.57 (*C*H$_2$CHO), 37.56 (C_2), 31.93 (C_6), 31.66 (C_3), 25.17 (C_4), 24.54 (C_5). IR (ATR): 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 113 (27), 96 (34), 95 (100, (furan-2-yl)CO$^+$), 85 (22), 83 (41), 81 (23), 79 (15), 67 (17). HRMS: Calculated for [$C_{13}H_{17}O_4$]$^+$: 237.1127 [(M+H)$^+$]; found: 237.1133. The ee (92%) was determined on compound **6p**. [α]$_D^{20}$: +42.8 (*c* = 1.0, CH_2Cl_2).



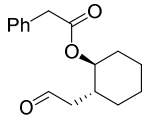
4q

(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl furan-3-carboxylate (**4q**). Following the *General Procedure F*, **4q** (27.2 mg, 0.12 mmol) was isolated as a yellow oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and 3-furoic acid **2q** (84.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 46%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.97 (s, 1H, C_{arom}-H), 7.52-7.33 (m, 1H, C_{arom}-H), 6.70 (d, *J* = 1.8 Hz, 1H, C_{arom}-H), 4.66 (td, *J* = 10.0, 4.5 Hz, 1H, C_1-H), 2.66-2.47 (m, 1H, C*H*$_a$H$_b$CHO), 2.33-2.18 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.17-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 1.95-1.85 (m, 1H, C_3-*H*$_a$H$_b$), 1.84-1.76 (m, 1H, C_5-*H*$_a$H$_b$), 1.75-1.63 (m, 1H, C_4-*H*$_a$H$_b$), 1.45-1.09 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.70 (CHO), 162.67 (COO), 147.91 (C_{arom}-H), 143.88 (C_{arom}-H), 119.55 (*C*$_{arom}$-C), 109.92 (C_{arom}-H), 76.87 (C_1), 47.72 (*C*H$_2$CHO), 37.61 (C_2), 31.96 (C_6), 31.75 (C_3), 25.23 (C_4), 24.55 (C_5). IR (ATR): 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 96 (28), 95 (100, (furan-3-yl)CO$^+$), 85 (25), 83 (46), 81 (26), 67 (18). HRMS: Calculated for [$C_{13}H_{17}O_4$]$^+$: 237.1127 [(M+H)$^+$]; found: 237.1136. The ee (89%) was determined on compound **6q**. $[\alpha]_D^{20}$: +40.5 (*c* = 1.0, CH_2Cl_2).



4r

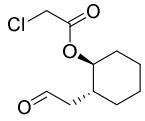
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl acetate (**4r**). Following the *General Procedure F*, **4r** was synthesized starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and acetic acid **2r** (42.9 µL, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Due to stability/purification issues, this aldehyde was not isolated and a reduction was carried out *in situ*. The ee (90%) was determined on compound **8a**.



4s

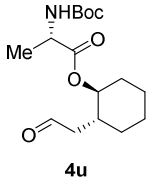
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-phenylacetate (**4s**). Following the *General Procedure F*, **4s** (51.4 mg, 0.20 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and phenylacetic acid **2s** (102.1 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (t, *J* = 2.0 Hz, 1H, CHO), 7.43-7.17 (m, 5H, C_{arom}-H), 4.48 (td, *J* = 9.8, 4.4 Hz, 1H, C_1-H), 3.57 (s, 2H, CH_2C_{arom}), 2.42-2.26 (m, 1H, C*H*$_a$H$_b$CHO), 2.21-1.95 (m, 3H, C_2-H, C_6-*H*$_a$H$_b$, CH$_a$*H*$_b$CHO), 1.90-1.71 (m, 2H, C_3-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$), 1.71-1.59 (m, 1H, C_4-*H*$_a$H$_b$), 1.40-1.01 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.81 (CHO), 171.22 (COO), 134.17 (*C*$_{arom}$-C), 129.33 (C_{arom}-H), 128.68 (C_{arom}-H), 127.23 (C_{arom}-H), 77.01 (C_1), 47.56 (*C*H$_2$CHO), 41.76 (*C*H$_2$C$_{arom}$), 37.34 (C_2), 31.78 (C_6), 31.63 (C_3), 25.15 (C_4), 24.46 (C_5). IR (ATR): 1727 (C=O st), 1702 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (23), 125 (17), 118 (15), 96 (19), 91 (100, PhCH$_2^+$),

85 (56), 83 (85), 81 (81), 79 (34). HRMS: Calculated for $[C_{16}H_{21}O_3]^+$: 261.1491 $[(M+H)^+]$; found: 261.1498. The ee (91%) was determined on compound **6s**. $[\alpha]_D^{20}$: +7.9 (*c* = 1.0, CH_2Cl_2).



4t

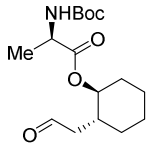
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl 2-chloroacetate (**4t**). Following the *General Procedure F*, **4t** (39.9 mg, 0.18 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and chloroacetic acid **2t** (70.9 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, *J* = 2.1 Hz, 1H, CHO), 4.57 (td, *J* = 10.1, 4.6 Hz, 1H, C_1-H), 4.00 (s, 2H, CH_2Cl), 2.50 (ddd, *J* = 16.1, 5.6, 2.6 Hz, 1H, C*H*$_a$H$_b$CHO), 2.34-2.13 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.13-2.02 (m, 1H, C_6-*H*$_a$H$_b$), 1.94-1.83 (m, 1H, C_3-*H*$_a$H$_b$), 1.83-1.76 (m, 1H, C_5-*H*$_a$H$_b$), 1.74-1.64 (m, 1H, C_4-*H*$_a$H$_b$), 1.43-1.11 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.55 (CHO), 166.96 (COO), 78.94 (C_1), 47.73 (*C*H$_2$CHO), 41.08 (CH_2Cl), 37.28 (C_2), 31.68 (C_6), 31.64 (C_3), 25.07 (C_4), 24.44 (C_5). IR (ATR): 1745 (C=O st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 85 (63), 83 (100). HRMS: Calculated for $[C_{10}H_{19}NO_3Cl]^+$: 236.1053 $[(M+NH_4)^+]$; found: 236.1053. The ee (87%) was determined on compound **8b**. $[\alpha]_D^{20}$: +42.2 (*c* = 1.0, CH_2Cl_2).



4u

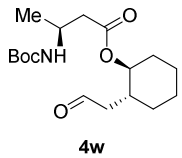
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl (*tert*-butoxycarbonyl)-L-alanitate (**4u**). Following the *General Procedure F*, **4u** (52.5 mg, 0.17 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and *N*-(*tert*-butoxycarbonyl)-L-alanine **2u** (71.0 mg, 0.38 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 67%. d.r. 11:1. ^{1}H NMR (500 MHz, DMSO-d_6) (* indicates minor diastereoisomer resonances) δ 9.64* (t, *J* = 2.0 Hz, 1H, CHO), 9.63 (t, *J* = 2.0 Hz, 1H, CHO), 7.10 (s, 1H, NH), 4.43 (td, *J* = 9.9, 4.5 Hz, 1H, C_1-H), 3.98-3.85 (m, 1H, CHN), 2.45 (ddd, *J* = 16.9, 4.5, 1.9 Hz, 1H, C*H*$_a$H$_b$CHO), 2.22 (ddd, *J* = 16.8, 8.1, 2.2 Hz, 1H, CH$_a$*H*$_b$CHO), 2.07-1.97 (m, 1H, C_2-H), 1.94-1.82 (m, 1H, C_6-*H*$_a$H$_b$), 1.79-1.73 (m, 1H, C_3-*H*$_a$H$_b$), 1.73-1.64 (m, 1H, C_5-*H*$_a$H$_b$), 1.60-1.53 (m, 1H, C_4-*H*$_a$H$_b$), 1.36 (s, 9H, CCH_3 × 3), 1.32-1.08 (m, 7H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CHC*H*$_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 202.32 (CHO), 172.37 (NCO), 155.05 (COO), 77.93 (CCH_3), 75.68 (C_1), 49.20 (CHN), 45.93 (*C*H$_2$CHO), 36.35 (C_2), 30.92 (C_6), 30.16 (C_3), 27.98 (C*C*H$_3$ × 3), 24.20 (C_4), 23.57 (C_5), 16.53 (CH*C*H$_3$). IR (ATR): 3361 (NH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 144 (25, $CH_3CH(NHBoc)CO^+$), 124 (30), 95 (29), 91 (16), 88 (40), 82 (21), 81 (100), 80 (17), 79 (34), 77 (15), 70 (19), 68 (20), 67 (43), 59 (23), 57 (100),

56 (72), 55 (72), 54 (17). HRMS: Calculated for $[C_{17}H_{31}NO_6Na]^+$: 368.2049 $[(M+CH_3OH+Na)^+]$; found: 368.2053. $[\alpha]_D^{20}$: +9.7 (*c* = 1.0, CH_2Cl_2).



4v

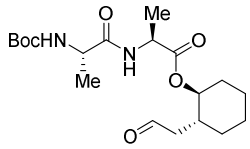
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl (*tert*-butoxycarbonyl)-D-alanitate (**4v**). Following the *General Procedure F*, **4v** (68.9 mg, 0.22 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and *N*-(*tert*-butoxycarbonyl)-D-alanine ***ent*-2u** (71.0 mg, 0.38 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 88%. d.r. 11:1. ^{1}H NMR (500 MHz, DMSO-d_6) (* indicates minor diastereoisomer resonances) δ 9.64 (t, *J* = 2.0 Hz, 1H, CHO), 9.63* (t, *J* = 2.0 Hz, 1H, CHO), 7.07 (s, 1H, NH), 4.44 (td, *J* = 9.9, 4.3 Hz, 1H, C_1-H), 4.00-3.87 (m, 1H, CHN), 2.52-2.49 (m, 1H, CH_aH$_b$CHO), 2.23 (ddd, *J* = 16.8, 8.0, 2.2 Hz, 1H, CH$_a$*H*$_b$CHO), 2.08-1.97 (m, 1H, C_2-H), 1.92-1.81 (m, 1H, C_6-*H*$_a$H$_b$), 1.78-1.73 (m, 1H, C_3-*H*$_a$H$_b$), 1.73-1.64 (m, 1H, C_5-*H*$_a$H$_b$), 1.60-1.53 (m, 1H, C_4-*H*$_a$H$_b$), 1.36 (s, 9H, CCH_3 × 3), 1.33-1.09 (m, 7H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CHC*H*$_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 202.34 (CHO), 172.36 (NCO), 155.05 (COO), 77.94 (*C*CH$_3$), 75.63 (C_1), 49.11 (CHN), 45.91 (*C*H$_2$CHO), 36.50 (C_2), 30.80 (C_6), 30.14 (C_3), 27.97 (C*C*H$_3$ x 3), 24.20 (C_4), 23.54 (C_5), 16.49 (CH*C*H$_3$). IR (ATR): 3372 (NH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 252 (19), 250 (15), 144 (52, $CH_3CH(NHBoc)CO^+$), 124 (20), 96 (15), 94 (27), 88 (47), 82 (20), 81 (79), 80 (33), 79 (24), 77 (16), 70 (29), 68 (16), 67 (52), 59 (32), 57 (77), 56 (88), 55 (100), 54 (25), 53 (21), 51 (15). HRMS: Calculated for $[C_{17}H_{31}NO_6Na]^+$: 368.2049 $[(M+CH_3OH+Na)^+]$; found: 368.2054. $[\alpha]_D^{20}$: +26.3 (*c* = 1.0, CH_2Cl_2).



4w

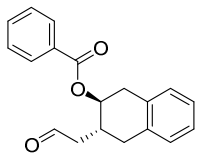
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl (*S*)-3-((*tert*-butoxycarbonyl)amino)butanoate (**4w**). Following the *General Procedure F*, **4w** (49.1 mg, 0.15 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and Boc-L-homoalanine **2v** (77.2 mg, 0.38 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 60%. d.r. 18:1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69-9.57 (m, 1H, CHO), 6.60 (s, 1H, NH), 4.42 (td, *J* = 10.5, 4.4 Hz, 1H, C_1-H), 3.89-3.71 (m, 1H, CHN), 2.46-2.35 (m, 2H, C*H*$_a$H$_b$CHO, C*H*$_a$H$_b$COO), 2.33-2.16 (m, 2H, CH$_a$*H*$_b$CHO, CH$_a$*H*$_b$COO), 2.09-1.98 (m, 1H, C_2-H), 1.93-1.84 (m, 1H, C_6-*H*$_a$H$_b$), 1.80-1.71 (m, 1H, C_3-*H*$_a$H$_b$), 1.71-1.63 (m, 1H, C_5-*H*$_a$H$_b$), 1.62-1.53 (m, 1H, C_4-*H*$_a$H$_b$), 1.40-1.31 (m, 9H, CCH_3 × 3), 1.31-1.07 (m, 4H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$), 1.04 (d, *J* = 6.7 Hz, 1H, CHC*H*$_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ (* indicates minor rotamer resonances) 202.28 (CHO), 172.19* (NCO), 170.10 (NCO), 154.46 (COO), 77.41 (*C*CH$_3$), 75.43 (C_1), 46.42 (*C*H$_2$CHO), 43.26 (CHN), 40.97 (*C*H$_2$COO), 36.51 (C_2),

31.05 (C_6), 30.99 (C_3), 28.10 (CCH_3 x 3), 24.34 (C_4), 23.66 (C_5), 20.37 ($CHCH_3$). IR (ATR): 3310 (NH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 125 (21), 102 (16), 85 (31), 81 (38), 71 (46), 70 (31), 69 (31), 67 (24), 59 (15), 57 (100), 55 (45). HRMS: Calculated for $[C_{17}H_{29}NO_5Na]^+$: 350.1943 [$(M+Na)^+$]; found: 350.1943. $[\alpha]_D^{20}$: +2.7 (*c* = 1.0, CH_2Cl_2).



4x

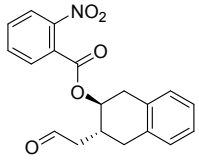
(1*S*,2*R*)-2-(2-Oxoethyl)cyclohexyl (*tert*-butoxycarbonyl)-L-alanyl-L-alanitate (**4x**). Following the *General Procedure F*, **4x** (31.7 mg, 0.08 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1a** (31.0 mg, 0.25 mmol) and N-(*tert*-butoxycarbonyl)-L-alanyl-L-alanine **2w** (98.9 mg, 0.38 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 33%. d.r. 7.5:1. ^{1}H NMR (500 MHz, DMSO-d_6) (* indicates minor diastereoisomer resonances) δ 9.63* (t, *J* = 2.0 Hz, 1H, CHO), 9.60 (t, *J* = 2.0 Hz, 1H, CHO), 8.15 (d, *J* = 6.8 Hz, 1H, NH), 6.82 (d, *J* = 7.8 Hz, 1H, NH), 4.42 (td, *J* = 9.9, 4.2 Hz, 1H, C_1-H), 4.18 (t, *J* = 7.1 Hz, 1H, OCOC*H*NH), 4.02-3.91 (m, 1H, NHCOC*H*), 2.42 (ddd, *J* = 16.7, 4.7, 2.0 Hz, 1H, CH_aH$_b$CHO), 2.21 (ddd, *J* = 16.7, 7.9, 2.2 Hz, 1H, CH$_a$*H*$_b$CHO), 2.07-1.96 (m, 1H, C_2-H), 1.88-1.80 (m, 1H, C_6-*H*$_a$H$_b$), 1.78-1.70 (m, 1H, C_3-*H*$_a$H$_b$), 1.70-1.63 (m, 1H, C_5-*H*$_a$H$_b$), 1.62-1.53 (m, 1H, C_4-*H*$_a$H$_b$), 1.36 (s, 9H, CCH_3 x 3), 1.29-1.04 (m, 10H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CHC*H*$_3$ x 2). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 202.36 (CHO), 172.44 (COO), 171.67 (NH*C*OCHNH), 154.73 (*C*OC(CH$_3$)$_3$), 77.83 (*C*CH$_3$), 75.80 (C_1), 49.12 (OCO*C*HNH), 47.67 (NHCO*C*H), 45.99 (*C*H$_2$CHO), 36.30 (C_2), 30.89 (C_6), 30.19 (C_3), 27.99 (C*C*H$_3$ x 3), 24.21 (C_4), 23.56 (C_5), 17.98 (OCOCH*C*H$_3$), 16.57 (NHCOCH*C*H$_3$). IR (ATR): 3372 (NH st), 1713 (C=O st) cm^{-1}. HRMS: Calculated for $[C_{19}H_{33}N_2O_6]^+$: 385.2339 [$(M+H)^+$]; found: 385.2327. $[\alpha]_D^{20}$: -10.9 (*c* = 1.0, CH_2Cl_2).



5a

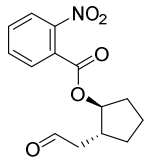
(2*S*,3*R*)-3-(2-Oxoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl benzoate (**5a**). Following the *General Procedure G*, **5a** (28.0 mg, 0.10 mmol) was isolated as a light brown oil, starting from formylcyclopropane **1d** (43.1 mg, 0.25 mmol) and benzoic acid **2a** (91.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 38%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (t, *J* = 1.6 Hz, 1H, CHO), 8.09-7.98 (m, 2H, C_{arom}-H), 7.66-7.53 (m, 1H, C_{arom}-H), 7.53-7.37 (m, 2H, C_{arom}-H), 7.24-7.05 (m, 4H, C_{arom}-H), 5.26 (td, *J* = 8.6, 5.4 Hz, 1H, C_2-H), 3.35 (dd, *J* = 16.5, 5.5 Hz, 1H, C_1-*H*$_a$H$_b$), 3.19 (dd, *J* = 16.2, 4.7 Hz, 1H, C_1-H$_a$*H*$_b$), 3.00 (dd, *J* = 16.6, 8.4 Hz, 1H, C_4-*H*$_a$H$_b$), 2.93-2.69 (m, 3H, C_3-H, C_4-H$_a$*H*$_b$, C*H*$_a$H$_b$CHO), 2.47 (ddd,

J = 17.1, 7.5, 1.7 Hz, 1H, CH_aH_bCHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.03 (CHO), 166.14 (COO), 134.15 (C_{arom}-C), 133.39 (C_{arom}-C), 133.33 (C_{arom}-H), 130.12 (C_{arom}-C), 129.79 (C_{arom}-H), 129.18 (C_{arom}-H), 128.73 (C_{arom}-H), 128.60 (C_{arom}-H), 126.52 (C_{arom}-H), 126.48 (C_{arom}-H), 73.66 (C_2), 46.56 (CH_2CHO), 34.36 (C_1), 34.04 (C_4), 33.59 (C_3). IR (ATR): 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (22), 141 (15), 129 (35), 128 (100), 105 (41, $PhCO^+$), 77 (22). HRMS: Calculated for $[C_{20}H_{22}O_4Na]^+$: 349.1416 [$(M+Na)^+$]; found: 349.1418. The ee (80%) was determined on compound **7a**. $[\alpha]_D^{20}$: +69.3 (*c* = 1.0, CH_2Cl_2).



5b

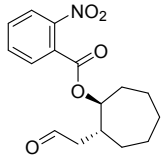
(2*S*,3*R*)-3-(2-Oxoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl 2-nitrobenzoate (**5b**). Following the *General Procedure G*, **5b** (60.2 mg, 0.18 mmol) was isolated as a light brown oil, starting from formylcyclopropane **1d** (43.1 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 71%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7 Hz, 1H, CHO), 8.01-7.87 (m, 1H, C_{arom}-H), 7.75-7.68 (m, 2H, C_{arom}-H), 7.68-7.60 (m, 1H, C_{arom}-H), 7.22-7.00 (m, 4H, C_{arom}-H), 5.28 (td, *J* = 8.4, 5.4 Hz, 1H, C_2-H), 3.39 (dd, *J* = 16.6, 5.4 Hz, 1H, C_1-H_aH_b), 3.17-3.07 (m, 1H, C_1-H_aH_b), 2.99 (dd, *J* = 16.6, 8.3 Hz, 1H, C_4-H_aH_b), 2.81-2.67 (m, 3H, C_3-H, C_4-H_aH_b, CH_aH_bCHO), 2.55-2.41 (m, 1H, CH_aH_bCHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.94 (CHO), 165.20 (COO), 147.79 (C_{arom}-N), 133.94 (C_{arom}-C), 133.29 (C_{arom}-H), 132.95 (C_{arom}-C), 131.81 (C_{arom}-H), 129.77 (C_{arom}-H), 129.15 (C_{arom}-H), 128.62 (C_{arom}-H), 127.96 (C_{arom}-C), 126.56 (C_{arom}-H), 126.50 (C_{arom}-H), 124.08 (C_{arom}-H), 75.45 (C_2), 46.46 (CH_2CHO), 33.81 (C_1), 33.57 (C_4), 33.12 (C_3). IR (ATR): 1716 (C=O st), 1530 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 207 (76), 129 (19), 128 (100), 104 (15), 51 (17). HRMS: Calculated for $[C_{19}H_{21}N_2O_5]^+$: 357.1450 [$(M+NH_4)^+$]; found: 357.1454. The ee (89%) was determined on compound **7b**. $[\alpha]_D^{20}$: +44.8 (*c* = 1.0, CH_2Cl_2).



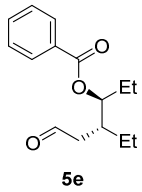
5c

(1*S*,2*R*)-2-(2-Oxoethyl)cyclopentyl 2-nitrobenzoate (**5c**). Following the *General Procedure G*, **5c** (27.7 mg, 0.10 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1b** (27.5 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 40%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7 Hz, 1H, CHO), 7.90 (dd, *J* = 7.8, 1.4 Hz, 1H, C_{arom}-H), 7.79-7.58 (m, 3H, C_{arom}-H), 5.11-5.02 (m, 1H, C_1-H), 2.83-2.69 (m, 1H, CH_aH_bCHO), 2.62-2.41 (m, 2H, C_2-H, CH_aH_bCHO), 2.15-2.01 (m, 2H, C_3-H_aH_b, C_5-H_aH_b), 1.89-1.68 (m, 3H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b), 1.35-1.20 (m, 1H, C_4-H_aH_b). ^{13}C NMR

(75.5 MHz, $CDCl_3$) δ 201.38 (CHO), 165.39 (COO), 148.36 (C_{arom}-N), 133.05 (C_{arom}-H), 131.84 (C_{arom}-H), 130.09 (C_{arom}-H), 127.94 (*C*$_{arom}$-C), 123.98 (C_{arom}-H), 82.95 (C_1), 47.54 (*C*H_2CHO), 39.67 (C_2), 31.16 (C_5), 30.40 (C_3), 22.80 (C_4). IR (ATR): 1724 (C=O st), 1530 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 251 (15), 207 (20), 151 (37), 150 (80, 2-$NO_2C_6H_4CO^+$), 121 (24), 83 (27), 82 (18), 81 (100), 80 (15), 79 (20), 77 (45), 71 (24), 67 (87), 66 (25), 65 (19), 57 (35), 55 (28), 54 (29), 53 (27), 51 (33), 50 (27). HRMS: Calculated for $[C_{15}H_{19}NO_6Na]^+$: 332.1110 [$(M+CH_3OH+Na)^+$]; found: 332.1113. The ee (66%) was determined on compound **7c**. $[\alpha]_D^{20}$: +15.1 (*c* = 0.4, CH_2Cl_2).

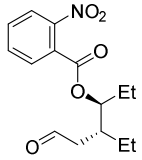

5d

(1*S*,2*R*)-2-(2-Oxoethyl)cycloheptyl 2-nitrobenzoate (**5d**)**.** Following the *General Procedure H*, **5d** (33.6 mg, 0.11 mmol) was isolated as an orange oil, starting from formylcyclopropane **1c** (34.6 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 44%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, *J* = 1.8 Hz, 1H, CHO), 7.90 (dd, *J* = 7.3, 1.4 Hz, 1H, C_{arom}-H), 7.71-7.58 (m, 3H, C_{arom}-H), 4.96 (ddd, *J* = 8.6, 6.7, 3.9 Hz, 1H, C_1-H), 2.59 (ddd, *J* = 15.9, 4.1, 1.9 Hz, 1H, C*H*$_a$H$_b$CHO), 2.48-2.31 (m, 2H, C_2-H, CH$_a$*H*$_b$CHO), 2.05-1.84 (m, 2H, C_3-*H*$_a$H$_b$, C_7-*H*$_a$H$_b$), 1.77-1.36 (m, 8H, C_3-H$_a$*H*$_b$, C_4-H$_2$, C_5-H$_2$, C_6-H$_2$, C_7-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.80 (CHO), 165.04 (COO), 148.00 (C_{arom}-N), 133.12 (C_{arom}-H), 131.74 (C_{arom}-H), 129.89 (C_{arom}-H), 128.13 (*C*$_{arom}$-C), 123.98 (C_{arom}-H), 81.22 (C_1), 48.96 (*C*H_2CHO), 38.85 (C_2), 32.38 (C_5), 30.29 (C_3), 28.54 (C_7), 26.58 (C_4), 22.51 (C_6). IR (ATR): 1720 (C=O st), 1533 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 207 (31), 151 (100), 150 (84, 2-$NO_2C_6H_4CO^+$), 138 (28), 123 (24), 121 (30), 110 (17), 109 (17), 105 (26), 96 (20), 95 (75), 94 (63), 93 (53), 92 (15), 91 (38), 83 (29), 82 (31), 81 (97), 80 (15), 79 (54), 78 (18), 77 (84), 76 (38), 70 (21), 68 (39), 67 (61), 66 (20), 65 (77), 63 (15), 55 (50), 54 (28), 53 (32), 51 (64). HRMS: Calculated for $[C_{16}H_{19}NO_5Na]^+$: 328.1161 [$(M+Na)^+$]; found: 328.1170. The ee (82%) was determined on compound **7d**. $[\alpha]_D^{20}$: +36.6 (*c* = 1.0, CH_2Cl_2).


5e

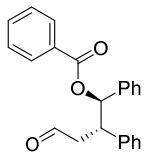
(3*S*,4*R*)-4-Ethyl-6-oxohexan-3-yl benzoate (**5e**). Following the *General Procedure H*, **5e** (25.6 mg, 0.10 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1e** (31.6 mg, 0.25 mmol) and benzoic acid **2a** (91.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 38%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (t, *J* = 2.0 Hz, 1H, C_6-H), 8.07-7.97 (m, 2H, C_{arom}-H), 7.61-7.52 (m, 1H, C_{arom}-H), 7.50-7.41 (m, 2H, C_{arom}-H), 5.19 (dt, *J* = 7.7, 4.9 Hz, 1H, C_3-H), 2.63 (ddd, *J* = 17.0, 5.4, 1.8 Hz, 1H, C_5-*H*$_a$H$_b$), 2.46 (ddd, *J* = 17.0, 6.8, 2.3 Hz, 1H, C_5-H$_a$*H*$_b$), 2.36-

2.25 (m, 1H, C_4-H), 1.81-1.60 (m, 2H, C_2-H_2), 1.58-1.45 (m, 1H, C_4-HC$H_a$$H_b$$CH_3$), 1.45-1.32 (m, 1H, C_4-HC$H_a$$H_b$$CH_3$), 1.02-0.89 (m, 6H, CH_3 × 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.16 (C_6), 166.34 (COO), 133.14 (C_{arom}-H), 130.34 (C_{arom}-C), 129.73 (C_{arom}-H), 128.58 (C_{arom}-H), 77.07 (C_3), 44.42 (C_5), 37.95 (C_4), 25.33 (C_2), 24.55 (C_4-HCH_2CH_3), 11.80 (C_4-HCH_2CH_3), 10.03 (C_1). IR (ATR): 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 105 (100, $PhCO^+$), 77 (19), 55 (15). HRMS: Calculated for $[C_{15}H_{20}O_3Na]^+$: 271.1310 [$(M+Na)^+$]; found: 271.1311. The ee (91%) was determined on compound **7e**. $[\alpha]_D^{20}$: +0.8 (*c* = 1.0, CH_2Cl_2).



5f

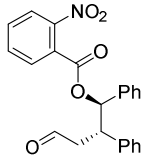
(3*S*,4*R*)-4-Ethyl-6-oxohexan-3-yl 2-nitrobenzoate (**5f**). Following the *General Procedure H*, **5f** (54.3 mg, 0.19 mmol) was isolated as a colorless oil, starting from formylcyclopropane **1e** (31.6 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.8 Hz, 1H, C_6-H), 7.89-7.83 (m, 2H, C_{arom}-H), 7.78-7.71 (m, 1H, C_{arom}-H), 7.71-7.59 (m, 2H, C_{arom}-H), 5.27-5.08 (m, 1H, C_3-H), 2.56 (ddd, *J* = 17.3, 5.0, 1.7 Hz, 1H, C_5-$H_a$$H_b$), 2.39 (ddd, *J* = 17.3, 7.0, 1.9 Hz, 1H, C_5-$H_a$$H_b$), 2.34-2.22 (m, 1H, C_4-H), 1.80-1.57 (m, 2H, C_2-H_2), 1.57-1.28 (m, 2H, C_4-HCH_2CH_3), 1.05-0.90 (m, 6H, CH_3 × 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.91 (C_6), 164.98 (COO), 148.45 (C_{arom}-N), 132.82 (C_{arom}-H), 131.99 (C_{arom}-H), 130.15 (C_{arom}-H), 127.54 (C_{arom}-C), 123.90 (C_{arom}-H), 79.28 (C_3), 44.18 (C_5), 37.05 (C_4), 24.70 (C_2), 24.44 (C_4-HCH_2CH_3), 11.60 (C_4-HCH_2CH_3), 9.93 (C_1). IR (ATR): 1720 (C=O st), 1530 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 151 (55), 150 (100, 2-$NO_2C_6H_4CO^+$), 121 (29), 97 (54), 93 (16), 83 (22), 77 (26), 76 (18), 69 (15), 67 (17), 65 (21), 55 (34), 51 (25). HRMS: Calculated for $[C_{15}H_{23}N_2O_5]^+$: 311.1607 [$(M+NH_4)^+$]; found: 311.1607. The ee (92%) was determined on compound **7f**. $[\alpha]_D^{20}$: +34.6 (*c* = 1.0, CH_2Cl_2).



5g

(1*S*,2*R*)-4-Oxo-1,2-diphenylbutyl benzoate (**5g**). Following the *General Procedure H*, **5g** (30.1 mg, 0.10 mmol) was isolated as an orange oil, starting from formylcyclopropane **1f** (55.6 mg, 0.25 mmol) and benzoic acid **2a** (91.6 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 35%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, *J* = 1.8 Hz, 1H, CHO), 8.16-8.00 (m, 2H, C_{arom}-H), 7.64-7.55 (m, 1H, C_{arom}-H), 7.52-7.43 (m, 2H, C_{arom}-H), 7.24-7.14 (m, 8H, C_{arom}-H), 7.13-7.04 (m, 2H, C_{arom}-H), 6.13 (d, *J* = 8.1 Hz, 1H, CHOCO), 3.92 (td, *J* = 8.2, 6.0 Hz, 1H, C*H*CH_2), 3.19-2.91 (m, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.74 (CHO), 165.55 (COO), 139.24 (C_{arom}-C), 138.45 (C_{arom}-C), 133.42 (C_{arom}-H), 130.01 (C_{arom}-C), 129.84 (C_{arom}-H),

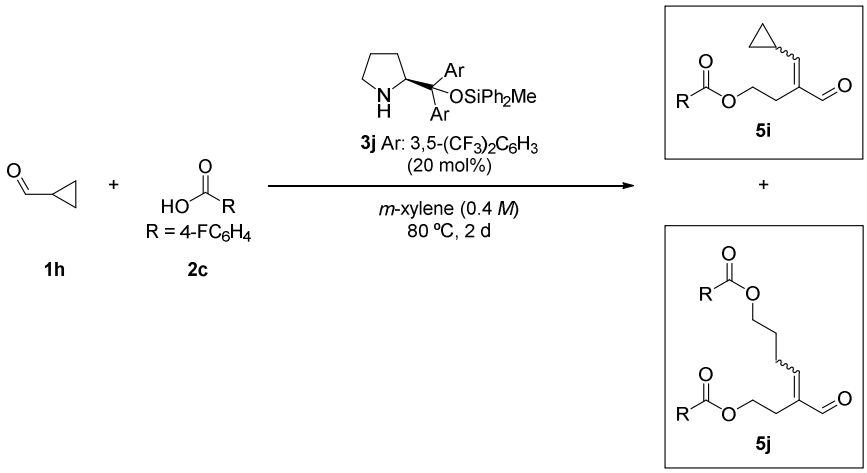
128.68 (C_{arom}-H), 128.34 (C_{arom}-H), 128.21 (C_{arom}-H), 127.44 (C_{arom}-H), 127.00 (C_{arom}-H), 79.66 (*C*HOCO), 46.13 (*C*HCH_2), 45.92 (CH_2). IR (ATR): 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 115 (22), 105 (100, $PhCO^+$), 77 (34), 51 (15). HRMS: Calculated for $[C_{23}H_{20}O_3Na]^+$: 367.1310 [$(M+Na)^+$]; found: 367.1311. The ee (94%) was determined on compound **7g**. $[\alpha]_D^{20}$: -24.1 (*c* = 0.5, CH_2Cl_2).



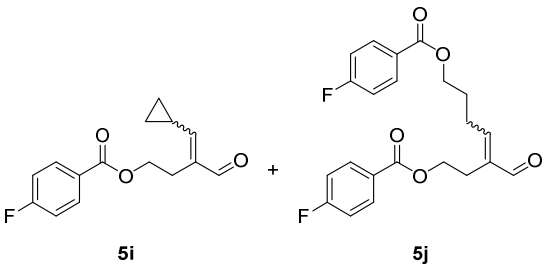
5h

(1*S*,2*R*)-4-Oxo-1,2-diphenylbutyl 2-nitrobenzoate (**5h**). Following the *General Procedure H*, **5h** (80.8 mg, 0.21 mmol) was isolated as an orange oil, starting from formylcyclopropane **1f** (55.6 mg, 0.25 mmol) and 2-nitrobenzoic acid **2f** (125.3 mg, 0.75 mmol) in the presence of catalyst **3j** (36.1 mg, 0.05 mmol). Yield: 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (t, *J* = 1.7 Hz, 1H, CHO), 7.98-7.82 (m, 1H, C_{arom}-H), 7.71-7.55 (m, 3H, C_{arom}-H), 7.29-7.09 (m, 8H, C_{arom}-H), 7.09-6.99 (m, 2H, C_{arom}-H), 6.10 (d, *J* = 8.7 Hz, 1H, CHOCO), 3.86 (td, *J* = 8.7, 5.5 Hz, 1H, C*H*CH_2), 3.18-2.93 (m, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.54 (CHO), 164.29 (COO), 148.11 (C_{arom}-N), 138.90 (*C*$_{arom}$-C), 137.61 (*C*$_{arom}$-C), 132.98 (C_{arom}-H), 132.14 (C_{arom}-H), 130.05 (C_{arom}-H), 128.64 (C_{arom}-H), 128.41 (C_{arom}-H), 128.35 (C_{arom}-H), 127.40 (C_{arom}-H), 127.14 (C_{arom}-H), 123.98 (C_{arom}-H), 81.59 (*C*HOCO), 45.95 (CH_2), 45.71 (*C*HCH_2). IR (ATR): 1724 (C=O st), 1533 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 207 (64), 193 (92), 179 (20), 178 (27), 165 (19), 150 (50, 2-$NO_2C_6H_4CO^+$), 115 (100), 105 (80), 104 (17), 91 (26), 89 (18), 78 (23), 77 (77), 76 (18), 65 (22), 51 (34). HRMS: Calculated for $[C_{23}H_{19}NO_5Na]^+$: 412.1161 [$(M+Na)^+$]; found: 412.1162. The ee (96%) was determined on compound **7h**. $[\alpha]_D^{20}$: +7.6 (*c* = 1.0, CH_2Cl_2).

*2.2.2. Preparation and characterization of aldehydes **5i-j***



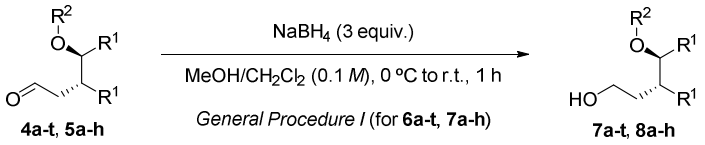
Scheme 2.3. General overview of the synthesis of products **5i-j**.

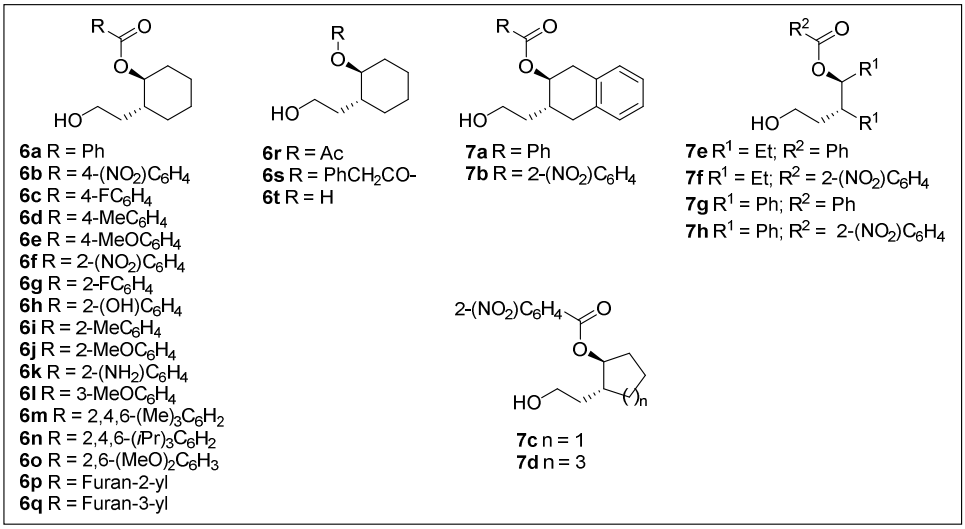


4-Cyclopropyl-3-formylbut-3-en-1-yl 4 fluorobenzoate (**5i**) and 3-Formylhept-3-ene-1,7-diyl bis(4-fluorobenzoate) (**5j**)**.** 4-fluorobenzoic acid **2c** (35.0 mg, 0.25 mmol) was added to a solution of (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl-((methyldiphenylsilyl)oxy)methyl)pyrro-lidine **3j** (0.05 mmol, 20 mol%) and formylcyclopropane **1h** (56.0 µL, 0.75 mmol) in *m*-xylene (625 µL, 0.4 *M*) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at 80 °C for 2 days. Then the solvent was evaporated *in vacuo*, the crude diluted in Et_2O (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 7:3) to afford the aldehydes **5i**, as a yellow oil (50.5 mg, 0.19 mmol), and **5j**.(traces), as a yellow oil. Yield: 77%. Ratio: >20:1. Data for **5i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H, CHO), 8.09-7.99 (m, 2H, C_{arom}-H), 7.15-7.03 (m, 2H, C_{arom}-H), 5.91 (d, *J* = 10.8 Hz, 1H, C_4-H), 4.38 (t, *J* = 6.7 Hz,

2H, C_1-H), 2.85 (t, *J* = 6.7 Hz, 2H, C_2-H), 1.96-1.86 (m, 1H, CH), 1.08-1.00 (m, 2H, CHC*H*$_2$), 0.76-0.68 (m, 2H, CHC*H*$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 193.70 (CHO), 165.88 (d, $^1J_{CF}$ = 253.8 Hz, C_{arom}-F), 165.72 (COO), 162.73 (C_4), 137.34 (C_3), 132.27 (d, $^3J_{CF}$ = 9.1 Hz, C_{arom}-H), 126.62 (d, $^4J_{CF}$ = 2.8 Hz, *C*$_{arom}$-C), 115.58 (d, $^2J_{CF}$ = 22.0 Hz, C_{arom}-H), 63.45 (C_1), 23.94 (C_2), 12.75 (CH), 10.02 (CH*C*H$_2$ x 2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.72. IR (ATR): 1720 (C=O st), 1670 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (100, 4-$FC_6H_4CO^+$), 95 (55), 94 (45), 79 (34), 77 (18), 75 (16), 55 (17). Data for **5j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 8.41-8.25 (m, 4H, C_{arom}-H), 7.50-7.39 (m, 4H, C_{arom}-H), 6.99 (t, *J* = 7.5 Hz, 1H, C_4-H), 4.73-4.62 (m, 4H, C_1-H$_2$, C_7-H$_2$), 3.10 (t, *J* = 6.9 Hz, 1H, C_2-H$_2$), 2.92 (q, *J* = 7.5 Hz, 2H, C_5-H$_2$), 2.39-2.25 (m, 2H, C_6-H$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) 194.39 (CHO), 165.62 (COO), 155.36 (C_4), 140.13 (C_3), 132.22 (d, $^3J_{CF}$ = 9.5 Hz, C_{arom}-H), 126.41 (*C*$_{arom}$-C), 115.76 (d, $^2J_{CF}$ = 22.4 Hz, C_{arom}-H), 115.71 (d, $^2J_{CF}$ = 21.6 Hz, C_{arom}-H), 64.16 (C_7), 63.15 (C_1), 27.97 (C_6), 25.99 (C_5), 24.00 (C_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.29, -105.41. IR (ATR): 1713 (C=O st), 1687 (C=O st) cm^{-1}. MS (EI) m/z (%): 281 (36), 207 (100), 123 (66, 4-$FC_6H_4CO^+$), 122 (19), 96 (20), 95 (31), 79 (18), 75 (15), 73 (26).

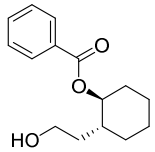
2.3. Synthesis of alcohols 6a-t and 7a-h





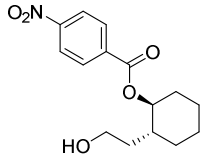
Scheme 2.4. General overview of the synthesis of products **6a-t** and **7a-h**.

General Procedure I for the synthesis of alcohols **6a-t** and **7a-h**. $NaBH_4$ (3 equiv.) was added to solution of the corresponding aldehyde **4a-t** or **5a-h** in CH_2Cl_2 (0.1 *M*) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 1 h. Then, a saturated aqueous solution of NH_4Cl (1 mL) was added and the reaction mixture was stirred for another 15 minutes. After that, the organic layer was separated, washed with H_2O (3 × 1 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient 9:1 to 5:5) to afford the corresponding alcohol **6a-t** and **7a-h**.



6a

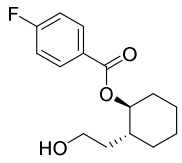
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl benzoate (**6a**). Following the *General Procedure I*, **6a** (44.3 mg, 0.18 mmol) was isolated as a colorless oil, starting from aldehyde **4a** (45.6 mg, 0.19 mmol) and $NaBH_4$ (21.6 mg, 0.57 mmol). Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12-8.00 (m, 2H, C_{arom}-H), 7.61-7.51 (m, 1H, C_{arom}-H), 7.51-7.37 (m, 2H, C_{arom}-H), 4.80 (td, *J* = 9.5, 4.3 Hz, 1H, C_1-H), 3.80-3.61 (m, 2H, C*H*$_2$OH), 2.15-2.06 (m, 1H, C_6-*H*$_a$H$_b$), 2.00-1.89 (m, 1H, C_3-*H*$_a$H$_b$), 1.89-1.75 (m, 3H, C_2-H, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.75-1.60 (m, 1H, C_4-*H*$_a$H$_b$), 1.47-1.36 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.33-1.24 (m, 1H, C_4-H$_a$*H*$_b$), 1.24-1.12 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.39 (COO), 132.94 (C_{arom}-H), 130.77 (*C*$_{arom}$-C), 129.67 (C_{arom}-H), 128.45 (C_{arom}-H), 77.55 (C_1), 60.79 (CH_2OH), 38.96 (C_2), 35.53 (*C*H$_2$CH$_2$OH), 31.84 (C_6), 30.54 (C_3), 25.11 (C_4), 24.46 (C_5). IR (ATR): 3449 (OH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (16), 122 (16), 105 (100, $PhCO^+$), 83 (33), 79 (38), 77 (56), 67 (16), 51 (33). HRMS: Calculated for $[C_{15}H_{21}O_3]^+$: 249.1491 [$(M+H)^+$]; found: 249.1501. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 7.6 min, τ_2 = 13.3 min (92%). $[\alpha]_D^{20}$: +73.1 (*c* = 0.9, CH_2Cl_2).



6b

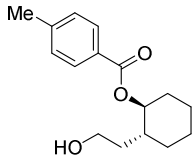
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 4-nitrobenzoate (**6b**). Following the *General Procedure I*, **6b** (52.2 mg, 0.18 mmol) was isolated as a yellow oil, starting from aldehyde **4b** (58.3 mg, 0.20 mmol) and $NaBH_4$ (22.7 mg, 0.60 mmol). Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31-8.26 (m, 2H, C_{arom}-H), 8.24-8.18 (m, 2H, C_{arom}-H), 4.83 (td, *J* = 9.6, 4.3 Hz, 1H, C_1-H), 3.80-3.60 (m, 2H, C*H*$_2$OH), 2.18-2.07 (m, 1H, C_6-*H*$_a$H$_b$), 2.02-1.92 (m, 1H, C_3-*H*$_a$H$_b$), 1.92-1.77 (m, 3H, C_2-H, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.77-1.67 (m, 1H, C_4-*H*$_a$H$_b$), 1.50-1.34 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.37-1.25 (m, 1H, C_4-H$_a$*H*$_b$), 1.25-1.13 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.49 (COO), 150.62 (C_{arom}-N), 136.20 (*C*$_{arom}$-C), 130.82 (C_{arom}-H), 123.66 (C_{arom}-H), 78.83 (C_1), 60.63 (CH_2OH), 38.89 (C_2), 35.37 (*C*H$_2$CH$_2$OH), 31.77 (C_6), 30.41 (C_3), 25.01 (C_4), 24.43 (C_5). IR (ATR): 3404 (OH st), 1716 (C=O st), 1605 (NO_2 st), 1527 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 355 (17), 282 (19), 281 (29), 252 (33), 250 (34), 235 (22), 219 (18), 209 (22), 208 (29), 207 (80), 151 (23), 150 (68, 4-$NO_2C_6H_4CO^+$), 147 (17), 125 (35), 122 (15), 121 (26), 120 (19), 108 (42), 104 (56), 98 (45), 96 (17), 95 (24), 94 (24), 93 (53), 92 (27), 91 (35), 85 (26), 83 (100), 82 (33), 81 (53), 80 (35), 79 (56), 78 (40), 77 (49), 76 (30), 75 (24), 74 (16), 73 (20), 69 (15), 68 (19), 67 (46), 65 (47), 63 (21), 57 (16), 55 (36), 54 (24), 53 (25), 52 (16), 51 (19). HRMS: Calculated for $[C_{15}H_{19}NO_5Na]^+$: 316.1161 [$(M+Na)^+$]; found: 316.1150. The ee

was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 16.8 min, τ_2 = 44.5 min (86%). $[\alpha]_D^{20}$: +65.75 (*c* = 0.9, CH_2Cl_2).



6c

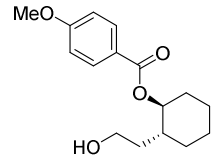
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 4-fluorobenzoate (**6c**). Following the *General Procedure I*, **6c** (49.1 mg, 0.18 mmol) was isolated as a colorless oil, starting from aldehyde **4c** (50.2 mg, 0.19 mmol) and $NaBH_4$ (21.6 mg, 0.57 mmol). Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12-8.00 (m, 2H, C_{arom}-H), 7.16-7.06 (m, 2H, C_{arom}-H), 4.78 (td, *J* = 9.5, 4.3 Hz, 1H, C_1-H), 3.81-3.58 (m, 2H, C*H*$_2$OH), 2.15-2.05 (m, 1H, C_6-*H*$_a$H$_b$), 2.00-1.90 (m, 1H, C_3-*H*$_a$H$_b$), 1.86-1.65 (m, 4H, C_2-H, C_4-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.49-1.32 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.32-1.24 (m, 1H, C_4-H$_a$*H*$_b$), 1.24-1.11 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.85 (d, $^1J_{CF}$ = 253.6 Hz, C_{arom}-F), 165.45 (COO), 132.21 (d, $^3J_{CF}$ = 9.2 Hz, C_{arom}-H), 127.03 (d, $^4J_{CF}$ = 2.8 Hz, *C*$_{arom}$-C), 115.60 (d, $^2J_{CF}$ = 22.0 Hz, C_{arom}-H), 77.75 (C_1), 60.80 (CH_2OH), 38.98 (C_2), 35.51 (*C*H$_2$CH$_2$OH), 31.88 (C_6), 30.53 (C_3), 25.11 (C_4), 24.47 (C_5). ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.98. IR (ATR): 3412 (OH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (100, 4-$FC_6H_4CO^+$), 95 (40), 83 (15), 75 (16). HRMS: Calculated for $[C_{15}H_{19}FO_3]^+$: 267.1396 [(M+H)$^+$]; found: 267.1400. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 7.1 min, τ_2 = 15.5 min (91%). $[\alpha]_D^{20}$: +57.2 (*c* = 1.0, CH_2Cl_2).



6d

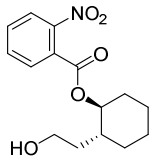
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 4-methylbenzoate (**6d**). Following the *General Procedure I*, **6d** (26.0 mg, 0.10 mmol) was isolated as a colorless oil, starting from aldehyde **4d** (29.3 mg, 0.11 mmol) and $NaBH_4$ (12.5 mg, 0.33 mmol). Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.23 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 4.78 (td, *J* = 9.6, 4.3 Hz, 1H, C_1-H), 3.82-3.60 (m, 2H, C*H*$_2$OH), 2.41 (s, 3H, CH_3), 2.18-2.04 (m, 1H, C_6-*H*$_a$H$_b$), 1.99-1.87 (m, 1H, C_3-*H*$_a$H$_b$), 1.89-1.74 (m, 3H, C_2-H, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.74-1.64 (m, 1H, C_4-*H*$_a$H$_b$), 1.46-1.32 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.32-1.23 (m, 1H, C_4-H$_a$*H*$_b$), 1.23-1.10 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.48 (COO), 143.61 (*C*$_{arom}$-CH_3), 129.72 (C_{arom}-H), 129.18 (C_{arom}-H), 128.07 (*C*$_{arom}$-CO), 77.33 (C_1), 60.90 (CH_2OH), 39.02 (C_2), 35.62 (*C*H$_2$CH$_2$OH), 31.91 (C_6), 30.63 (C_3), 25.17 (C_4), 24.50 (C_5), 21.77 (CH_3). IR (ATR): 3441 (OH st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 281 (16), 207 (36), 137 (20), 119 (100, 4-$MeC_6H_4CO^+$), 108 (33), 93 (18), 91 (54), 83 (36), 79 (24), 65 (20). HRMS: Calculated for $[C_{16}H_{22}O_3Na]^+$: 285.1467 [(M+Na)$^+$]; found: 285.1467. The ee was

determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 7.0 min, τ_2 = 13.3 min (93%). $[\alpha]_D^{20}$: +70.0 (*c* = 0.9, CH_2Cl_2).



6e

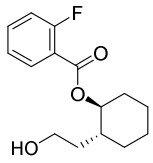
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 4-methoxybenzoate (**6e**). Following the *General Procedure I*, **6e** (13.4 mg, 0.05 mmol) was isolated as a colorless oil, starting from aldehyde **4e** (12.4 mg, 0.05 mmol) and $NaBH_4$ (5.7 mg, 0.15 mmol). Yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 4.76 (td, *J* = 9.6, 4.4 Hz, 1H, C_1-H), 3.85 (s, 3H, CH_3), 3.81-3.54 (m, 2H, C*H*$_2$OH), 2.14-2.04 (m, 1H, C_6-*H*$_a$H$_b$), 1.98-1.88 (m, 1H, C_3-*H*$_a$H$_b$), 1.88-1.73 (m, 3H, C_2-H, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.73-1.64 (m, 1H, C_4-*H*$_a$H$_b$), 1.52-1.36 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.36-1.23 (m, 1H, C_4-H$_a$*H*$_b$), 1.23-1.10 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.18 (COO), 163.42 (C_{arom}-O), 131.70 (C_{arom}-H), 123.23 (*C*$_{arom}$-C), 113.72 (C_{arom}-H), 77.16 (C_1), 60.89 (CH_2OH), 55.56 (CH_3), 39.03 (C_2), 35.61 (*C*H$_2$CH$_2$OH), 31.94 (C_6), 30.62 (C_3), 25.16 (C_4), 24.49 (C_5). IR (ATR): 3437 (OH st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (86), 153 (27), 152 (81), 135 (100, 4-MeOC$_6$H$_4$CO$^+$), 108 (33), 93 (18), 92 (21), 91 (23), 83 (23), 79 (34), 77 (34), 55 (20). HRMS: Calculated for $[C_{16}H_{23}O_4]^+$: 279.1596 [(M+H)$^+$]; found: 279.1602. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 11.4 min, τ_2 = 27.4 min (92%). $[\alpha]_D^{20}$: +63.3 (*c* = 0.3, CH_2Cl_2).



6f

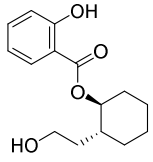
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-nitrobenzoate (**6f**). Following the *General Procedure I*, **6f** (55.7 mg, 0.19 mmol) was isolated as a yellow oil, starting from aldehyde **4f** (87.0 mg, 0.20 mmol) and $NaBH_4$ (22.7 mg, 0.60 mmol). Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.85 (m, 1H, C_{arom}-H), 7.78-7.72 (m, 1H, C_{arom}-H), 7.70-7.57 (m, 2H, C_{arom}-H), 4.80 (td, *J* = 9.8, 4.5 Hz, 1H, C_1-H), 3.78-3.58 (m, 2H, C*H*$_2$OH), 2.23-2.12 (m, 1H, C_6-*H*$_a$H$_b$), 1.97-1.87 (m, 1H, C_3-*H*$_a$H$_b$), 1.87-1.62 (m, 4H, C_2-H, C_4-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.49-1.34 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.34-1.19 (m, 1H, C_4-H$_a$*H*$_b$), 1.19-1.05 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.19 (COO), 148.19 (C_{arom}-N), 132.97 (C_{arom}-H), 131.72 (C_{arom}-H), 129.99 (C_{arom}-H), 128.15 (*C*$_{arom}$-C), 123.91 (C_{arom}-H), 79.49 (C_1), 60.57 (CH_2OH), 38.59 (C_2), 35.27 (*C*H$_2$CH$_2$OH), 31.12 (C_6), 30.46 (C_3), 24.93 (C_4), 24.36 (C_5). IR (ATR): 3389 (OH st), 1720 (C=O st), 1530 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 281 (21), 252 (17), 207 (83), 151 (51), 150 (34, 2-NO$_2$C$_6$H$_4$CO$^+$), 126 (19), 125 (24), 121 (26), 93 (23), 92 (16), 91 (31), 85 (18), 83 (100), 81 (23), 80 (18), 79 (28), 78 (20), 77 (37), 76 (20), 67

(36), 65 (19), 55 (41), 54 (16), 53 (16), 51 (28). HRMS: Calculated for $[C_{15}H_{20}NO_5]^+$: 294.1341 $[(M+H)^+]$; found: 294.1346. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 36.0 min, τ_2 = 47.4 min (92%). $[\alpha]_D^{20}$: +96.6 (*c* = 1.0, CH_2Cl_2).



6g

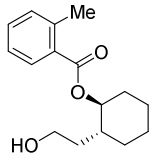
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-fluorobenzoate (**6g**). Following the *General Procedure I*, **6g** (47.6 mg, 0.18 mmol) was isolated as a colorless oil, starting from aldehyde **4g** (49.6 mg, 0.19 mmol) and $NaBH_4$ (21.6 mg, 0.57 mmol). Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (td, *J* = 7.6, 1.9 Hz, 1H, C_{arom}-H), 7.59-7.43 (m, 1H, C_{arom}-H), 7.23-7.07 (m, 2H, C_{arom}-H), 4.80 (td, *J* = 9.6, 4.2 Hz, 1H, C_1-H), 3.80-3.60 (m, 2H, C*H*$_2$OH), 2.19-2.08 (m, 1H, C_6-*H*$_a$H$_b$), 2.00-1.73 (m, 4H, C_2-H, C_3-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.73-1.63 (m, 1H, C_4-*H*$_a$H$_b$), 1.52-1.36 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.36-1.06 (m, 2H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.34 (d, $^3J_{CF}$ = 3.8 Hz, COO), 162.04 (d, $^1J_{CF}$ = 259.6 Hz, C_{arom}-F), 134.41 (d, $^3J_{CF}$ = 8.9 Hz, C_{arom}-H), 132.19 (C_{arom}-H), 124.07 (d, $^3J_{CF}$ = 3.9 Hz, C_{arom}-H), 119.41 (d, $^2J_{CF}$ = 9.9 Hz, *C*$_{arom}$-C), 117.10 (d, $^2J_{CF}$ = 22.5 Hz, C_{arom}-H), 78.10 (C_1), 60.81 (CH_2OH), 38.79 (C_2), 35.50 (*C*H$_2$CH$_2$OH), 31.72 (C_6), 30.54 (C_3), 25.04 (C_4), 24.42 (C_5). ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.40. IR (ATR): 3404 (OH st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (100, 2-$FC_6H_4CO^+$), 95 (33), 93 (15), 79 (21). HRMS: Calculated for $[C_{15}H_{20}FO_3]^+$: 267.1396 $[(M+H)^+]$; found: 267.1402. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 10.2 min, τ_2 = 21.9 min (95%). $[\alpha]_D^{20}$: +58.6 (*c* = 1.0, CH_2Cl_2).



6h

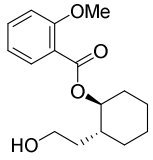
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-hydroxybenzoate (**6h**). Following the *General Procedure I*, **6h** (51.3 mg, 0.19 mmol) was isolated as a colorless oil, starting from aldehyde **4h** (51.8 mg, 0.20 mmol) and $NaBH_4$ (22.7 mg, 0.60 mmol). Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1H, C_{arom}-OH), 7.85 (dd, *J* = 8.0, 1.7 Hz, 1H, C_{arom}-H), 7.52-7.38 (m, 1H, C_{arom}-H), 6.97 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.93-6.82 (m, 1H, C_{arom}-H), 4.82 (td, *J* = 9.6, 4.2 Hz, 1H, C_1-H), 3.82-3.60 (m, 2H, C*H*$_2$OH), 2.17-2.06 (m, 1H, C_6-*H*$_a$H$_b$), 2.02-1.91 (m, 1H, C_3-*H*$_a$H$_b$), 1.91-1.76 (m, 3H, C_2-H, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.76-1.63 (m, 1H, C_4-*H*$_a$H$_b$), 1.52-1.33 (m, 3H, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.33-1.24 (m, 1H, C_4-H$_a$*H*$_b$), 1.24-1.07 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.00 (COO), 161.85 (C_{arom}-O), 135.73 (C_{arom}-H), 129.95 (C_{arom}-H), 119.25 (C_{arom}-H), 117.71 (C_{arom}-H), 112.91 (*C*$_{arom}$-C), 78.29 (C_1), 60.69 (CH_2OH), 38.80 (C_2), 35.45 (*C*H$_2$CH$_2$OH), 31.74 (C_6), 30.45 (C_3), 24.99 (C_4), 24.40 (C_5).

IR (ATR): 3289 (OH st), 1666 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (18), 138 (89), 121 (47, 2-$OHC_6H_4CO^+$), 120 (100), 109 (21), 108 (24), 93 (46), 92 (33), 91 (25), 83 (36), 81 (18), 79 (39), 77 (27), 67 (28), 65 (27), 55 (27), 54 (18), 53 (24). HRMS: Calculated for $[C_{15}H_{20}O_4Na]^+$: 287.1259 $[(M+Na)^+]$; found: 287.1264. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_1 = 11.5 min, τ_2 = 20.8 min (95%). $[\alpha]_D^{20}$: +65.4 (*c* = 1.1, CH_2Cl_2).



6i

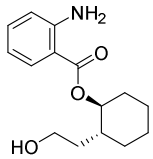
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-methylbenzoate (**6i**). Following the *General Procedure I*, **6i** (28.3 mg, 0.11 mmol) was isolated as a colorless oil, starting from aldehyde **4i** (28.6 mg, 0.11 mmol) and $NaBH_4$ (12.5 mg, 0.33 mmol). Yield: 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.88 (m, 1H, C_{arom}-H), 7.45-7.33 (m, 1H, C_{arom}-H), 7.33-7.17 (m, 2H, C_{arom}-H), 4.80 (td, *J* = 9.6, 4.3 Hz, 1H, C_1-H), 3.80-3.59 (m, 2H, CH_2OH), 2.60 (s, 3H, CH_3), 2.20-2.03 (m, 1H, C_6-H_aH_b), 1.99-1.89 (m, 1H, C_3-H_aH_b), 1.89-1.62 (m, 4H, C_2-H, C_4-H_aH_b, C_5-H_aH_b, CH_aH_bCH$_2$OH), 1.53-1.36 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, CH_aH_bCH$_2$OH), 1.34-1.08 (m, 2H, C_3-H_aH_b, C_4-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.51 (COO), 140.18 (C_{arom}-CH_3), 131.95 (C_{arom}-H), 131.83 (C_{arom}-H), 130.53 (C_{arom}-H), 130.27 (C_{arom}-CO), 125.85 (C_{arom}-H), 77.20 (C_1), 60.83 (CH_2OH), 38.97 (C_2), 35.49 (CH_2CH$_2$OH), 31.93 (C_6), 30.53 (C_3), 25.10 (C_4), 24.51 (C_5), 21.95 (CH_3). IR (ATR): 3418 (OH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 281 (15), 207 (27), 136 (19), 127 (15), 119 (100, 2-$MeC_6H_4CO^+$), 118 (27), 109 (26), 108 (22), 105 (19), 93 (18), 91 (89), 83 (38), 79 (43), 77 (40), 67 (16), 65 (25). HRMS: Calculated for $[C_{16}H_{22}O_3Na]^+$: 285.1467 $[(M+Na)^+]$; found: 285.1471. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_1 = 11.5 min, τ_2 = 16.3 min (93%). $[\alpha]_D^{20}$: +56.7 (*c* = 0.9, CH_2Cl_2).



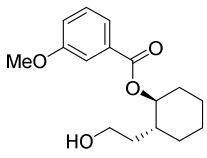
6j

(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-methoxybenzoate (**6j**). Following the *General Procedure I*, **6j** (21.8 mg, 0.08 mmol) was isolated as a colorless oil, starting from aldehyde **4j** (22.8 mg, 0.08 mmol) and $NaBH_4$ (9.1 mg, 0.24 mmol). Yield: 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.72 (m, 1H, C_{arom}-H), 7.52-7.39 (m, 1H, C_{arom}-H), 7.04-6.92 (m, 2H, C_{arom}-H), 4.78 (td, *J* = 9.7, 4.4 Hz, 1H, C_1-H), 3.89 (s, 3H, CH_3), 3.79-3.60 (m, 2H, CH_2OH), 2.19-2.08 (m, 1H, C_6-H_aH_b), 1.97-1.85 (m, 2H, C_2-H, C_3-H_aH_b), 1.83-1.60 (m, 3H, C_4-H_aH_b, C_5-H_aH_b, CH_aH_bCH$_2$OH), 1.52-1.35 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, CH_aH_bCH$_2$OH), 1.35-1.22 (m, 1H, C_4-H_aH_b), 1.22-1.08 (m, 1H, C_3-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.23 (COO), 159.11 (C_{arom}-O), 133.42 (C_{arom}-H), 131.55 (C_{arom}-H), 120.90 (C_{arom}-C), 120.31 (C_{arom}-H), 112.22 (C_{arom}-H), 77.44 (C_1),

60.85 (CH_2OH), 56.04 (CH_3), 38.85 (C_2), 35.58 (CH_2CH_2OH), 31.82 (C_6), 30.75 (C_3), 25.15 (C_4), 24.48 (C_5). IR (ATR): 3447 (OH st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (40), 153 (42), 135 (100, 2-$MeOC_6H_4CO^+$), 123 (24), 105 (43), 92 (17), 91 (21), 83 (60), 81 (22), 79 (43), 78 (20), 77 (43), 67 (19), 65 (15), 63 (16), 55 (21), 51 (17). HRMS: Calculated for $[C_{16}H_{23}O_4]^+$: 279.1596 [$(M+H)^+$]; found: 279.1605. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 12.4 min, τ_2 = 16.8 min (91%). $[\alpha]_D^{20}$: +85.1 (*c* = 0.1, CH_2Cl_2).

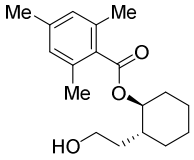

6k

(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-aminobenzoate (**6k**). Following the *General Procedure I*, **6k** (7.2 mg, 0.03 mmol) was isolated as an orange oil, starting from aldehyde **4k** (6.5 mg, 0.03 mmol) and $NaBH_4$ (3.4 mg, 0.09 mmol). Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.81 (m, 1H, C_{arom}-H), 7.33-7.17 (m, 1H, C_{arom}-H), 6.73-6.56 (m, 2H, C_{arom}-H), 5.71 (s, 2H, NH_2), 4.76 (td, *J* = 9.4, 4.3 Hz, 1H, C_1-H), 3.80-3.57 (m, 2H, CH_2OH), 2.15-2.01 (m, 1H, C_6-H_aH_b), 2.01-1.89 (m, 1H, C_3-H_aH_b), 1.89-1.74 (m, 3H, C_2-H, C_5-H_aH_b, $CH_aH_bCH_2OH$), 1.74-1.63 (m, 1H, C_4-H_aH_b), 1.50-1.33 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.33-1.05 (m, 2H, C_3-H_aH_b, C_4-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.95 (COO), 150.68 (C_{arom}-N), 134.15 (C_{arom}-H), 131.29 (C_{arom}-H), 116.87 (C_{arom}-H), 116.44 (C_{arom}-H), 111.37 (C_{arom}-C), 76.74 (C_1), 60.91 (CH_2OH), 39.96 (C_2), 35.62 (CH_2CH_2OH), 31.96 (C_6), 30.63 (C_3), 25.13 (C_4), 24.51 (C_5). IR (ATR): 3479 (NH_2 st), 3364 (NH_2 st), 1685 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (72), 137 (100), 120 (33, 2-$NH_2C_6H_4CO^+$), 119 (51), 92 (26), 91 (17), 83 (37), 81 (17), 79 (35), 77 (16), 67 (18), 65 (26), 55 (16), 54 (17), 52 (15). HRMS: Calculated for $[C_{15}H_{22}NO_3]^+$: 264.1600 [$(M+H)^+$]; found: 264.1619. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 16.6 min, τ_2 = 36.0 min (73%). $[\alpha]_D^{20}$: +134.6 (*c* = 0.1, CH_2Cl_2).


6l

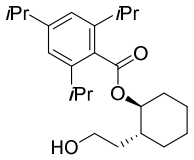
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 3-methoxybenzoate (**6l**). Following the *General Procedure I*, **6l** (47.6 mg, 0.17 mmol) was isolated as a colorless oil, starting from aldehyde **4l** (49.7 mg, 0.18 mmol) and $NaBH_4$ (20.4 mg, 0.54 mmol). Yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.60 (m, 1H, C_{arom}-H), 7.60-7.52 (m, 1H, C_{arom}-H), 7.33 (t, *J* = 7.9 Hz, 1H, C_{arom}-H), 7.09 (dd, *J* = 8.3, 2.7 Hz, 1H, C_{arom}-H), 4.78 (td, *J* = 9.5, 4.4 Hz, 1H, C_1-H), 3.85 (s, 3H, CH_3), 3.79-3.61 (m, 2H, CH_2OH), 2.16-2.05 (m, 1H, C_6-H_aH_b), 1.99-1.89 (m, 1H, C_3-H_aH_b), 1.88-1.74 (m, 3H, C_2-H, C_5-H_aH_b, $CH_aH_bCH_2OH$), 1.74-1.64 (m, 1H, C_4-H_aH_b), 1.50-1.36 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.33-1.23 (m, 1H, C_4-H_aH_b), 1.23-1.10 (m, 1H, C_3-

H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.26 (COO), 159.67 (C_{arom}-O), 132.12 (C_{arom}-C), 129.49 (C_{arom}-H), 122.05 (C_{arom}-H), 119.29 (C_{arom}-H), 114.36 (C_{arom}-H), 77.67 (C_1), 60.83 (CH_2OH), 55.57 (CH_3), 38.96 (C_2), 35.56 (CH_2CH_2OH), 31.82 (C_6), 30.57 (C_3), 25.11 (C_4), 24.46 (C_5). IR (ATR): 3426 (OH st), 1710 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (79), 152 (93), 135 (100, 3-$MeOC_6H_4CO^+$), 108 (24), 94 (15), 93 (15), 92 (19), 91 (18), 83 (35), 79 (58), 78 (29), 77 (52), 69 (16), 67 (16), 55 (26), 54 (19), 53 (28), 51 (20). HRMS: Calculated for $[C_{16}H_{23}O_4]^+$: 279.1596 [$(M+H)^+$]; found: 279.1605. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 9.3 min, τ_2 = 14.4 min (92%). $[\alpha]_D^{20}$: +49.4 (*c* = 1.0, CH_2Cl_2).



6m

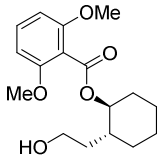
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2,4,6-trimethylbenzoate (**6m**). Following the *General Procedure I*, **6m** (54.1 mg, 0.19 mmol) was isolated as a colorless oil, starting from aldehyde **4m** (53.4 mg, 0.19 mmol) and $NaBH_4$ (21.6 mg, 0.57 mmol). Yield: 98%. ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2H, C_{arom}-H), 4.80 (td, *J* = 9.7, 4.4 Hz, 1H, C_1-H), 3.79-3.58 (m, 2H, CH_2OH), 2.30 (s, 6H, CH_3 × 2), 2.28 (s, 3H, CH_3), 2.26-2.18 (m, 1H, C_6-H_aH_b), 1.99-1.83 (m, 2H, C_2-H, C_3-H_aH_b), 1.83-1.75 (m, 1H, C_5-H_aH_b), 1.75-1.62 (m, 2H, C_4-H_aH_b, $CH_aH_bCH_2OH$), 1.49-1.34 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.30-1.21 (m, 1H, C_4-H_aH_b), 1.21-1.09 (m, 1H, C_3-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.21 (COO), 139.14 (C_{arom}-CH_3), 134.69 (C_{arom}-CH_3), 131.68 (C_{arom}-CO), 128.46 (C_{arom}-H), 77.79 (C_1), 60.68 (CH_2OH), 38.75 (C_2), 35.25 (CH_2CH_2OH), 32.87 (C_6), 30.51 (C_3), 25.08 (C_4), 24.50 (C_5), 21.22 (CH_3), 19.84 (CH_3 x 2). IR (ATR): 3408 (OH st), 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 164 (26), 147 (61, 2,4,6-$(Me)_3C_6H_2CO^+$), 146 (100), 119 (32), 117 (16), 108 (15), 93 (20), 91 (35), 83 (30), 79 (45), 78 (20), 77 (24), 67 (18), 65 (15), 55 (23). HRMS: Calculated for $[C_{18}H_{26}O_3Na]^+$: 313.1780 [$(M+Na)^+$]; found: 313.1791. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 7.5 min, τ_2 = 8.3 min (93%). $[\alpha]_D^{20}$: +44.8 (*c* = 1.1, CH_2Cl_2).



6n

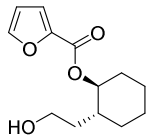
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2,4,6-triisopropylbenzoate (**6n**). Following the *General Procedure I*, **6n** (74.7 mg, 0.20 mmol) was isolated as a colorless oil, starting from aldehyde **4n** (78.2 mg, 0.21 mmol) and $NaBH_4$ (23.8 mg, 0.63 mmol). Yield: 95%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2H, C_{arom}-H), 4.80 (td, *J* = 9.7, 4.3 Hz, 1H, C_1-H), 3.78-3.57 (m, 2H, CH_2OH), 2.98-2.80 (m, 3H, $CHCH_3$ × 3), 2.33-2.17 (m, 1H, C_6-H_aH_b), 1.99-1.85 (m, 2H, C_2-H, C_3-H_aH_b), 1.84-1.74 (m, 1H, C_5-H_aH_b), 1.74-1.62 (m, 2H, C_4-H_aH_b, $CH_aH_bCH_2OH$), 1.50-1.34 (m, 3H, C_5-H_aH_b, C_6-

H_aH_b, $CH_aH_bCH_2OH$), 1.33-1.00 (m, 20H, C_3-H_aH_b, C_4-H_aH_b, CH_3 × 6). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.82 (COO), 150.10 (C_{arom}-CH), 144.70 (C_{arom}-CH), 130.91 (C_{arom}-CO), 121.00 (C_{arom}-H), 77.95 (C_1), 60.80 (CH_2OH), 38.69 (C_2), 35.19 (CH_2CH_2OH), 34.55 ($CH(CH_3)_2$), 31.62 (C_6), 31.53 ($CH(CH_3)_2$ x 2), 30.50 (C_3), 25.02 (C_4), 24.63 (CH_3 x 2), 24.50 (C_5), 24.22 (CH_3 x 2), 24.11 (CH_3), 24.10 (CH_3). IR (ATR): 3429 (OH st), 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 248 (22), 247 (19), 233 (61), 231 (58, 2,4,6-(iPr)$_3C_6H_2CO^+$), 230 (100), 212 (16), 91 (18), 79 (22), 67 (15). HRMS: Calculated for $[C_{24}H_{39}O_3]^+$: 375.2899 [$(M+H)^+$]; found: 375.2903. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_1 = 9.2 min, τ_2 = 10.8 min (91%). $[\alpha]_D^{20}$: +20.1 (*c* = 1.0, CH_2Cl_2).



6o

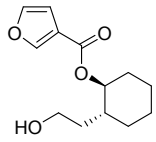
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2,6-dimethoxybenzoate (**6o**). Following the *General Procedure I*, **6o** (59.8 mg, 0.19 mmol) was isolated as colorless crystals, starting from aldehyde **4o** (62.0 mg, 0.20 mmol) and $NaBH_4$ (22.7 mg, 0.60 mmol). Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.55 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 4.82 (td, *J* = 10.0, 4.5 Hz, 1H, C_1-H), 3.81 (s, 6H, CH_3 × 2), 3.78-3.61 (m, 2H, CH_2OH), 2.24-2.12 (m, 1H, C_6-H_aH_b), 2.06-1.85 (m, 2H, C_2-H, C_3-H_aH_b), 1.83-1.73 (m, 1H, C_5-H_aH_b), 1.73-1.59 (m, 2H, C_4-H_aH_b, $CH_aH_bCH_2OH$), 1.56-1.34 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.30-1.09 (m, 2H, C_3-H_aH_b, C_4-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.47 (COO), 157.21 (C_{arom}-O), 130.94 (C_{arom}-H), 113.88 (C_{arom}-C), 104.12 (C_{arom}-H), 77.92 (C_1), 60.96 (CH_2OH), 56.06 (CH_3 × 2), 39.09 (C_2), 35.35 (CH_2CH_2OH), 31.99 (C_6), 31.02 (C_3), 25.34 (C_4), 24.62 (C_5). IR (ATR): 3376 (OH st), 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 183 (30), 182 (20), 165 (100, 2,6-$(MeO)_2C_6H_3CO^+$), 164 (15), 107 (16), 83 (15), 79 (22), 77 (21). HRMS: Calculated for $[C_{17}H_{25}O_5]^+$: 309.1702 [$(M+H)^+$]; found: 309.1707. M.p. (petroleum ether/EtOAc): 109-110 °C. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 18.1 min, τ_2 = 20.9 min (89%). $[\alpha]_D^{20}$: +10.4 (*c* = 1.1, CH_2Cl_2).



6p

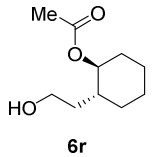
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl furan-2-carboxylate (**6p**). Following the *General Procedure I*, **6p** (30.3 mg, 0.13 mmol) was isolated as a colorless oil, starting from aldehyde **4p** (33.7 mg, 0.14 mmol) and $NaBH_4$ (15.9 mg, 0.42 mmol). Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.53 (s, 1H, C_{arom}-H), 7.17 (d, *J* = 3.5 Hz, 1H, C_{arom}-H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H, C_{arom}-H), 4.75 (td, *J* = 9.8, 4.4 Hz, 1H, C_1-H), 3.79-3.59 (m, 2H, CH_2OH), 2.15-2.04 (m, 1H, C_6-H_aH_b), 1.98-1.88 (m, 1H, C_3-H_aH_b), 1.86-

1.73 (m, 3H, C_2-H, C_5-H_aH_b, C$H_aH_bCH_2OH$), 1.73-1.62 (m, 1H, C_4-H_aH_b), 1.53-1.34 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.34-1.02 (m, 2H, C_3-H_aH_b, C_4-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.65 (COO), 146.36 (C_{arom}-H), 145.08 (C_{arom}-C), 117.91 (C_{arom}-H), 111.95 (C_{arom}-H), 77.91 (C_1), 60.86 (CH_2OH), 38.99 (C_2), 35.68 (CH_2CH_2OH), 31.97 (C_6), 30.79 (C_3), 25.17 (C_4), 24.51 (C_5). IR (ATR): 3408 (OH st), 1706 (C=O st) cm^{-1}. MS (EI) m/z (%): 113 (17), 115 (15), 108 (28), 95 (100, (furan-2-yl)CO$^+$), 93 (22), 91 (27), 83 (51), 80 (15), 79 (26), 67 (25), 55 (18), 54 (15). HRMS: Calculated for $[C_{13}H_{19}O_4]^+$: 239.1283 [$(M+H)^+$]; found: 239.1287. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 13.0 min, τ_2 = 27.1 min (92%). $[\alpha]_D^{20}$: +64.0 (*c* = 1.0, CH_2Cl_2).



6q

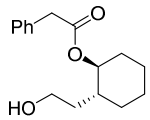
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl furan-3-carboxylate (**6q**). Following the *General Procedure I*, **6q** (26.9 mg, 0.11 mmol) was isolated as a colorless oil, starting from aldehyde **4q** (27.2 mg, 0.12 mmol) and $NaBH_4$ (13.6 mg, 0.36 mmol). Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-7.96 (m, 1H, C_{arom}-H), 7.45-7.38 (m, 1H, C_{arom}-H), 6.78-6.70 (m, 1H, C_{arom}-H), 4.71 (td, *J* = 9.7, 4.2 Hz, 1H, C_1-H), 3.79-3.59 (m, 2H, CH_2OH), 2.13-2.01 (m, 1H, C_6-H_aH_b), 1.97-1.87 (m, 1H, C_3-H_aH_b), 1.86-1.59 (m, 4H, C_2-H, C_4-H_aH_b, C_5-H_aH_b, C$H_aH_bCH_2OH$), 1.49-1.33 (m, 3H, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$), 1.33-1.20 (m, 1H, C_4-H_aH_b), 1.20-1.06 (m, 1H, C_3-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.04 (COO), 147.75 (C_{arom}-H), 143.82 (C_{arom}-H), 119.93 (C_{arom}-C), 110.00 (C_{arom}-H), 77.16 (C_1), 60.86 (CH_2OH), 38.99 (C_2), 35.60 (CH_2CH_2OH), 31.94 (C_6), 30.66 (C_3), 25.16 (C_4), 24.49 (C_5). IR (ATR): 3418 (OH st), 1710 (C=O st) cm^{-1}. MS (EI) m/z (%): 108 (15), 95 (100, (furan-3-yl)CO$^+$), 85 (18), 83 (75), 67 (16). HRMS: Calculated for $[C_{13}H_{19}O_4]^+$: 239.1283 [$(M+H)^+$]; found: 239.1289. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 8.7 min, τ_2 = 13.2 min (89%). $[\alpha]_D^{20}$: +69.8 (*c* = 0.8, CH_2Cl_2).



6r

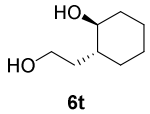
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl acetate (**6r**). Following the *General Procedure I*, **6r** (12.1 mg, 0.07 mmol) was isolated as a light yellow oil, starting from the reaction crude of aldehyde **4r** and $NaBH_4$ (28.4 mg, 0.75 mmol). Yield (asymmetric reaction + reduction): 26%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (td, *J* = 9.9, 4.3 Hz, 1H, C_1-H), 3.76-3.56 (m, 2H, CH_2OH), 2.04 (s, 3H, CH_3), 2.01-1.93 (m, 1H, C_6-H_aH_b), 1.93-1.80 (m, 1H, C_3-H_aH_b), 1.82-1.69 (m, 2H, C_2-H, C_5-H_aH_b), 1.69-1.54 (m, 2H, C_4-H_aH_b, C$H_aH_bCH_2OH$), 1.43-0.99 (m, 5H, C_3-H_aH_b, C_4-H_aH_b, C_5-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2OH$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.03 (COO), 77.06 (C_1), 60.82 (CH_2OH), 38.87 (C_2), 35.51

(*C*H_2CH_2OH), 31.90 (C_6), 30.64 (C_3), 25.17 (C_4), 24.47 (C_5), 21.50 (CH_3). IR (ATR): 3422 (OH st), 1724 (C=O st) cm^{-1}. MS (EI) m/z (%): 108 (25), 96 (22), 93 (41), 91 (52), 83 (82), 81 (59), 80 (23), 79 (100), 77 (26), 68 (18), 67 (55), 60 (15), 55 (66), 54 (23), 53 (29). HRMS: Calculated for $[C_{10}H_{18}O_3Na]^+$: 209.1154 [$(M+Na)^+$]; found: 209.1162. The ee (90%) was determined on compound **8a**. $[\alpha]_D^{20}$: +52.9 (*c* = 0.8, CH_2Cl_2).



6s

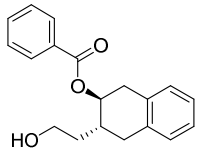
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexyl 2-phenylacetate (**6s**). Following the *General Procedure I*, **6s** (48.8 mg, 0.19 mmol) was isolated as a colorless oil, starting from aldehyde **4s** (51.4 mg, 0.20 mmol) and $NaBH_4$ (22.7 mg, 0.60 mmol). Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H, C_{arom}-H), 4.51 (td, *J* = 9.7, 4.3 Hz, 1H, C_1-H), 3.61 (s, 2H, CH_2C_{arom}), 3.59-3.48 (m, 2H, C*H*$_2$OH), 2.01-1.90 (m, 1H, C_6-*H*$_a$H$_b$), 1.89-1.77 (m, 1H, C_3-*H*$_a$H$_b$), 1.78-1.49 (m, 4H, C_2-H, C_4-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.36-1.15 (m, 4H, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH), 1.12-0.95 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.42 (COO), 134.46 (*C*$_{arom}$-C), 129.38 (C_{arom}-H), 128.64 (C_{arom}-H), 127.14 (C_{arom}-H), 77.38 (C_1), 60.67 (CH_2OH), 42.04 (*C*H$_2$C$_{arom}$), 38.76 (C_2), 35.36 (*C*H_2CH_2OH), 31.72 (C_6), 30.59 (C_3), 25.07 (C_4), 24.37 (C_5). IR (ATR): 3418 (OH st), 1727 (C=O st) cm^{-1}. MS (EI) m/z (%): 106 (19), 105 (16), 91 (100, $PhCH_2^+$), 83 (27), 79 (24), 77 (31), 67 (23), 65 (19), 55 (19), 51 (15). HRMS: Calculated for $[C_{16}H_{22}O_3Na]^+$: 285.1467 [$(M+Na)^+$]; found: 285.1473. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 8.5 min, τ_2 = 10.1 min (91%). $[\alpha]_D^{20}$: +38.3 (*c* = 1.0, CH_2Cl_2).



6t

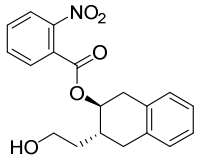
(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclohexan-1-ol (**6t**).[20] Following the *General Procedure I*, **6t** (17.6 mg, 0.12 mmol) was isolated as a colorless oil, starting from aldehyde **4t** (39.9 mg, 0.18 mmol) and $NaBH_4$ (20.4 mg, 0.54 mmol). Yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86-3.74 (m, 1H, C*H*$_a$H$_b$OH), 3.72-3.58 (m, 1H, CH$_a$*H*$_b$OH), 3.25 (td, *J* = 9.7, 4.5 Hz, 1H, C_1-H), 2.94 (s, 2H, OH × 2), 2.07-1.91 (m, 1H, C_6-*H*$_a$H$_b$), 1.85-1.48 (m, 5H, C_2-H, C_3-*H*$_a$H$_b$, C_4-*H*$_a$H$_b$, C_5-*H*$_a$H$_b$, C*H*$_a$H$_b$CH$_2$OH), 1.42-0.97 (m, 5H, C_3-H$_a$*H*$_b$, C_4-H$_a$*H*$_b$, C_5-H$_a$*H*$_b$, C_6-H$_a$*H*$_b$, CH$_a$*H*$_b$CH$_2$OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 75.27 (C_1), 61.97 (CH_2OH), 44.46 (C_2), 38.24 (*C*H_2CH_2OH), 35.86 (C_6), 32.78 (C_3), 25.76 (C_4), 25.02 (C_5). The ee (87%) was determined on compound **8b**. $[\alpha]_D^{20}$: +37.2 (*c* = 0.7, CH_2Cl_2).

[20] Fetizon, M.; Golfier, M.; Montaufier, M. T.; Rens, J. *Tetrahedron* **1975**, *31*, 987.



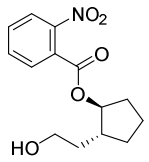
7a

(2*S*,3*R*)-3-(2-Hydroxyethyl)-1,2,3,4-tetrahydronaphthalen-2-yl benzoate (**7a**). Following the *General Procedure I*, **7a** (28.7 mg, 0.10 mmol) was isolated as a light brown oil, starting from aldehyde **5a** (28.0 mg, 0.10 mmol) and $NaBH_4$ (11.3 mg, 0.30 mmol). Yield: 97%. %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-8.00 (m, 2H, C_{arom}-H), 7.61-7.51 (m, 1H, C_{arom}-H), 7.49-7.38 (m, 2H, C_{arom}-H), 7.20-7.04 (m, 4H, C_{arom}-H), 5.37-5.26 (m, 1H, C_2-H), 3.91-3.74 (m, 2H, C*H*$_2$OH), 3.30 (dd, *J* = 16.8, 5.3 Hz, 1H, C_1-*H*$_a$H$_b$), 3.17 (dd, *J* = 16.6, 5.4 Hz, 1H, C_4-*H*$_a$H$_b$), 2.98 (dd, *J* = 16.8, 7.1 Hz, 1H, C_1-H$_a$*H*$_b$), 2.69 (dd, *J* = 16.6, 8.2 Hz, 1H, C_4-H$_a$*H*$_b$), 2.47-2.31 (m, 1H, C_3-H), 2.01-1.84 (m, 1H, C*H*$_a$H$_b$CH$_2$OH), 1.64-1.48 (m, 1H, CH$_a$*H*$_b$CH$_2$OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.39 (COO), 134.84 (*C*$_{arom}$-C), 133.59 (*C*$_{arom}$-C), 133.15 (C_{arom}-H), 130.53 (*C*$_{arom}$-C), 129.77 (C_{arom}-H), 129.10 (C_{arom}-H), 128.85 (C_{arom}-H), 128.53 (C_{arom}-H), 126.34 (C_{arom}-H), 126.24 (C_{arom}-H), 74.01 (C_2), 60.76 (CH_2OH), 35.01 (C_3), 34.72 (*C*H$_2$CH$_2$OH), 33.80 (C_1), 32.91 (C_4). IR (ATR): 3411 (OH st), 1713 (C=O st) cm^{-1}. HRMS: Calculated for $[C_{19}H_{20}O_3Na]^+$: 319.1310 [(M+Na)$^+$]; found: 319.1311. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 9.9 min, τ_2 = 14.7 min (80%). $[\alpha]_D^{20}$: +69.1 (*c* = 0.8, CH_2Cl_2).



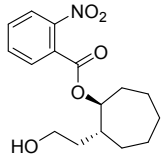
7b

(2*S*,3*R*)-3-(2-Hydroxyethyl)-1,2,3,4-tetrahydronaphthalen-2-yl 2-nitrobenzoate (**7b**). Following the *General Procedure I*, **7b** (57.1 mg, 0.17 mmol) was isolated as a light brown oil, starting from aldehyde **5b** (60.2 mg, 0.18 mmol) and $NaBH_4$ (20.4 mg, 0.54 mmol). Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.7, 1.6 Hz, 1H, C_{arom}-H), 7.79-7.56 (m, 3H, C_{arom}-H), 7.18-7.04 (m, 4H, C_{arom}-H), 5.33 (ddd, *J* = 8.0, 7.0, 5.2 Hz, 1H, C_2-H), 3.88-3.70 (m, 2H, C*H*$_2$OH), 3.33 (dd, *J* = 16.9, 5.3 Hz, 1H, C_1-*H*$_a$H$_b$), 3.09 (dd, *J* = 16.7, 5.5 Hz, 1H, C_4-*H*$_a$H$_b$), 2.97 (dd, *J* = 16.9, 7.0 Hz, 1H, C_1-H$_a$***H*$_b$**), 2.65 (dd, *J* = 16.7, 8.0 Hz, 1H, C_4-H$_a$***H*$_b$**), 2.40-2.26 (m, 1H, C_3-H), 1.95-1.81 (m, 1H, C*H*$_a$H$_b$CH$_2$OH), 1.61-1.47 (m, 1H, CH$_a$***H*$_b$**CH$_2$OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.32 (COO), 148.08 (C_{arom}-N), 134.65 (*C*$_{arom}$-C), 133.12 (C_{arom}-H), 131.77 (C_{arom}-H), 129.91 (C_{arom}-H), 129.07 (C_{arom}-H), 128.78 (C_{arom}-H), 128.13 (*C*$_{arom}$-C), 126.39 (C_{arom}-H), 126.26 (C_{arom}-H), 124.03 (C_{arom}-H), 75.94 (C_2), 60.55 (CH_2OH), 34.58 (C_3), 34.55 (*C*H$_2$CH$_2$OH), 33.06 (C_1), 32.61 (C_4). IR (ATR): 3389 (OH st), 1724 (C=O st), 1530 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{19}H_{19}NO_5K]^+$: 380.0900 [(M+K)$^+$]; found: 380.0903. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 39.5 min, τ_2 = 46.7 min (89%). $[\alpha]_D^{20}$: +32.8 (*c* = 1.0, CH_2Cl_2).



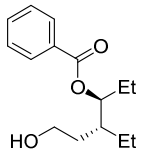
7c

(1*S*,2*R*)-2-(2-Hydroxyethyl)cyclopentyl 2-nitrobenzoate (**7c**). Following the *General Procedure I*, **7c** (27.1 mg, 0.10 mmol) was isolated as a colorless oil, starting from aldehyde **5c** (27.7 mg, 0.10 mmol) and $NaBH_4$ (11.3 mg, 0.30 mmol). Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.6, 1.7 Hz, 1H, C_{arom}-H), 7.75 (dd, *J* = 7.2, 2.0 Hz, 1H, C_{arom}-H), 7.71-7.59 (m, 2H, C_{arom}-H), 5.19-5.04 (m, 1H, C_1-H), 3.87-3.62 (m, 2H, C*H*$_2$OH), 2.29-2.16 (m, 1H, C_5-*H*$_a$H$_b$), 2.08-1.92 (m, 2H, C_2-H, C_3-*H*$_a$H$_b$), 1.88-1.65 (m, 4H, C_4-*H*$_a$H$_b$, C_5-H$_a$*H*$_b$, C*H*$_2$CH$_2$OH), 1.65-1.51 (m, 1H, C_4-H$_a$*H*$_b$), 1.35-1.18 (m, 1H, C_3-H$_a$*H*$_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.57 (COO), 148.53 (C_{arom}-N), 132.92 (C_{arom}-H), 131.85 (C_{arom}-H), 130.15 (C_{arom}-H), 127.95 (*C*$_{arom}$-C), 123.92 (C_{arom}-H), 83.90 (C_1), 61.63 (CH_2OH), 42.13 (C_2), 36.76 (*C*H$_2$CH$_2$OH), 31.48 (C_5), 30.89 (C_3), 23.12 (C_4). IR (ATR): 3386 (OH st), 1720 (C=O st), 1530 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{14}H_{17}NO_5Na]^+$: 302.1004 [$(M+Na)^+$]; found: 302.1010. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 34.0 min, τ_2 = 44.8 min (66%). $[\alpha]_D^{20}$: +12.7 (*c* = 0.6, CH_2Cl_2).



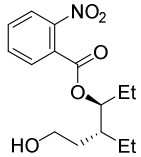
7d

(1*S*,2*R*)-2-(2-Hydroxyethyl)cycloheptyl 2-nitrobenzoate (**7d**). Following the *General Procedure I*, **7d** (31.1 mg, 0.10 mmol) was isolated as a colorless oil, starting from aldehyde **5d** (33.6 mg, 0.11 mmol) and $NaBH_4$ (12.5 mg, 0.33 mmol). Yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.6, 1.6 Hz, 1H, C_{arom}-H), 7.76 (dd, *J* = 7.4, 1.9 Hz, 1H, C_{arom}-H), 7.72-7.57 (m, 2H, C_{arom}-H), 5.02 (ddd, *J* = 8.0, 6.2, 3.8 Hz, 1H, C_1-H), 3.82-3.59 (m, 2H, C*H*$_2$OH), 2.00-1.84 (m, 3H, C_2-H, C_3-*H*$_a$H$_b$, C_7-*H*$_a$H$_b$), 1.77-1.31 (m, 10H, C_3-H$_a$*H*$_b$, C_4-H$_2$, C_5-H$_2$, C_6-H$_2$, C_7-H$_a$*H*$_b$, C*H*$_2$CH$_2$OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.15 (COO), 148.34 (C_{arom}-N), 132.94 (C_{arom}-H), 131.75 (C_{arom}-H), 130.11 (C_{arom}-H), 128.19 (*C*$_{arom}$-C), 123.90 (C_{arom}-H), 81.90 (C_1), 60.77 (CH_2OH), 40.30 (C_2), 37.18 (*C*H$_2$CH$_2$OH), 32.17 (C_7), 29.31 (C_3 + C_5), 26.63 (C_4), 22.67 (C_7). IR (ATR): 3414 (OH st), 1720 (C=O st), 1530 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 281 (16), 252 (16), 209 (18), 207 (100), 123 (15), 93 (18), 83 (27), 79 (27), 77 (30), 67 (22), 55 (19), 52 (16), 51 (15). HRMS: Calculated for $[C_{16}H_{21}NO_5K]^+$: 346.1057 [$(M+K)^+$]; found: 346.1058. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 26.2 min, τ_2 = 39.0 min (82%). $[\alpha]_D^{20}$: +21.2 (*c* = 1.0, CH_2Cl_2).



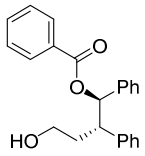
7e

(3*S*,4*R*)-4-Ethyl-6-hydroxyhexan-3-yl benzoate (**7e**). Following the *General Procedure I*, **7e** (24.8 mg, 0.10 mmol) was isolated as a colorless oil, starting from aldehyde **5e** (25.6 mg, 0.10 mmol) and $NaBH_4$ (11.3 mg, 0.30 mmol). Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 2H, C_{arom}-H), 7.63-7.51 (m, 1H, C_{arom}-H), 7.51-7.38 (m, 2H, C_{arom}-H), 5.16 (dt, *J* = 8.3, 4.0 Hz, 1H, C_3-H), 3.91-3.63 (m, 2H, C_6-H_2), 1.89-1.55 (m, 5H, C_4-H, C*H*$_2$CH$_3$ × 2), 1.54-1.28 (m, 2H, C_5-H_2), 0.95 (t, *J* = 7.4 Hz, 6H, CH_3 × 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.77 (COO), 133.00 (C_{arom}-H), 130.73 (*C*$_{arom}$-C), 129.70 (C_{arom}-H), 128.52 (C_{arom}-H), 77.92 (C_3), 61.37 (C_6), 39.74 (C_4), 32.64 (C_5), 24.05 (C_4-H*C*H$_2$CH$_3$), 23.30 (C_2), 11.94 (C_4-HCH$_2$*C*H$_3$), 10.51 (C_1). IR (ATR): 3408 (OH st), 1710 (C=O st) cm^{-1}. MS (EI) m/z (%): 122 (20), 105 (100, PhCO$^+$), 99 (15), 77 (35), 55 (17), 51 (20). HRMS: Calculated for [$C_{15}H_{22}O_3Na$]$^+$: 273.1467 [(M+Na)$^+$]; found: 273.1467. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 5.7 min, τ_2 = 6.4 min (91%). [α]$_D^{20}$: +3.9 (*c* = 0.9, CH_2Cl_2).

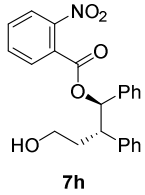


7f

(3*S*,4*R*)-4-Ethyl-6-hydroxyhexan-3-yl 2-nitrobenzoate (**7f**). Following the *General Procedure I*, **7f** (52.2 mg, 0.18 mmol) was isolated as a yellow oil, starting from aldehyde **5f** (54.3 mg, 0.19 mmol) and $NaBH_4$ (21.6 mg, 0.57 mmol). Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.4, 1.7 Hz, 1H, C_{arom}-H), 7.74 (dd, *J* = 7.2, 2.0 Hz, 1H, C_{arom}-H), 7.70-7.58 (m, 2H, C_{arom}-H), 5.17 (dt, *J* = 8.3, 4.4 Hz, 1H, C_3-H), 3.85-3.58 (m, 2H, C_6-H_2), 1.80-1.52 (m, 5H, C_4-H, C*H*$_2$CH$_3$ × 2), 1.51-1.28 (m, 2H, C_5-H_2), 1.02-0.91 (m, 6H, CH_3 × 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.41 (COO), 148.36 (C_{arom}-N), 132.83 (C_{arom}-H), 131.78 (C_{arom}-H), 129.98 (C_{arom}-H), 128.01 (*C*$_{arom}$-C), 123.92 (C_{arom}-H), 80.14 (C_3), 61.21 (C_6), 39.27 (C_4), 32.35 (C_5), 23.61 (C_4-H*C*H$_2$CH$_3$), 23.04 (C_2), 11.83 (C_4-HCH$_2$*C*H$_3$), 10.36 (C_1). IR (ATR): 3386 (OH st), 1724 (C=O st), 1533 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 151 (100), 150 (59, 2-$NO_2C_6H_4CO^+$), 99 (21), 97 (17), 81 (27), 77 (51), 76 (17), 69 (28), 65 (31), 57 (24), 55 (54), 51 (31). HRMS: Calculated for [$C_{15}H_{21}NO_5Na$]$^+$: 318.1317 [(M+Na)$^+$]; found: 318.1329. The ee was determined by HPLC using a *Chiralcel OZ-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 13.9 min, τ_2 = 22.1 min (92%). [α]$_D^{20}$: +0.4 (*c* = 1.0, CH_2Cl_2).

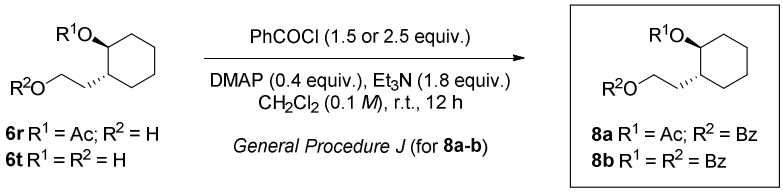

7g

(1*S*,2*R*)-4-Hydroxy-1,2-diphenylbutyl benzoate (**7g**). Following the *General Procedure I*, **7g** (32.9 mg, 0.10 mmol) was isolated as a colorless oil, starting from aldehyde **5g** (30.1 mg, 0.10 mmol) and $NaBH_4$ (11.3 mg, 0.30 mmol). Yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16-8.08 (m, 2H, C_{arom}-H), 7.65-7.53 (m, 1H, C_{arom}-H), 7.53-7.40 (m, 2H, C_{arom}-H), 7.24-7.11 (m, 8H, C_{arom}-H), 7.11-7.03 (m, 2H, C_{arom}-H), 6.15 (d, *J* = 7.8 Hz, 1H, CHOCO), 3.68-3.53 (m, 1H, C*H*CH_2), 3.53-3.34 (m, 2H, C*H*$_2$OH), 2.31 (dddd, *J* = 13.8, 8.3, 7.0, 4.0 Hz, 1H, C*H*$_a$H$_b$CH), 2.18-1.99 (m, 1H, CH$_a$*H*$_b$CH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.78 (COO), 139.74 (*C*$_{arom}$-C), 139.06 (*C*$_{arom}$-C), 133.24 (C_{arom}-H), 130.40 (*C*$_{arom}$-CO), 129.84 (C_{arom}-H), 128.99 (C_{arom}-H), 128.61 (C_{arom}-H), 128.47 (C_{arom}-H), 128.11 (C_{arom}-H), 127.85 (C_{arom}-H), 127.11 (C_{arom}-H), 127.08 (C_{arom}-H), 79.98 (*C*HOCO), 60.88 (CH_2OH), 48.54 (*C*HCH_2), 34.01 (*C*H$_2$CH). IR (ATR): 3408 (OH st), 1710 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (97), 122 (27), 118 (34), 117 (35), 106 (20), 105 (100, PhCO$^+$), 77 (54), 51 (31). HRMS: Calculated for $[C_{23}H_{23}O_3]^+$: 347.1647 [(M+H)$^+$]; found: 347.1649. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 15.9 min, τ_2 = 30.5 min (94%). $[\alpha]_D^{20}$: -22.6 (*c* = 0.3, CH_2Cl_2).


7h

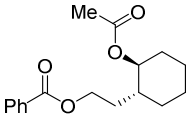
(1*S*,2*R*)-4-Hydroxy-1,2-diphenylbutyl 2-nitrobenzoate (**7h**). Following the *General Procedure I*, **7h** (74.0 mg, 0.19 mmol) was isolated as a yellow oil, starting from aldehyde **5h** (80.8 mg, 0.21 mmol) and $NaBH_4$ (23.8 mg, 0.63 mmol). Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.82 (m, 1H, C_{arom}-H), 7.76-7.61 (m, 3H, C_{arom}-H), 7.25-7.07 (m, 8H, C_{arom}-H), 7.06-6.94 (m, 2H, C_{arom}-H), 6.11 (d, *J* = 8.8 Hz, 1H, CHOCO), 3.65-3.53 (m, 1H, C*H*CH_2), 3.48-3.31 (m, 2H, C*H*$_2$OH), 2.29 (dddd, *J* = 13.7, 8.6, 6.8, 3.7 Hz, 1H, C*H*$_a$H$_b$CH), 2.03 (dddd, *J* = 13.8, 10.8, 5.8, 4.5 Hz, 1H, CH$_a$*H*$_b$CH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.33 (COO), 148.52 (C_{arom}-N), 139.33 (*C*$_{arom}$-C), 138.20 (*C*$_{arom}$-C), 132.76 (C_{arom}-H), 132.13 (C_{arom}-H), 130.29 (C_{arom}-H), 128.96 (C_{arom}-H), 128.48 (C_{arom}-H), 128.13 (C_{arom}-H), 128.10 (C_{arom}-H), 127.32 (C_{arom}-H), 127.15 (*C*$_{arom}$-CO), 127.06 (C_{arom}-H), 123.89 (C_{arom}-H), 82.09 (*C*HOCO), 60.67 (CH_2OH), 48.24 (*C*HCH_2), 34.48 (*C*H$_2$CH). IR (ATR): 3364 (OH st), 1727 (C=O st), 1533 (NO_2 st) cm^{-1}. MS (EI) m/z (%): 441 (100), 281 (15), 207 (95), 191 (15), 147 (15), 57 (42). HRMS: Calculated for $[C_{23}H_{21}NO_5Na]^+$: 414.1317 [(M+Na)$^+$]; found: 414.1321. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 44.8 min, τ_2 = 85.1 min (96%). $[\alpha]_D^{20}$: +10.6 (*c* = 1.0, CH_2Cl_2).

2.4. Synthesis of benzoylated adducts 8a-b



Scheme 2.5. General overview of the synthesis of products **8a-b**.

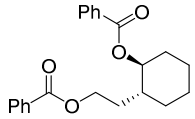
General Procedure J for the synthesis of esters **8a-b**. An ordinary vial equipped with a magnetic stirring bar was charged, under inert atmosphere, with a solution of the corresponding alcohol **6r** or **6t** (1 equiv.), DMAP (0.4 equiv.) and trimethylamine (1.8 equiv.) in dry CH_2Cl_2 (0.1 *M*). Then, benzoyl chloride (1.5 or 2.5 equiv.) was added and the mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O (1 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford the corresponding benzoylated products **8a-b**.



8a

2-((1*R*,2*S*)-2-Acetoxycyclohexyl)ethyl benzoate (**8a**). Following the *General Procedure J*, **8a** (9.8 mg, 0.03 mmol) was isolated as a colorless oil, starting from alcohol **6r** (12.2 mg, 0.07 mmol), DMAP (3.4 mg, 0.03 mmol), Et_3N (17.6 µL, 0.13 mmol) and BzCl (12.2 µL, 0.11 mmol). Yield: 48%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-7.98 (m, 2H, C_{arom}-H), 7.64-7.51 (m, 1H, C_{arom}-H), 7.52-7.40 (m, 2H, C_{arom}-H), 4.54 (td, *J* = 9.9, 4.3 Hz, 1H, C_2-H), 4.43-4.28 (m, 2H, CH_2O), 2.06 (s, 3H, CH_3), 2.04-1.90 (m, 3H, C_1-H, C_3-H_aH_b, $CH_aH_bCH_2O$), 1.82-1.45 (m, 4H, C_3-H_aH_b, C_4-H_aH_b, C_6-H_aH_b, $CH_aH_bCH_2O$), 1.40-1.04 (m, 4H, C_4-H_aH_b, C_5-H_2, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.96 (CH_3C), 166.73 (C_{arom}-*C*), 133.02 (C_{arom}-H), 130.52 (*C*$_{arom}$-C), 129.69 (C_{arom}-H), 128.49 (C_{arom}-H), 77.00 (C_2), 63.24 (CH_2O), 39.37 (C_1), 31.94 (C_3), 31.59 (C_6), 30.63 (*C*H_2CH_2O), 25.23 (C_5), 24.50 (C_4), 21.51 (CH_3). IR (ATR): 1716 (C=O st) cm^{-1}. MS (EI) m/z (%): 122 (15), 108 (66), 105 (100, $PhCO^+$), 104 (17), 93 (28), 91 (16), 79 (41), 77 (78), 51 (19). HRMS: Calculated for $[C_{17}H_{22}O_4Na]^+$: 313.1416 [$(M+Na)^+$]; found: 313.1422. The ee was determined by HPLC using a *Chiralpak AZ-3* column [*n*-

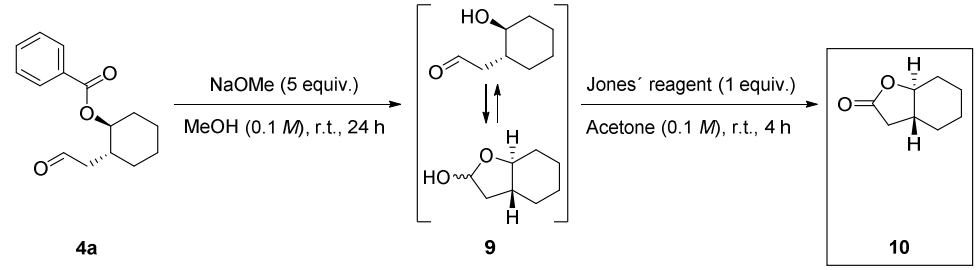
hexane/*i*-PrOH (98:2)]; flow rate 0.7 mL/min; τ_1 = 25.1 min, τ_2 = 41.7 min (90%). $[\alpha]_D^{20}$: +19.1 (*c* = 1.0, CH_2Cl_2).



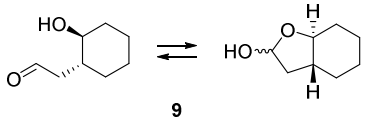
8b

2-((1*R*,2*S*)-2-(Benzoyloxy)cyclohexyl)ethyl benzoate (**8b**). Following the *General Procedure J*, **8b** (26.6 mg, 0.08 mmol) was isolated as a colorless oil, starting from alcohol **6t** (17.6 mg, 0.12 mmol), DMAP (5.9 mg, 0.05 mmol), Et_3N (30.1 µL, 0.22 mmol) and BzCl (34.8 µL, 0.30 mmol). Yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-7.99 (m, 4H, C_{arom}-H), 7.61-7.51 (m, 2H, C_{arom}-H), 7.49-7.37 (m, 4H, C_{arom}-H), 4.81 (td, *J* = 9.9, 4.2 Hz, 1H, C_2-H), 4.46-4.30 (m, 2H, CH_2O), 2.22-1.98 (m, 3H, C_1-H, C_3-H_2), 1.92-1.70 (m, 3H, C_6-H_aH_b, CH_2CH_2O), 1.69-1.52 (m, 1H, C_4-H_aH_b), 1.51-1.38 (m, 2H, C_5-H_2), 1.35-1.17 (m, 2H, C_4-H_aH_b, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.72 (*C*OOCH), 166.30 (*C*OOCH$_2$), 132.99 (C_{arom}-H), 130.77 (C_{arom}-C), 130.53 (C_{arom}-C), 129.70 (C_{arom}-H), 128.49 (C_{arom}-H), 77.48 (C_2), 63.26 (CH_2O), 39.59 (C_1), 31.93 (C_3), 31.60 (C_6), 30.63 (*C*H$_2$CH$_2$O), 25.21 (C_5), 24.52 (C_4). IR (ATR): 1713 (C=O st) cm^{-1}. MS (EI) m/z (%): 207 (16), 122 (20), 108 (33), 105 (100, PhCO$^+$), 79 (23), 77 (43). HRMS: Calculated for $[C_{22}H_{24}O_4Na]^+$: 375.1572 [(M+Na)$^+$]; found: 375.1565. The ee was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_1 = 10.7 min, τ_2 = 11.5 min (87%). $[\alpha]_D^{20}$: +21.2 (*c* = 0.8, CH_2Cl_2).

2.5. Synthesis of lactone 10



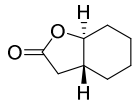
Scheme 2.6. General overview of the synthesis of product **10**.



9

2-((1*R*,2*S*)-2-Hydroxycyclohexyl)acetaldehyde and (3a*R*,7a*S*)-Octahydrobenzofuran-2-ol (**9**). NaOMe (95%, 288.6 mg, 5.07 mmol) was added to a solution of aldehyde **4a** (250.2 mg, 1.01 mmol) in MeOH (10 mL, 0.1 *M*), in an ordinary vial equipped with a magnetic stirring bar. The

reaction mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding product **9** (102.0 mg, 0.72 mmol) as an equilibrium mixture between the hemiacetal and the δ-hidroxyaldehyde. Yield: 71%. Product ratio: 1:1. d.r. (hemiacetal): 1.9:1. Due to stability issues, this mixture was not characterized and the next reaction step was immediately performed after column chromatography.[21] Several characteristic signals could be distinguished in the crude NMR. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 9.80 (t, *J* = 2.3 Hz, 1H, CHO), 5.60-5.52 (m, 1H, OC*H*OH), 5.48-5.41* (m, 1H, OC*H*OH), 2.72 (ddd, *J* = 16.4, 6.5, 2.2 Hz, 1H, CH_2CH_2CHOH).



10

(3a*R*,7a*S*)-Hexahydrobenzofuran-2(3*H*)-one (**10**).[22] A solution of the previous mixture **9** (51.5 mg, 0.36 mmol) in acetone (3.5 mL, 0.1 *M*) was placed in an ordinary vial equipped with a magnetic stirring bar, and Jones´ reagent (1.5 *M* in H_2O, 0.36 mmol, 0.24 mL) was added. The reaction mixture was stirred at room temperature for 4 h. After that, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added, the mixture was extracted with CH_2Cl_2 (3 mL × 3), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 7:3) to afford the corresponding lactone **10** (42.9 mg, 0.31 mmol) as a colorless oil. Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (td, *J* = 10.8, 3.8 Hz, 1H, C_{7a}-H), 2.50 (dd, *J* = 16.2, 6.3 Hz, 1H, C_3-H_aH_b), 2.30-2.17 (m, 2H, C_3-H_aH_b, C_{3a}-H), 2.03-1.85 (m, 3H, C_4-H_aH_b, C_7-H_2), 1.84-1.74 (m, 1H, C_6-H_aH_b), 1.58-1.24 (m, 4H, C_4-H_aH_b, C_5-H_2, C_6-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.69 (C_2), 85.29 (C_{7a}), 44.91 (C_{3a}), 36.00 (C_3), 30.32 (C_4), 28.47 (C_7), 25.45 (C_6), 24.19 (C_5).

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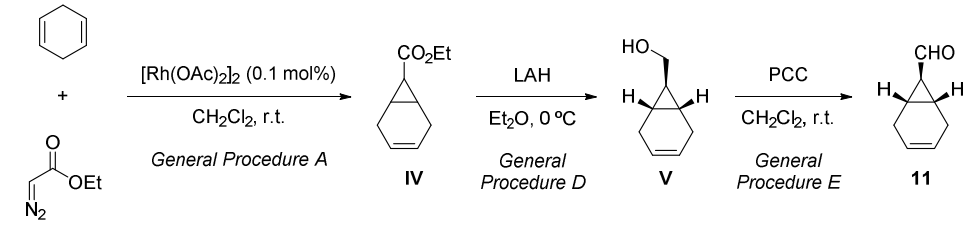
21 Reduction of this mixture using *General Procedure K* yield compound **7t** in 81% yield and observing a 90% e.e. $[\alpha]_D^{20}$: +38.4 (*c* = 0.4, CH_2Cl_2).

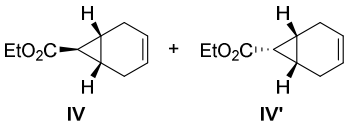
22 Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149.

3. TOTAL SYNTHESIS OF SPECIOSIN H

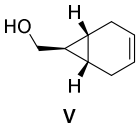
3.1. Synthesis of formylcyclopropane 11



Scheme 3.1. General overview of the synthesis of formylcyclopropane **11**.



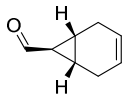
Ethyl (1*R*,6*S*,7*r*)-bicyclo[4.1.0]hept-3-ene-7-carboxylate (**IV**) and Ethyl (1*R*,6*S*,7*s*)-bicyclo[4.1.0]hept-3-ene-7-carboxylate (**IV'**).[23] Following the *General Procedure A*, **IV** and **IV'** (1.93 g, 11.6 mmol) were isolated as a colorless oil, starting from 1,4-cyclohexadiene (2.9 mL, 30.4 mmol) and ethyl diazoacetate (3.2 mL, 30.4 mmol) in the presence of rhodium(II)acetate dimmer (13.4 mg, 0.03 mmol). Yield: 38%. d.r.: 7:1. Data for **IV**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53-5.41 (m, 2H, C_3-H, C_4-H), 4.11 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 2.48-2.25 (m, 4H, C_2-H_2, C_5-H_2), 1.75-1.59 (m, 3H, C_1-H, C_6-H, C_7-H), 1.25 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.75 (COO), 123.15 (C_3, C_4), 60.23 (CH_3CH_2), 22.65 (C_2, C_5), 22.33 (C_7), 21.40 (C_1, C_6), 14.33 (CH_3). Data for **IV'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57-5.45 (m, 2H, C_3-H, C_4-H), 4.03 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 2.50-2.15 (m, 4H, C_2-H_2, C_5-H_2), 1.71-1.56 (m, 1H, C_7-H), 1.48-1.34 (m, 2H, C_1-H, C_6-H), 1.18 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.77 (COO), 124.06 (C_3, C_4), 59.90 (CH_3CH_2), 21.27 (C_7), 20.09 (C_2, C_5), 14.28 (CH_3), 14.12 (C_1, C_6).



((1*R*,6*S*,7*r*)-Bicyclo[4.1.0]hept-3-en-7-yl)methanol (**V**). Following the *General Procedure D*, **V** (1.31 g, 6.11 mmol) was isolated as a colorless oil, starting from ethyl (1*R*,6*S*,7*r*)-bicyclo[4.1.0]hept-3-ene-7-carboxylate **IV** (1.08 g, 6.5 mmol) in the presence of lithium aluminum hydride (318.8 mg, 8.4 mmol). Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42-5.27 (m, 2H, C_3-H, C_4-H), 3.37 (d, *J* = 7.0 Hz, 2H, CH_2OH), 3.32 (s, 1H, OH), 2.34-2.09 (m, 4H,

[23] Rosenberg, M. L.; Krivokapic, A.; Tilset, M. *Org. Lett.* **2009**, *11*, 547.

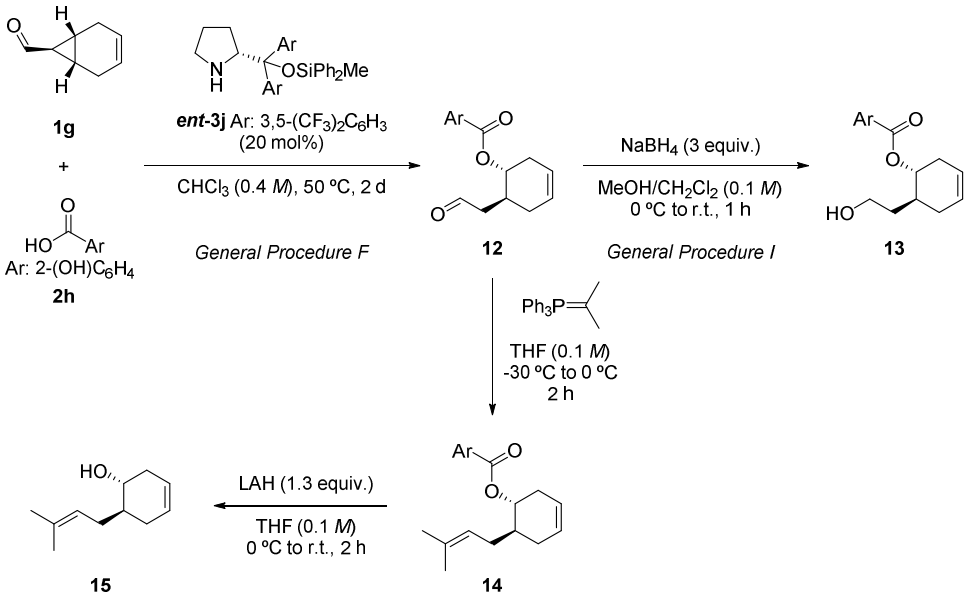
C_2-H_2, C_5-H_2), 1.00-0.87 (m, 1H, C_7-H), 0.84-0.72 (m, 2H, C_1-H, C_6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 123.60 (C_3, C_4), 66.06 (CH_2OH), 23.06 (C_2, C_5), 22.17 (C_7), 14.71 (C_1, C_6). IR (ATR): 3325 (OH st) cm^{-1}. MS (EI) m/z (%): 91 (66), 85 (60), 83 (100), 79 (35), 78 (72), 77 (28).



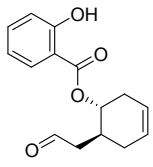
11

(1*R*,6*S*,7*r*)-Bicyclo[4.1.0]hept-3-ene-7-carbaldehyde (**11**). Following the *General Procedure E*, **11** (193.5 mg, 1.6 mmol) was isolated as a colorless oil, starting from ((1*R*,6*S*,7*r*)-bicyclo[4.1.0]hept-3-en-7-yl)methanol **V** (198.7 mg, 1.6 mmol) in the presence of pyridinium chlorochromate (646.7 mg, 3.0 mmol). Yield: 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, *J* = 5.1 Hz, 1H, CHO), 5.52-5.38 (m, 2H, C_3-H, C_4-H), 2.50-2.22 (m, 4H, C_2-H_2, C_5-H_2), 1.97-1.90 (m, 1H, C_7-H), 1.87-1.79 (m, 2H, C_1-H, C_6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.83 (CHO), 122.97 (C_3, C_4), 33.19 (C_7), 22.41 (C_2, C_5), 22.06 (C_1, C_6). IR (ATR): 1698 (C=O st) cm^{-1}. MS (EI) m/z (%): 122 (33, M^+), 93 (17), 91 (50), 85 (17), 83 (34), 81 (16), 79 (28), 78 (49), 77 (100), 68 (89), 66 (24), 65 (28), 53 (18), 51 (37).

3.2. Synthesis of products 12, 13, 14 and 15

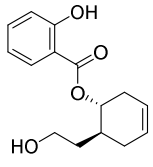


Scheme 3.2. General overview of the synthesis of compounds **12**, **13**, **14** and **15**.



12

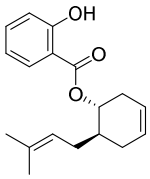
(1*R*,6*S*)-6-(2-Oxoethyl)cyclohex-3-en-1-yl 2-hydroxybenzoate (**12**). Following the *General Procedure F*, **12** (200.6 mg, 0.77 mmol) was isolated as a light yellow oil, starting from formylcyclopropane **11** (100.0 mg, 0.82 mmol) and 2-hydroxybenzoic acid **2h** (339.2 mg, 2.46 mmol) in the presence of catalyst ***ent*-3j** (59.2 mg, 0.08 mmol). Yield: 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 1H, OH), 9.81 (t, *J* = 1.6 Hz, 1H, CHO), 7.77 (dd, *J* = 7.9, 1.7 Hz, 1H, C_{arom}-H), 7.46 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1H, C_{arom}-H), 6.98 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.88 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, C_{arom}-H), 5.75-5.57 (m, 2H, C_3-H, C_4-H), 5.12 (ddd, *J* = 9.3, 7.8, 5.4 Hz, 1H, C_1-H), 2.73-2.56 (m, 3H, C_2-$H_a$$H_b$, C_6-H, C$H_a$$H_b$CHO), 2.51-2.35 (m, 2H, C_5-$H_a$$H_b$, $CH_a$$H_b$CHO), 2.31-2.20 (m, 1H, C_2-$H_a$$H_b$), 2.03-1.93 (m, 1H, C_5-$H_a$$H_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.99 (CHO), 169.76 (COO), 161.97 (C_{arom}-O), 136.02 (C_{arom}-H), 129.93 (C_{arom}-H), 125.58 (C_4), 123.77 (C_3), 119.39 (C_{arom}-H), 117.81 (C_{arom}-H), 112.47 (*C*$_{arom}$-C), 74.06 (C_1), 46.54 (*C*H_2CHO), 32.60 (C_6), 30.54 (C_5), 30.44 (C_2). IR (ATR): 3181 (OH st), 1724 (C=O st), 1670 (C=O st) cm^{-1}. MS (EI) m/z (%): 123 (19), 122 (16), 121 (18, 2-$OHC_6H_4CO^+$), 120 (22), 93 (15), 92 (25), 91 (22), 79 (100), 78 (20), 77 (18), 68 (24), 65 (53), 64 (17), 51 (16). HRMS: Calculated for $[C_{15}H_{16}O_4Na]^+$: 283.0946 [$(M+Na)^+$]; found: 283.0946. The ee (92%) was determined on compound **13**. $[\alpha]_D^{20}$: -99.2 (*c* = 0.8, CH_2Cl_2).



13

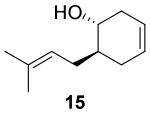
(1*R*,6*S*)-6-(2-Hydroxyethyl)cyclohex-3-en-1-yl 2-hydroxybenzoate (**13**). Following the *General Procedure I*, **13** (23.9 mg, 0.09 mmol) was isolated as a colorless oil, starting from aldehyde **12** (26.0 mg, 0.10 mmol) and $NaBH_4$ (11.3 mg, 0.30 mmol). Yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H, C_{arom}-OH), 7.83 (dd, *J* = 8.0, 1.7 Hz, 1H, C_{arom}-H), 7.44 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H, C_{arom}-H), 6.97 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.87 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H, C_{arom}-H), 5.72-5.65 (m, 1H, C_3-H), 5.64-5.57 (m, 1H, C_4-H), 5.14 (ddd, *J* = 8.9, 7.1, 5.3 Hz, 1H, C_1-H), 3.80-3.67 (m, 2H, CH_2OH), 2.59-2.50 (m, 1H, C_2-$H_a$$H_b$), 2.48-2.38 (m, 1H, C_5-$H_a$$H_b$), 2.27-2.14 (m, 2H, C_2-$H_a$$H_b$, C_6-H), 2.00-1.90 (m, 1H, C_5-$H_a$$H_b$), 1.90-1.82 (m, 1H, C$H_a$$H_b$$CH_2$OH), 1.54-1.43 (m, 1H, $CH_a$$H_b$$CH_2$OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.92 (COO), 161.88 (C_{arom}-O), 135.81 (C_{arom}-H), 129.99 (C_{arom}-H), 125.84 (C_4), 123.48 (C_3), 119.29 (C_{arom}-H), 117.75 (C_{arom}-H), 112.86 (*C*$_{arom}$-C), 74.50 (C_1), 60.67 (CH_2OH), 34.70 (*C*$H_2$$CH_2$OH), 34.08 ($C_6$), 30.19 ($C_5$), 29.39 ($C_2$). IR (ATR): 3343 (OH st), 1670 (C=O st) cm^{-1}. MS (EI) m/z (%): 252 (25), 138 (84), 121 (91, 2-$OHC_6H_4CO^+$), 120 (83), 93 (19), 92 (77), 91 (100), 81 (17), 80 (17), 79 (80), 78 (25), 77 (50), 70 (39), 65 (72), 63 (16), 54 (20), 53 (44), 52 (21), 51 (17). HRMS: Calculated for $[C_{15}H_{18}O_4Na]^+$: 285.1103 [$(M+Na)^+$];

found: 285.1103. The ee was determined by HPLC using a *Chiralpak AS-H* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1 = 8.3 min, τ_2 = 11.2 min (92%). $[\alpha]_D^{20}$: -236.9 (*c* = 0.3, CH_2Cl_2).



14

(1*R*,6*S*)-6-(3-Methylbut-2-en-1-yl)cyclohex-3-en-1-yl 2-hydroxybenzoate (**14**). A solution of isopropyltriphenylphosphonium iodide (302.6 mg, 0.70 mmol) in dry THF (7 mL, 0.1 *M*) at -30 °C, was treated with the slow addition of NaHMDS (1 *M* in THF, 0.8 mL, 0.77 mmol), under inert athmosphere. The orange-colored mixture was stirred at 0 °C for 1 h. A solution of the aldehyde **12** (100.0 mg, 0.35 mmol) in dry THF (3.5 mL, 0.1 *M*) was added to the previous mixture dropwise at -30 °C, and the reaction was stirred at 0 °C for 2 h. After that, it was treated with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with AcOEt (3 × 3 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc 19:1) to afford the corresponding alkene **14** (70.2 mg, 0.25 mmol) as a colorless oil. Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.90 (s, 1H, OH), 7.86 (dd, *J* = 8.0, 1.7 Hz, 1H, C_{arom}-H), 7.52-7.38 (m, 1H, C_{arom}-H), 6.98 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 6.95-6.83 (m, 1H, C_{arom}-H), 5.78-5.55 (m, 2H, C_3-H, C_4-H), 5.23-5.09 (m, 2H, C_1-H, $(CH_3)_2CCH$), 2.63-2.49 (m, 1H, C_2-H_aH_b), 2.41-2.29 (m, 1H, C_5-H_aH_b), 2.29-2.15 (m, 2H, C_2-H_aH_b, C_6-H), 2.15-1.85 (m, 3H, C_5-H_aH_b, $(CH_3)_2CCHCH_2$), 1.67 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.89 (COO), 161.86 (C_{arom}-O), 135.64 (C_{arom}-H), 133.35 ($(CH_3)_2C$), 130.02 (C_{arom}-H), 126.28 (C_4), 123.34 (C_3), 121.69 ($(CH_3)_2CCH$), 119.18 (C_{arom}-H), 117.67 (C_{arom}-H), 113.00 (C_{arom}-C), 74.47 (C_1), 37.82 (C_6), 30.29 (C_5), 30.26 (C_2), 29.30 ($(CH_3)_2CCHCH_2$), 25.90 (CH_3), 17.95 (CH_3). IR (ATR): 1670 (C=O st) cm^{-1}. MS (EI) m/z (%): 149 (23), 148 (94), 138 (27), 133 (39), 121 (70, 2-$OHC_6H_4CO^+$), 120 (44), 105 (22), 93 (35), 92 (45), 91 (25), 82 (17), 79 (77), 77 (28), 70 (26), 69 (100, $(CH_3)_2CHC^+$), 67 (22), 65 (29), 55 (17). $[\alpha]_D^{20}$: -98.5 (*c* = 1.0, CH_2Cl_2).

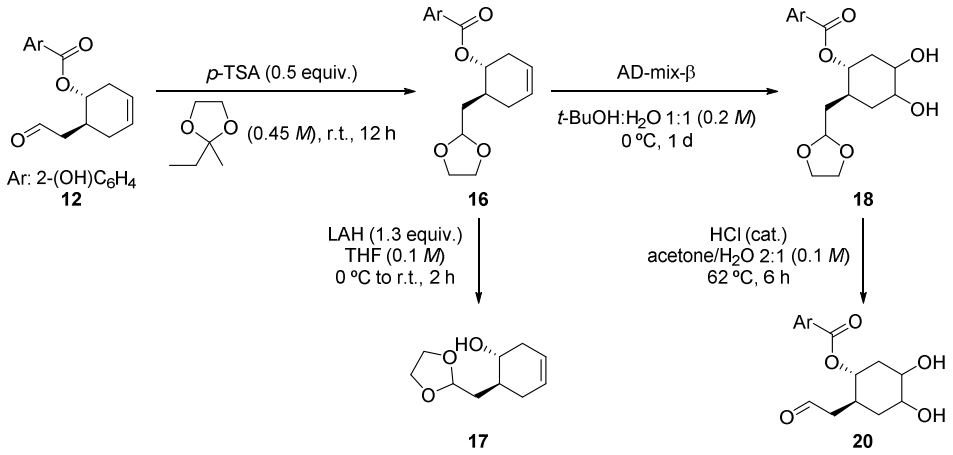


15

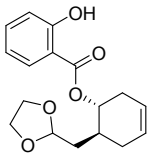
(1*R*,6*S*)-6-(3-Methylbut-2-en-1-yl)cyclohex-3-en-1-ol (**15**). Lithium aluminium hydride (12.9 mg, 0.34 mmol) was added, under inert atmosphere, to a solution of compound **14** (75.0 mg, 0.26 mmol) in dry THF (8.5 mL, 0.03 *M*) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar. After stirring the reaction mixture for 3 h at room temperature, it was cooled down to 0 °C and treated with the addition of H_2O (13 µL), an aqueous solution of NaOH (15% w/v, 13 µL) and H_2O (39 µL). The mixture was stirred for 30 min. at room temperature, filtered, dried over Na_2SO_4 and

concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc 9:1) to afford the corresponding alcohol **15** (49.2 mg, 0.30 mmol) as a colorless oil. Yield: 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68-5.59 (m, 2H, C_3-H, C_4-H), 5.19 (t, *J* = 7.3 Hz, 1H, $(CH_3)_2CCH$), 3.76-3.62 (m, 1H, C_1-H), 2.44-2.32 (m, 1H, C_2-H_aH_b), 2.31-2.15 (m, 2H, C_5-H_aH_b, $(CH_3)_2CCHCH_aH_b$), 2.08-1.91 (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 1.87-1.67 (m, 5H, C_6-H, $(CH_3)_2CCHCH_aH_b$, CH_3), 1.63 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.15 ($(CH_3)_2C$), 126.44 (C_4), 124.08 (C_3), 122.50 ($(CH_3)_2CCH$), 71.22 (C_1), 40.73 (C_6), 33.93 (C_5), 30.67 (C_2), 29.75 ($(CH_3)_2CCHCH_2$), 25.99 (CH_3), 18.00 (CH_3). IR (ATR): 3354 (OH st) cm^{-1}. MS (EI) m/z (%): 133 (16), 109 (18), 105 (30), 97 (31), 96 (41), 95 (100), 94 (19), 92 (34), 91 (34), 83 (25), 82 (38), 81 (27), 80 (21), 79 (93), 78 (17), 77 (37), 70 (19), 69 (36, $(CH_3)_2CHC^+$), 67 (56), 57 (15), 56 (25), 55 (49), 53 (27). $[\alpha]_D^{20}$: -66.7 (*c* = 1.0, CH_2Cl_2).

3.3. Synthesis of products 16, 17, 18 and 19

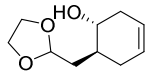


Scheme 3.3. General overview of the synthesis of compounds **16**, **17**, **18** and **19**.


16

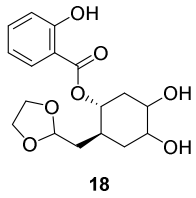
(1*R*,6*S*)-6-((1,3-Dioxolan-2-yl)methyl)cyclohex-3-en-1-yl 2-hydroxybenzoate (**16**). To a solution of the aldehyde **12** (1.2 g, 4.6 mmol) in 2-ethyl-2-methyl-1,3-dioxalane (10 mL, 0.45 *M*), was added *p*-toluenesulfonic acid (427.5 mg, 2.3 mmol). After stirring the solution at room temperature for 12 h, it was concentrated *in vacuo* and the residue was purified by flash column chromatography

(petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford the corresponding acetal **16** (1.3 g, 4.3 mmol) as a yellow oil. Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.84 (s, 1H, OH), 7.84 (dd, *J* = 8.0, 1.8 Hz, 1H, C_{arom}-H), 7.52-7.37 (m, 1H, C_{arom}-H), 6.97 (dd, *J* = 8.3, 1.1 Hz, 1H, C_{arom}-H), 6.92-6.76 (m, 1H, C_{arom}-H), 5.77-5.51 (m, 2H, C_3-H, C_4-H), 5.18 (ddd, *J* = 8.5, 6.7, 5.1 Hz, 1H, C_1-H), 4.97 (t, *J* = 4.9 Hz, 1H, $CH_2OC\mathit{H}$), 4.05-3.76 (m, 4H, CH_2O × 2), 2.64-2.44 (m, 2H, C_2-H_aH$_b$, C_5-H_aH$_b$), 2.35-2.15 (m, 2H, C_2-H$_a\mathit{H}_b$, C_6-H), 2.10-1.86 (m, 2H, C_5-H$_a\mathit{H}_b$, C_6-HCH_aH$_b$CHO), 1.72-1.58 (m, 1H, C_6-HCH$_a\mathit{H}_b$CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.74 (COO), 161.80 (C_{arom}-O), 135.64 (C_{arom}-H), 129.96 (C_{arom}-H), 125.74 (C_4), 123.25 (C_3), 119.14 (C_{arom}-H), 117.60 (C_{arom}-H), 112.82 (C_{arom}-C), 103.31 ($CH_2O\mathit{C}$H), 73.98 (C_1), 64.92 (CH_2O), 64.75 (CH_2O), 35.90 (C_6-H$\mathit{C}H_2$CHO), 33.37 (C_6), 29.82 (C_2), 29.57 (C_5). IR (ATR): 1674 (C=O st) cm^{-1}. MS (EI) m/z (%): 121 (19, 2-$OHC_6H_4CO^+$), 92 (19), 73 (100, $(CH_2)_2O_2CH^+$). HRMS: Calculated for $[C_{17}H_{20}O_5Na]^+$: 327.1208 [$(M+Na)^+$]; found: 327.1199. $[\alpha]_D^{20}$: -101.1 (*c* = 1.0, CH_2Cl_2).



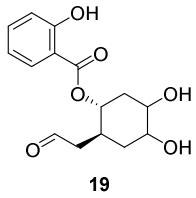
17

(1*R*,6*S*)-6-((1,3-Dioxolan-2-yl)methyl)cyclohex-3-en-1-ol (**17**). Lithium aluminium hydride (16.3 mg, 0.43 mmol) was added, under inert atmosphere, to a solution of compound **16** (100.0 mg, 0.33 mmol) in dry THF (11 mL, 0.03 *M*) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar. After stirring the reaction mixture for 3 h at room temperature, it was cooled down to 0 °C and treated with the addition of H_2O (16 µL), an aqueous solution of NaOH (15% w/v, 16 µL) and H_2O (48 µL). The mixture was stirred for 30 min. at room temperature, filtered, dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 8:2 to 6:4) to afford the corresponding alcohol **17** (55.3 mg, 0.30 mmol) as a colorless oil. Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63-5.50 (m, 2H, C_3-H, C_4-H), 4.98 (t, *J* = 4.3 Hz, 1H, $CH_2OC\mathit{H}$), 4.05-3.79 (m, 4H, CH_2O × 2), 3.62 (td, *J* = 8.7, 5.3 Hz, 1H, C_1-H), 3.08 (s, 1H, OH), 2.49-2.33 (m, 1H, C_2-H_aH$_b$), 2.30-2.19 (m, 1H, C_5-H_aH$_b$), 2.07-1.99 (m, 1H, C_6-H), 1.99-1.71 (m, 4H, C_5-H$_a\mathit{H}_b$, C_2-H$_a\mathit{H}_b$, C_6-HCH_2CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 126.07 (C_4), 124.85 (C_3), 103.57 ($CH_2O\mathit{C}$H), 71.02 (C_1), 65.16 (CH_2O), 64.94 (CH_2O), 37.01 (C_6), 36.85 (C_6-H$\mathit{C}H_2$CHO), 34.44 (C_2), 31.96 (C_5). IR (ATR): 3429 (OH st) cm^{-1}. MS (EI) m/z (%): 123 (27), 94 (32), 91 (31), 85 (35), 83 (54), 79 (100), 78 (27), 77 (32), 73 (68, $(CH_2)_2O_2CH^+$), 66 (18), 57 (24). $[\alpha]_D^{20}$: -58.4 (*c* = 0.6, CH_2Cl_2).



18

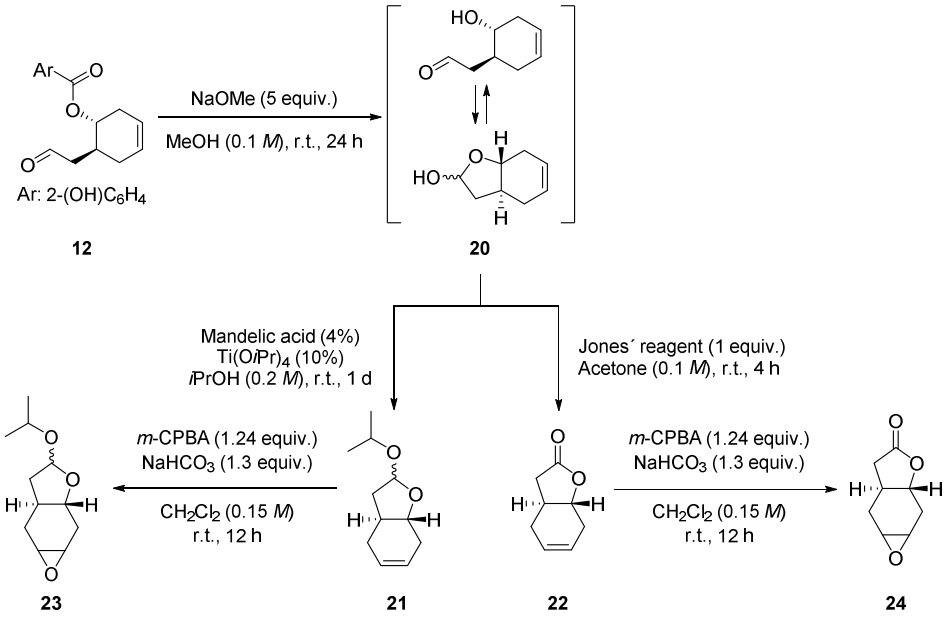
(1*R*,2*S*)-2-((1,3-Dioxolan-2-yl)methyl)-4,5-dihydroxycyclohexyl 2-hydroxybenzoate (**18**). To a solution of compound **16** (60.0 mg, 0.20 mmol) in *t*-BuOH (1 mL) and H_2O (1 mL) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar, was added AD-mix-β (208 mg). After stirring the reaction at 0 °C for 24 h, Na_2SO_3 (100 mg) was added and the mixture was stirred for 1 h at room temperature, followed by an extraction with $CHCl_3$ (3 × 3 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 7:3 to 1:9) to afford the corresponding diol **18** (44.7 mg, 0.13 mmol) as a colorless oil. Yield: 66%. d.r.: 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 10.81* (s, 1H, C_{arom}-OH), 10.74 (s, 1H, C_{arom}-OH), 7.90-7.78 (m, 1H, C_{arom}-H), 7.51-7.40 (m, 1H, C_{arom}-H), 7.02-6.94 (m, 1H, C_{arom}-H), 6.93-6.84 (m, 1H, C_{arom}-H), 4.97-4.89 (m, 1H, C_1-H), 4.89-4.79 (m, 1H, CH_2OCH), 4.05-3.74 (m, 6H, C_4-H, C_5-H, CH_2O × 2), 2.46-2.15 (m, 4H, C_2-H, C_3-H_aH_b, C_6-H_2), 2.14-1.83 (m, 3H, C_3-H_aH_b, C_2-HCH_2CHOCH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.67 (COO), 161.86 (C_{arom}-O), 135.93 (C_{arom}-H), 130.09 (C_{arom}-H), 119.37 (C_{arom}-H), 117.76 (C_{arom}-H), 112.67 (C_{arom}-C), 103.29 (CH_2OCH), 74.82 (C_1), 69.73 (C_4), 68.16 (C_5), 65.04 (CH_2O), 64.74 (CH_2O), 35.82 (C_6), 33.96 (C_2-HCH_2CHOCH_2), 33.67 (C_3), 31.49 (C_2). IR (ATR): 3454 (OH st), 1670 (C=O st) cm^{-1}.



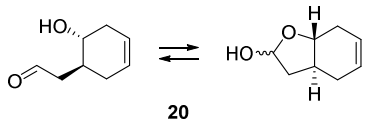
19

(1*R*,2*S*)-4,5-Dihydroxy-2-(2-oxoethyl)cyclohexyl 2-hydroxybenzoate (**19**). To a solution of compound **18** (20.0 mg, 0.06 mmol) in H_2O (0.5 mL) and acetone (1 mL), in an ordinary vial equipped with a magnetic stirring bar, was added silica gel (20 mg) and concentrated hydrochloric acid (1.6 µL, 0.02 mmol). After stirring the reaction mixture at 62 °C for 6 h, it was cooled down to room temperature, taken up in Et_2O (3 mL), filtered, washed with H_2O (3 × 3 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The corresponding aldehyde **19** (10.1 mg, 0.04 mmol) was obtained without further purification. Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.67 (s, 1H, C_{arom}-OH), 9.76 (t, *J* = 1.8 Hz, 1H, CHO), 7.83-7.72 (m, 1H, C_{arom}-H), 7.54-7.42 (m, 1H, C_{arom}-H), 7.02-6.94 (m, 1H, C_{arom}-H), 6.94-6.83 (m, 1H, C_{arom}-H), 4.84 (td, *J* = 11.1, 4.5 Hz, 1H, C_1-H), 4.08-3.99 (m, 1H, C_4-H), 3.91-3.76 (m, 1H, C_5-H), 2.88-1.85 (m, 7H, C_2-H, C_3-H_2, C_6-H_2, C_2-HCH_2CHCHO).

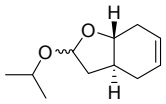
3.4. Synthesis of products 20, 21, 22, 23 and 24



Scheme 3.4. General overview of the synthesis of compounds **20**, **21**, **22**, **23** and **24**.

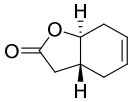


2-((1*S*,6*R*)-2-Hydroxycyclohex-3-en-1-yl)acetaldehyde and (3a*S*,7a*R*)-2,3,3a,4,7,7a-Hexahydrobenzofuran-2-ol (**20**). NaOMe (95%, 221.8 mg, 3.90 mmol) was added to a solution of aldehyde **12** (200.0 mg, 0.78 mmol) in MeOH (7.5 mL, 0.1 *M*), in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding product **20** (82.3 mg, 0.61 mmol) as an equilibrium mixture between the hemiacetal and the δ-hidroxyaldehyde. Yield: 78%. Due to stability issues, this mixture was not characterized and the next reaction step was immediately performed after column chromatography.



21

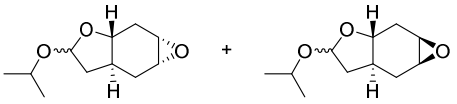
(3a*S*,7a*R*)-2-Isopropoxy-2,3,3a,4,7,7a-hexahydrobenzofuran (**21**). The mixture **20** (52.6 mg, 0.38 mmol) and mandelic acid (2.3 mg, 0.02 mmol) were suspended in *i*PrOH (1.9 mL, 0.2 *M*) and Ti(O*i*Pr)$_4$ (11.3 µL, 0.04 mmol) was added, in an ordinary vial equipped with a magnetic stirring bar. After stirring the reaction mixture for 24 h at room temperature, it was concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 19:1 to 9:1) to afford the corresponding acetal **21** (40.9 mg, 0.22 mmol) as a colorless oil. Yield: 59%. d.r.: 3:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 5.71-5.56 (m, 2H, C_5-H, C_6-H), 5.34 (t, *J* = 5.2 Hz, 1H, C_2-H), 5.29-5.20* (m, 1H, C_2-H), 4.01-3.84 (m, 1H, $(CH_3)_2CH$), 3.66 (td, *J* = 10.2, 5.3 Hz, 1H, C_{7a}-H), 3.47* (td, *J* = 10.0, 5.3 Hz, 1H, C_{7a}-H), 2.57-2.43 (m, 1H, C_7-H_aH_b), 2.43-2.24 (m, 2H, C_3-H_aH_b, C_4-H_aH_b), 2.17-1.85 (m, 2H, C_4-H_aH_b, C_7-H_aH_b), 1.76-1.56 (m, 1H, C_3-H_aH_b), 1.48 (td, *J* = 11.9, 4.5 Hz, 1H, C_{3a}-H), 1.22 (d, *J* = 6.2 Hz, 3H, CH_3), 1.15 (d, *J* = 6.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 127.42 (C_5), 125.28* (C_6), 124.94 (C_6), 102.47 (C_2), 101.78* (C_2), 80.78* (C_{7a}), 77.43 (C_{7a}), 69.80 ($(CH_3)_2CH$), 69.00* ($(CH_3)_2CH$), 41.38 (C_{3a}), 39.05 (C_3), 38.95* (C_3), 38.90* (C_{3a}), 32.92* (C_4), 31.67 (C_4), 30.54* (C_7), 30.47 (C_7), 23.98 (CH_3), 23.85* (CH_3), 21.99* (CH_3), 21.84 (CH_3). IR (ATR): 1038 (C-O st) cm^{-1}. MS (EI) m/z (%): 94 (37), 86 (17), 79 (100), 77 (18), 57 (30). $[\alpha]_D^{20}$: -27.4 (*c* = 1.0, CH_2Cl_2).



22

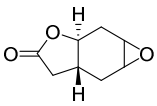
(3a*S*,7a*R*)-3a,4,7,7a-Tetrahydrobenzofuran-2(3*H*)-one (**22**). A solution of the mixture **20** (42.5 mg, 0.30 mmol) in acetone (3 mL, 0.1 *M*) was placed in an ordinary vial equipped with a magnetic stirring bar, and Jones´ reagent (1.5 *M* in H_2O, 0.30 mmol, 0.20 mL) was added. The reaction mixture was stirred at room temperature for 4 h. After that, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added, the mixture was extracted with CH_2Cl_2 (3 mL × 3), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 6:4) to afford the corresponding lactone **22** (29.0 mg, 0.21 mmol) as a colorless oil. Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79-5.59 (m, 2H, C_5-H, C_6-H), 4.10 (td, *J* = 10.2, 5.4 Hz, 1H, C_{7a}-H), 2.71-2.52 (m, 2H, C_3-H_aH_b, C_7-H_aH_b), 2.50-2.15 (m, 4H, C_3-H_aH_b, C_{3a}-H, C_4-H_aH_b, C_7-H_aH_b), 2.15-1.98 (m, 1H, C_4-H_aH_b). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.48 (C_2), 127.11 (C_5), 124.36 (C_6), 81.48 (C_{7a}), 40.28 (C_{3a}), 35.57 (C_3), 30.78 (C_4), 29.89 (C_7). IR (ATR): 1764 (C=O st) cm^{-1}. MS (EI) m/z (%):

138 (22), 83 (19), 81 (16), 79 (100), 77 (30), 67 (28), 66 (99), 55 (29), 54 (60), 53 (22). $[\alpha]_D^{20}$: -71.1 (*c* = 0.9, CH_2Cl_2).



23 **23´**

(1a*S*,2a*R*,5a*S*,6a*R*)-4-Isopropoxyoctahydrooxireno[2,3-*f*]benzofuran (**23**) and (1a*R*,2a*R*,5a*S*,6a*S*)-4-isopropoxyoctahydrooxireno[2,3-*f*]benzofuran (**23´**). To a solution of compound **21** (19.8 mg, 0.11 mmol) in CH_2Cl_2 (1 mL, 0.15 *M*) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar, were added sodium bicarbonate (12.0 mg, 0.14 mmol) and *m*-chloroperbenzoic acid (70%, 33.6 mg, 0.14 mmol). After stirring the reaction mixture at room temperature for 12 h, an aqueous solution of $Na_2S_2O_3$ (20% w/v, 1 mL) was added and the reaction mixture was stirred for another 15 minutes. After that, the organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding epoxides **23** and **23´** (16.4 mg, 0.09 mmol) as a colorless oil. Yield: 82%. d.r.: 1:1. Data for **23**: d.r.: 3:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 5.25 (t, *J* = 5.3 Hz, 1H, C_4-H), 5.23-5.18* (m, 1H, C_4-H), 3.94-3.83 (m, 1H, $(CH_3)_2CH$), 3.47 (td, *J* = 10.5, 6.2 Hz, 1H, C_{2a}-H), 3.20-3.09 (m, 2H, C_{1a}-H, C_{6a}-H), 2.51-2.34 (m, 2H, C_2-H_aH_b, C_6-H_aH_b), 2.33-2.20 (m, 1H, C_5-H_aH_b), 1.93-1.77 (m, 1H, C_2-H_aH_b), 1.77-1.61 (m, 2H, C_5-H_aH_b, C_6-H_aH_b), 1.40 (ddd, *J* = 12.7, 9.7, 4.8 Hz, 1H, C_{5a}-H), 1.20 (d, *J* = 6.3 Hz, 3H, CH_3), 1.13 (d, *J* = 6.1 Hz, 3H, CH_3). Data for **23´**: d.r.: 3:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 5.29 (t, *J* = 5.0 Hz, 1H, C_4-H), 5.20-5.15* (m, 1H, C_4-H), 3.98-3.77 (m, 1H, $(CH_3)_2CH$), 3.65 (td, *J* = 10.3, 4.9 Hz, 1H, C_{2a}-H), 3.34-3.21 (m, 1H, C_{6a}-H), 3.21-3.08 (m, 1H, C_{1a}-H), 3.21-3.08* (m, 1H, C_{2a}-H), 2.68 (ddd, *J* = 13.7, 5.0, 2.0 Hz, 1H, C_2-H_aH_b), 2.51-2.36* (m, 2H, C_2-H_aH_b, C_6-H_aH_b), 2.36-2.20 (m, 1H, C_6-H_aH_b), 2.36-2.20* (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 2.10-1.59 (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 2.10-1.59* (m, 2H, C_5-H_aH_b, C_6-H_aH_b), 1.54-1.23 (m, 2H, C_5-H_aH_b, C_{5a}-H), 1.54-1.23* (m, 1H, C_{5a}-H), 1.19 (d, *J* = 6.3 Hz, 3H, CH_3), 1.12 (d, *J* = 6.2 Hz, 3H, CH_3).

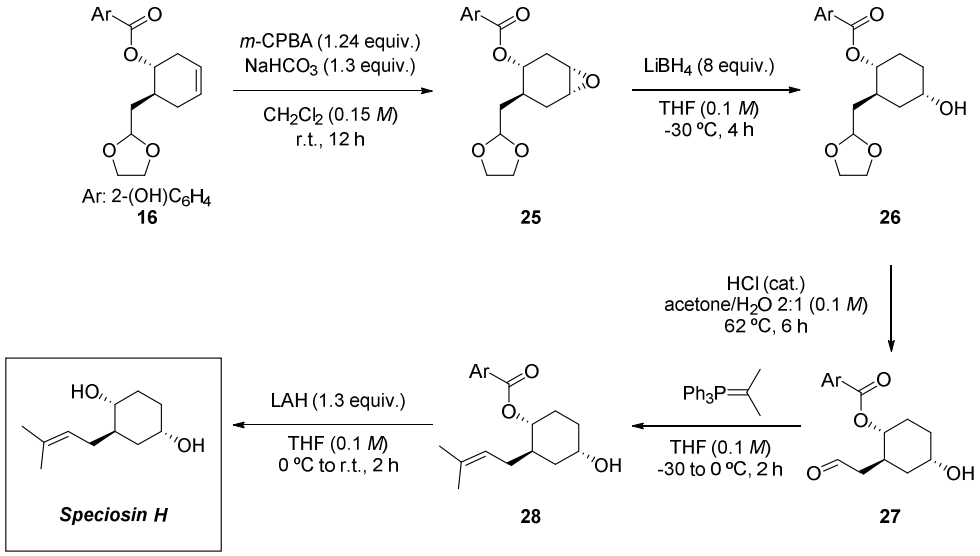


24

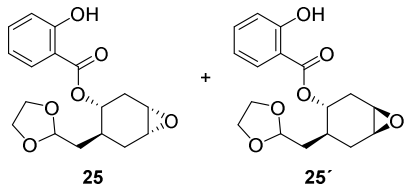
(2a*R*,5a*S*)-Hexahydrooxireno[2,3-*f*]benzofuran-4(1a*H*)-one (**24**). To a solution of compound **22** (29.0 mg, 0.21 mmol) in CH_2Cl_2 (1.5 mL, 0.15 *M*) at 0 °C, in an ordinary vial equipped with a magnetic stirring bar, were added sodium bicarbonate (22.9 mg, 0.27 mmol) and *m*-

chloroperbenzoic acid (70%, 64.0 mg, 0.26 mmol). After stirring the reaction mixture at room temperature for 12 h, an aqueous solution of $Na_2S_2O_3$ (20% w/v, 1 mL) was added and the reaction mixture was stirred for another 15 minutes. After that, the organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 8:2 to 6:4) to afford the corresponding epoxide **24** (28.5 mg, 0.18 mmol) as a colorless oil. Yield: 88%. d.r.: 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 4.08 (td, *J* = 10.5, 4.9 Hz, 1H, C_{2a}-H), 3.85* (td, *J* = 10.9, 46.3 Hz, 1H, C_{2a}-H), 3.36-3.27 (m, 1H, C_{6a}-H), 3.26-3.14 (m, 1H, C_{5a}-H), 3.26-3.14* (m, 2H, C_{5a}-H, C_{6a}-H), 2.82 (ddd, *J* = 13.6, 5.0, 2.0 Hz, 1H, C_{5a}-H), 2.63-2.46 (m, 2H, C_5-H_2), 2.46-2.34* (m, 1H, C_{5a}-H), 2.31-1.68 (m, 4H, C_2-H_2, C_6-H_2).

3.5. Synthesis of products 25, 26, 27, 28 and speciosin H



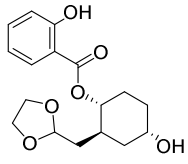
Scheme 3.5. General overview of the synthesis of compounds **25**, **26**, **27**, **28** and speciosin H.



25 **25´**

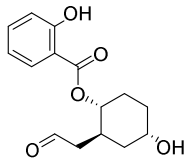
(1*S*,3*R*,4*S*,6*R*)-4-((1,3-Dioxalan-2-yl)methyl)-7-oxabicyclo[4.1.0.]heptan-3-yl 2-hydroxybenzoate (**25**) and (1*R*,3*R*,4*S*,6*S*)-4-((1,3-Dioxalan-2-yl)methyl)-7-oxabicyclo[4.1.0.]heptan-3-yl 2-hydroxybenzoate (**25´**). To a solution of compound **16** (1.1 g, 3.6 mmol) in CH_2Cl_2 (24 mL, 0.15 *M*) at 0 °C, were added sodium bicarbonate (393.2 mg, 4.7 mmol) and *m*-chloroperbenzoic acid (70%, 1.1 g, 4.5 mmol). After stirring the reaction mixture at room temperature for 12 h, an aqueous solution of $Na_2S_2O_3$ (20% w/v, 10 mL) was added and the reaction mixture was stirred for another 15 minutes. After that, the organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 8:1) to afford the corresponding epoxides **25** and **25´** (1.1 g, 3.5 mmol) as a colorless oil. Yield: 96%. d.r.: 1.6:1. Data for **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.69 (s, 1H, OH), 7.89-7.73 (m, 1H, C_{arom}-H), 7.52-7.38 (m, 1H, C_{arom}-H), 6.96 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.86 (t, *J* = 7.6 Hz, 1H, C_{arom}-H), 4.89 (t, *J* = 4.9 Hz, 1H, CH_2OCH), 4.81 (td, *J* = 10.0, 6.8 Hz, 1H, C_3-H), 3.98-3.72 (m, 4H, CH_2O × 2), 3.22-3.12 (m, 2H, C_1-H, C_6-H), 2.63-2.49 (m, 2H, C_2-H_aH_b, C_5-H_aH_b), 2.28-2.12 (m, 1H, C_4-H), 2.03-1.83 (m, 2H, C_2-H_aH_b, C_4-HCH_aH_bCHOCH$_2$), 1.79-1.66 (m, 1H, C_5-H_aH_b), 1.51 (ddd, *J* = 14.0, 8,8, 5.0 Hz, 1H, C_4-HCH$_a$$H_b$CHOCH$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.62 (COO), 161.76 (C_{arom}-O), 135.87 (C_{arom}-H), 130.05 (C_{arom}-H), 119.31 (C_{arom}-H), 117.68 (C_{arom}-H), 112.51 (C_{arom}-C), 103.09 (CH_2OCH), 73.11 (C_3), 64.97 (CH_2O), 64.66 (CH_2O), 51.87 (C_6), 50.44 (C_1), 35.42 (C_4-HCH$_2$CHOCH$_2$), 30.42 (C_4), 30.03 (C_2), 29.92 (C_5). IR (ATR): 1666 (C=O st) cm^{-1}. MS (EI) m/z (%): 121 (15, 2-OHC$_6$H$_4$CO$^+$), 73 (100, (CH$_2$)$_2$O$_2$CH$^+$), 65 (16). HRMS: Calculated for [$C_{17}H_{20}O_6Na$]$^+$: 343.1158 [(M+Na)$^+$]; found: 343.1154. $[\alpha]_D^{20}$: -81.9 (*c* = 1.0, CH_2Cl_2). Data for **25´**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.78 (s, 1H, OH), 7.90-7.72 (m, 1H, C_{arom}-H), 7.44 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H, C_{arom}-H), 6.97 (d, *J* = 8.4 Hz, 1H, C_{arom}-H), 6.86 (t, *J* = 7.6 Hz, 1H, C_{arom}-H), 5.09 (td, *J* = 8.5, 4.7 Hz, 1H, C_3-H), 4.90 (t, *J* = 4.9 Hz, 1H, CH_2OCH), 4.00-3.73 (m, 4H, CH_2O × 2), 3.30-3.14 (m, 2H, C_1-H, C_6-H), 2.68-2.55 (m, 1H, C_5-H_aH_b), 2.42 (ddd, *J* = 15.4, 6.4, 4.5 Hz, 1H, C_2-H_aH_b,), 2.14-2.00 (m, 1H, C_4-H), 2.00-1.83 (m, 3H, C_2-H_aH_b, C_5-H_aH_b, C_4-HCH_aH_bCHOCH$_2$), 1.66-1.48 (m, 1H, C_4-CH$_a$$H_b$CHOCH$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.44 (COO), 161.92 (C_{arom}-O), 135.83 (C_{arom}-H), 129.83 (C_{arom}-H), 119.20 (C_{arom}-H), 117.77 (C_{arom}-H), 112.62 (C_{arom}-C), 103.14 (CH_2OCH), 72.41 (C_3), 64.96 (CH_2O), 64.82 (CH_2O), 52.50 (C_6), 51.13 (C_1), 36.19 (C_4-HCH$_2$CHOCH$_2$), 33.02 (C_4), 29.97 (C_2), 28.89 (C_5). IR (ATR): 1674 (C=O st) cm^{-1}. MS (EI) m/z (%): 121 (17, 2-OHC$_6$H$_4$CO$^+$), 92 (15),

73 (100, $(CH_2)_2O_2CH^+$), 65 (16). HRMS: Calculated for $[C_{17}H_{20}O_6Na]^+$: 343.1158 [$(M+Na)^+$]; found: 343.1160. $[\alpha]_D^{20}$: -50.0 (*c* = 1.0, CH_2Cl_2).



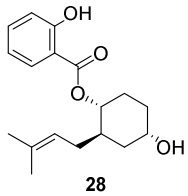
26

(1*R*,2*S*,4*S*)-2-((1,3-Dioxalan-2-yl)methyl)-4-hydroxycyclohexyl 2-hydroxybenzoate (**26**). Lithium borohydride (163.1 mg, 7.49 mmol) was added in one portion, under inert atmosphere, to a stirred solution of epoxide **25** (300 mg, 0.94 mmol) in dry THF (9 mL, 0.1 *M*) at -30 °C. After stirring the reaction mixture for 4 h at the same temperature, a saturated aqueous solution of NH_4Cl (5 mL) was added and it was stirred for another 15 minutes at room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 7:3 to 3:7) to afford the corresponding alcohol **26** (260.6 mg, 0.81 mmol) as a colorless oil. Yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H, C_{arom}-OH), 7.84 (dd, *J* = 8.0, 1.7 Hz, 1H, C_{arom}-H), 7.42 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H, C_{arom}-H), 6.95 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.85 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, C_{arom}-H), 4.97-4.79 (m, 2H, C_1-H, CH_2OCH), 4.08-3.99 (m, 1H, C_4-H), 3.97-3.72 (m, 4H, CH_2O × 2), 2.48-2.32 (m, 1H, C_2-H), 2.18-2.01 (m, 2H, C_3-H_aH_b, C_4-OH), 1.97-1.87 (m, 2H, C_6-H_2), 1.87-1.75 (m, 2H, C_5-H_aH_b, C_2-HCH_aH_bCHOCH$_2$), 1.75-1.64 (m, 1H, C_5-H_aH_b), 1.63-1.46 (m, 2H, C_3-H_aH_b, C_2-HCH$_a$$H_b$CHOCH$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.72 (COO), 161.73 (C_{arom}-O), 135.69 (C_{arom}-H), 129.96 (C_{arom}-H), 119.20 (C_{arom}-H), 117.59 (C_{arom}-H), 112.80 (C_{arom}-C), 103.31 (CH_2OCH), 76.41 (C_1), 65.07 (C_4), 64.89 (CH_2O), 64.68 (CH_2O), 37.14 (C_3), 36.16 (C_2-HCH_2CHOCH$_2$), 32.84 (C_2), 30.79 (C_5), 25.43 (C_6). IR (ATR): 3436 (OH st), 1666 (C=O st) cm^{-1}. MS (EI) m/z (%): 167 (26), 121 (19, 2-$OHC_6H_4CO^+$), 73 (100, $(CH_2)_2O_2CH^+$). HRMS: Calculated for $[C_{17}H_{22}O_6Na]^+$: 345.1314 [$(M+Na)^+$]; found: 345.1317. $[\alpha]_D^{20}$: -57.6 (*c* = 0.8, CH_2Cl_2).

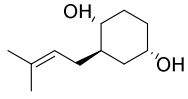


27

(1*R*,2*S*,4*S*)-4-Hydroxy-2-(2-oxoethyl)cyclohexyl 2-hydroxybenzoate (**27**). To a solution of compound **26** (100 mg, 0.31 mmol) in H_2O (1 mL) and acetone (2 mL), was added silica gel (60 mg) and concentrated hydrochloric acid (8.8 µL, 0.11 mmol). After stirring the reaction mixture at 62 °C for 6 h, it was cooled down to room temperature, taken up in Et_2O (5 mL), filtered, washed with H_2O (3 × 3 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was used directly in the next reaction without further purification.


28

(1*R*,2*S*,4*S*)-4-Hydroxy-2-(3-methylbut-2-en-1-yl)cyclohexyl 2-hydroxybenzoate (**28**). A solution of isopropyltriphenylphosphonium iodide (402.0 mg, 0.93 mmol) in dry THF (9 mL, 0.1 *M*) at -30 °C, was treated with the slow addition of NaHMDS (1 *M* in THF, 1.0 mL, 1.0 mmol), under inert athmosphere. The orange-colored mixture was stirred at 0 °C for 1 h. A solution of the crude aldehyde **27** in dry THF (3 mL, 0.1 *M*) was added to the previous mixture dropwise at -30 °C, and the reaction was stirred at 0 °C for 2 h. After that, it was treated with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with AcOEt (3 × 3 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc 7:3) to afford the corresponding alkene **28** (53.8 mg, 0.18 mmol) as a colorless oil. Yield: 76% (over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.90 (s, 1H, C_{arom}-OH), 7.87 (dd, *J* = 8.0, 1.8 Hz, 1H, C_{arom}-H), 7.45 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H, C_{arom}-H), 6.98 (dd, *J* = 8.4, 1.1 Hz, 1H, C_{arom}-H), 6.88 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, C_{arom}-H), 5.18-5.04 (m, 1H, $(CH_3)_2CC\mathit{H}$), 4.97-4.79 (m, 1H, C_1-H), 4.12-4.04 (m, 1H, C_4-H), 2.27-2.10 (m, 2H, C_2-H, C_2-HCH_aH$_b$CHC$(CH_3)_2$), 2.01-1.88 (m, 4H, C_3-H_aH$_b$, C_6-H$_2$, C_2-HCH$_a\mathit{H}_b$CHC$(CH_3)_2$), 1.88-1.78 (m, 1H, C_5-H_aH$_b$), 1.78-1.66 (m, 1H, C_5-H$_a\mathit{H}_b$), 1.64 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.45 (ddd, *J* = 13.7, 10.5, 2.9 Hz, 1H, C_3-H$_a\mathit{H}_b$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.93 (COO), 161.86 (C_{arom}-O), 135.70 (C_{arom}-H), 133.43 ($(CH_3)_2\mathit{C}$), 130.04 (C_{arom}-H), 121.58 ($(CH_3)_2C\mathit{C}$H), 119.26 (C_{arom}-H), 117.68 (C_{arom}-H), 112.98 (C_{arom}-C), 76.74 (C_1), 65.53 (C_4), 36.92 (C_2), 36.71 (C_3), 31.20 (C_5), 30.58 (C_2-HCH$_2$CHC$(CH_3)_2$), 25.92 (CH_3), 25.61 (C_6), 17.93 (CH_3). IR (ATR): 3357 (OH st), 1666 (C=O st) cm^{-1}. MS (EI) m/z (%): 166 (54), 149 (17), 148 (32), 138 (20), 133 (53), 121 (60, 2-OH$C_6H_4CO^+$), 120 (44), 109 (18), 107 (23), 105 (21), 96 (15), 95 (16), 93 (37), 92 (24), 91 (21), 83 (15), 81 (21), 79 (38), 77 (15), 69 (100, $(CH_3)_2CHC^+$), 67 (27), 65 (27), 57 (17), 55 (29), 53 (16). HRMS: Calculated for $[C_{18}H_{25}O_4]^+$: 305.1753 [(M+H)$^+$]; found: 305.1749. $[\alpha]_D^{20}$: -52.9 (*c* = 0.2, CH_2Cl_2).


Speciosin H

Speciosin H.[24] Lithium aluminium hydride (4.0 mg, 0.11 mmol) was added, under inert atmosphere, to a solution of compound **28** (9.3 mg, 0.03 mmol) in dry THF (1 mL, 0.03 *M*) at 0 °C. After stirring the reaction mixture for 3 h at room temperature, it was cooled down to 0 °C and treated with the addition of water (4 µL), an aqueous solution of NaOH (15% w/v, 4 µL) and water (12 µL). The mixture was stirred for 30

[24] Jiang, M.-Y.; Zhang, L.; Liu, R.; Dong, Z.-J.; Liu, J.-K. *J. Nat. Prod.* **2009**, *72*, 1405.

min. at room temperature, filtered, dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (CH_2Cl_2/MeOH 19:1) to afford *Speciosin H* (5.0 mg, 0.03 mmol) as a white solid. Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22-5.16 (m, 1H, $(CH_3)_2CC\mathit{H}$), 4.01 (p, *J* = 3.4 Hz, 1H, C_4-H), 3.35 (td, *J* = 9.5, 4.1 Hz, 1H, C_1-H), 2.31 (dt, *J* = 13.5, 6.3 Hz, 1H, C_2-HCH_aH$_b$CHC$(CH_3)_2$), 1.94 (dt, *J* = 14.6, 7.5 Hz, 1H, C_2-HCH$_a\mathit{H}_b$CHC$(CH_3)_2$), 1.86-1.73 (m, 4H, C_2-H, C_3-H_aH$_b$, C_5-H_aH$_b$, C_6-H_aH$_b$), 1.71 (s, 3H, CH_3), 1.69-1.66 (m, 1H, C_6-H$_a\mathit{H}_b$), 1.63 (s, 3H, CH_3), 1.61-1.52 (m, 2H, C_3-H$_a\mathit{H}_b$, OH), 1.32-1.22 (m, 2H, C_5-H$_a\mathit{H}_b$, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.34 ($(CH_3)_2\mathit{C}$), 121.64 ($(CH_3)_2C\mathit{C}$H), 73.17 (C_1), 64.95 (C_4), 38.78 (C_2), 35.94 (C_5), 30.35 (C_3), 30.22 (C_2-HCH$_2$CHC$(CH_3)_2$), 28.08 (C_6), 25.03 (CH_3) 17.01 (CH_3). IR (ATR): 3329 (OH st) cm^{-1}. MS (EI) m/z (%): 184 (17), 133 (53), 110 (16), 109 (64), 107 (22), 105 (29), 97 (19), 96 (65), 95 (51), 93 (22), 91 (27), 85 (15), 83 (33), 82 (29), 81 (54), 80 (21), 79 (60), 77 (25), 71 (24), 70 (34), 69 (100, $(CH_3)_2CHC^+$), 68 (25), 67 (67), 57 (40), 56 (22), 55 (79), 54 (16), 53 (33). HRMS: Calculated for $[C_{11}H_{21}O_2]^+$: 185.1542 [$(M+Na)^+$]; found: 185.1547. M.p. (petroleum ether/EtOAc): 99-101 °C. $[\alpha]_D^{20}$: -32.1 (*c* = 0.2, CH_2Cl_2).

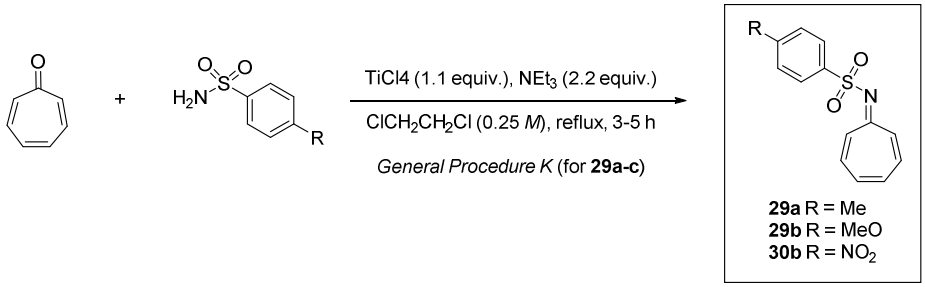
4. PHOSPHINE CATALYSED ENANTIOSELECTIVE [8+4] HIGH-ORDER CYCLOADDITION

4.1. Synthesis of azaheptafulvenes 29a-d

Azaheptafulvenes **29a-c** were synthesised modifying a previously described literature procedure.[25]

Azaheptafulvene **29d**[26] was prepared following a procedure previously described in the literature.

*4.1.1. Standard procedure K for the synthesis of azaheptafulvenes **29a-c***



Scheme 4.1. General overview of the synthesis of azaheptafulvenes **29a-c**.

General Procedure K for the synthesis of azaheptafulvenes **29a-c**. The corresponding sulfonamide (1 equiv.) and tropone (1 equiv.) were disolved in 1,2-dicloroethane (0.25 *M*) and $TiCl_4$ (1.1 equiv.) was added with stirring, followed by dropwise addition of NEt_3 (2.2 equiv.). The reaction mixture was heated at reflux for 3-5 h. Then, it was quenched with the addition of water, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (x 3). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 7:3 to 3:7) to afford the corresponding azaheptafulvenes **29a-c**.

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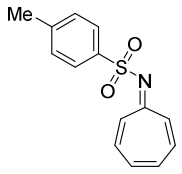
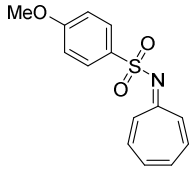
[25] Ram, R. N.; Kahn, A. A. *Synth. Commun.* **2001**, *31*, 841.

[26] Sanechika, K.-I.; Kajigaeshi, S.; Kanemasa, S. *Synthesis* **1977**, 202.



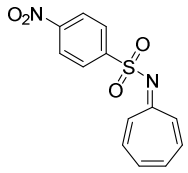
29a

N-(Cyclohepta-2,4,6-trien-1-ylidene)-4-methylbenzenesulfonamide (**29a**). Following the *General Procedure K*, **29a** (2.2 g, 8.6 mmol) was isolated as a light green solid, starting from tropone (1.1 g, 10. mmol), 4-methylbenzenesulfonamide (1.7 g, 10 mmol), $TiCl_4$ (1.2 mL, 11 mmol) and NEt_3 (2.8 mL, 22 mmol). Yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29-6.98 (m, 10H, C_{arom}-H), 2.41 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.53 (C_1), 143.02 (C_{arom}-S), 139.53 (C_{arom}-CH_3), 139.00 (C_3, C_4, C_5, C_6), 136.81 (C_2, C_7), 129.44 (SC_{arom}-C_{arom}-H x 2), 126.86 (CH_3C_{arom}-C_{arom}-H x 2), 21.63 (CH_3). IR (ATR): 1135 (S=O st) cm^{-1}. HRMS: Calculated for $[C_{14}H_{14}NO2S]^+$: 260.0745 [$(M+H)^+$]; found: 260.0745.



29b

N-(Cyclohepta-2,4,6-trien-1-ylidene)-4-methoxybenzenesulfonamide (**29b**). Following the *General Procedure K*, **29b** (2.0 g, 7.2 mmol) was isolated as a light green solid, starting from tropone (1.1 g, 10. mmol), 4-methoxybenzenesulfonamide (1.9 g, 10 mmol), $TiCl_4$ (1.2 mL, 11 mmol) and NEt_3 (2.8 mL, 22 mmol). Yield: 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-6.87 (m, 10H, C_{arom}-H), 3.86 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.40 (C_1), 162.75 (C_{arom}-O), 138.86 (C_3, C_4, C_5, C_6), 136.74 (C_2, C_7), 134.39 (C_{arom}-S), 129.01 (OC_{arom}-C_{arom}-H x 2), 114.05 (SC_{arom}-C_{arom}-H x 2), 55.71 (CH_3).



29c

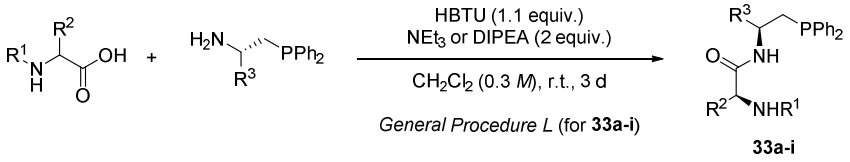
N-(Cyclohepta-2,4,6-trien-1-ylidene)-4-nitrobenzenesulfonamide (**29c**). Following the *General Procedure K*, **29c** (2.4 g, 8.1 mmol) was isolated as a yellow solid, starting from tropone (1.1 g, 10. mmol), 4-nitrobenzenesulfonamide (2.0 g, 10 mmol), $TiCl_4$ (1.2 mL, 11 mmol) and NEt_3 (2.8 mL, 22 mmol). Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39-8.31 (m, 2H, NC_{arom}-C_{arom}-H), 8.24-8.15 (m, 2H, SC_{arom}-C_{arom}-H), 7.69 (s, 2H, C_3, C_6), 7.41-7.28 (m, 2H, C_4, C_5), 7.25-7.15 (m, 2H, C_2, C_7). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.01 (C_1), 149.80 (C_{arom}-NO_2), 148.15 (C_{arom}-S), 140.13 (C_3, C_4, C_5, C_6), 137.62 (C_2, C_7), 128.13 (SC_{arom}-C_{arom}-H x 2), 124.08 (NO_2C_{arom}-C_{arom}-H x 2), 21.63 (CH_3).

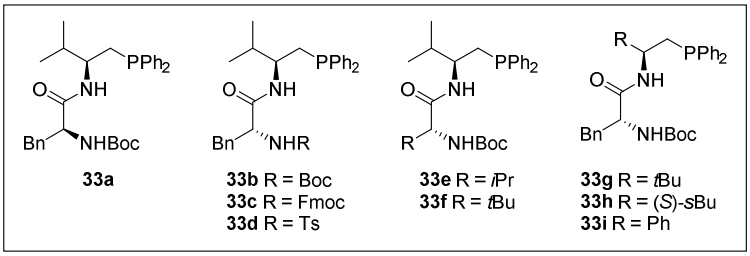
4.2. Synthesis of of chiral phosphines 31h-l, 32a-j and 33a-k

Catalysts, **31h**[27], **31i**[28], **32a-e,g**[29], **32f**[30], **32h-j**[31] and **33j-k**[31] were prepared following procedures previously described in the literature.

Catalysts **33a-l** were synthesised modifying a previously described literature procedure.[32]

*4.2.1. Standard procedure L for the synthesis of amino acid derived catalysts **33a-i***





Scheme 4.2. General overview of the synthesis of amino acid derived catalysts **33a-i**.

General Procedure L for the synthesis of amino acid derived catalysts **33a-i**. To a solution of the corresponding phosphine (1 equiv.) in anhydrous CH_2Cl_2 (0.3 *M*) was added the corresponding amino acid (1.1 equiv.), HBTU (1.1 equiv.) and NEt_3

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27 Qian, J.-Y.; Wang, C.-C.; Sha, F.; Wu, X.-Y. *RSC Adv.* **2012**, *2*, 6042.

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29 Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4467.

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31 Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231.

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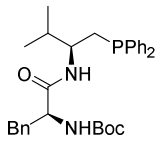
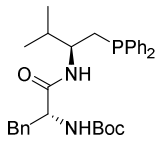
(2 equiv.) or *N*,*N*-diisopropylethylamine (2 equiv.) under inert atmosphere. The reaction mixture was degassed by bubbling argon through the solution and it was stirred at room temperature for three days. Then, the reaction mixture was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/EtOAc) to afford the corresponding phosphine catalyst **32a-l**, which was stored under inert atmosphere to avoid oxidation.



33a

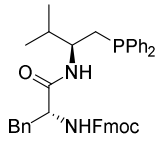
tert-Butyl ((S)-1-(((S)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**33a**). Following the *General Procedure L*, **33a** (200 mg, 0.39 mmol) was isolated by FC (petroleum ether/EtOAc 8:2) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (202 mg, 0.75 mmol), Boc-L-phenylalanine (218 mg, 0.82 mmol), HBTU (310 mg, 0.82 mmol) and NEt_3 (0.21 mL, 1.50 mmol). Yield: 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.12 (m, 15H, C_{arom}-H), 5.81 (d, *J* = 9.2 Hz, 1H, CHCON*H*), 5.04 (s, 1H, BocNH), 4.18 (q, *J* = 7.4 Hz, 1H, CHCO), 3.96-3.76 (m, 1H, C*H*CH_2P), 3.03 (d, *J* = 7.1 Hz, 2H, C*H*$_2C_{arom}$), 2.08 (d, *J* = 7.2 Hz, 2H, C*H*$_2$P), 2.03-1.88 (m, 1H, C*H*$(CH_3)_2$), 1.40 (s, 9H, CCH_3 x 3), 0.79 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 0.76 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.66 (NH*C*OCH), 155.59 (COO), 138.53 (d, $^1J_{CP}$ = 12.7 Hz, C_{arom}-P), 138.24 (d, $^1J_{CP}$ = 12.0 Hz, C_{arom}-P), 137.10 (*C*$_{arom}$-C), 133.06 (d, $^2J_{CP}$ = 18.7 Hz, C_{arom}-H), 132.81 (d, $^2J_{CP}$ = 18.4 Hz, C_{arom}-H), 129.52 (C_{arom}-H), 128.89 C_{arom}-H), 128.81 (C_{arom}-H), 128.70 (C_{arom}-H), 128.61 (C_{arom}-H), 128.54 (C_{arom}-H), 126.89 (C_{arom}-H), 80.12 (*C*$(CH_3)_3$), 55.90 (*C*HCO), 52.14 (d, $^2J_{CP}$ =14.9 Hz, *C*HCH_2P), 38.06 (*C*H_2C_{arom}), 31.05 (d, $^1J_{cp}$ = 13.4 Hz, CH_2P), 31.77 (*C*H$(CH_3)_2$), 28.39 (C*C*H_3 x 3), 19.17 (CH*C*H_3), 17.04 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.71. IR (ATR): 3280 (N-H st), 1685 (C=O st), 1630 (C=O st), 1540 (N-C=O st) cm^{-1}. HRMS: Calculated for $[C_{31}H_{40}N_2O_3P]^+$: 519.2777 [(M+H)$^+$]; found: 519.2804. M.p. (petroleum ether/EtOAc): 163-165 °C. $[\alpha]_D^{20}$: +20.5 (*c*=0.7, $CHCl_3$).



33b

tert-Butyl ((R)-1-(((S)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**33b**). Following the *General Procedure L*, **33b** (205 mg, 0.40 mmol) was isolated by FC (petroleum ether/EtOAc 8:2) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (175 mg, 0.65 mmol), Boc-D-phenylalanine (190 mg, 0.72 mmol), HBTU (275 mg, 0.72 mmol) and NEt_3 (0.18 mL, 1.30 mmol). Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.11 (m, 15H, C_{arom}-H), 5.71 (s, 1H, CHCON*H*), 4.69 (s, 1H, BocNH), 4.24-4.12 (m, 1H, CHCO), 4.10-

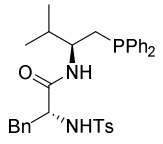
3.89 (m, 1H, C*H*CH_2P), 3.05 (dd, *J* = 13.9, 6.9 Hz, 1H, C$H_a$$H_b$$C_{arom}$), 2.99-2.81 (m, 1H, $CH_a$$H_b$$C_{arom}$), 2.26-2.12 (m, 2H, CH_2P), 2.06-1.78 (m, 1H, C*H*$(CH_3)_2$), 1.40 (s, 9H, CCH_3 x 3), 0.75 (d, *J* = 6.7 Hz, 6H, CHCH_3 x 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.39 (NH*C*OCH), 155.32 (COO), 138.69 (d, $^1J_{CP}$ = 9.0 Hz, C_{arom}-P), 138.54 (d, $^1J_{CP}$ = 8.6 Hz, C_{arom}-P), 137.06 (*C*$_{arom}$-C), 132.90 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-H), 132.80 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-H), 129.32 (C_{arom}-H), 128.84 (C_{arom}-H), 128.79 (C_{arom}-H), 128.71 (C_{arom}-H), 128.62 (C_{arom}-H), 128.52 (C_{arom}-H), 126.86 (C_{arom}-H), 80.07 (*C*$(CH_3)_3$), 56.10 (*C*HCO), 52.45 (d, $^2J_{CP}$ =14.8 Hz, *C*HCH_2P), 38.25 (*C*H_2C_{arom}), 32.23 (d, $^3J_{CP}$ = 8.4 Hz, *C*H$(CH_3)_2$), 31.58 (d, $^1J_{CP}$ = 15.0 Hz, CH_2P), 28.32 (C*C*H_3 x 3), 18.83 (CH*C*H_3), 17.48 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.31. IR (ATR): 3307 (N-H st), 1687 (C=O st), 1652 (C=O st), 1529 (N-C=O st), 1497 (N-C=O st) cm^{-1}. HRMS: Calculated for $[C_{31}H_{40}N_2O_3P]^+$: 519.2777 [$(M+H)^+$]; found: 519.2800. M.p. (petroleum ether/EtOAc): 108-110 °C. $[\alpha]_D^{20}$: +22.0 (*c*=0.8, $CHCl_3$).



33c

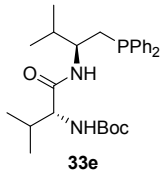
(9*H*-Fluoren-9-yl)methyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate (**33c**). Following the *General Procedure L*, **33c** (205 mg, 0.32 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 2:8) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (170 mg, 0.63 mmol), Fmoc-D-phenylalanine (265 mg, 0.69 mmol), HBTU (265 mg, 0.69 mmol) and *N*,*N*-diisopropylethylamine (0.2 mL, 1.26 mmol). Yield: 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H, C_{arom}-H), 7.64-7.48 (m, 2H, C_{arom}-H), 7.48-7.10 (m, 19H, C_{arom}-H), 5.54 (d, *J* = 9.3 Hz, 1H, CHCON*H*), 4.95 (d, *J* = 8.2 Hz, 1H, FmocNH), 4.51-4.32 (m, 2H, CH_2O), 4.32-4.12 (m, 2H, C*H*CH_2O, CHCO), 3.98 (dt, *J* = 9.5, 4.9 Hz, 1H, C*H*CH_2P), 3.13-2.83 (m, 2H, CH_2C_{arom}), 2.29-2.06 (m, 2H, CH_2P), 1.93-1.75 (m, 1H, C*H*$(CH_3)_2$), 0.84-0.66 (m, 6H, CHCH_3 x 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.85 (NH*C*OCH), 155.96 (COO), 143.86 (*C*$_{arom}$-C), 143.83 (*C*$_{arom}$-C), 141.43 (*C*$_{arom}$-C), 138.57 (d, $^1J_{CP}$ = 13.7 Hz, C_{arom}-P), 138.55 (d, $^1J_{CP}$ = 12.7 Hz, C_{arom}-P), 136.83 (*C*$_{arom}$-C), 132.90 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-H), 132.80 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-P), 129.37 (C_{arom}-H), 128.87 (C_{arom}-H), 128.84 (C_{arom}-H), 128.81 (C_{arom}-H), 128.75 (C_{arom}-H), 128.66 (C_{arom}-H), 128.57 (C_{arom}-H), 127.85 (C_{arom}-H), 127.84 (C_{arom}-H), 127.20 (C_{arom}-H), 127.17 (C_{arom}-H), 127.03 (C_{arom}-H), 125.12 (C_{arom}-H), 125.06 (C_{arom}-H), 120.09 (C_{arom}-H), 66.90 (CH_2O), 56.42 (*C*HCO), 52.79 (d, $^2J_{CP}$ = 14.4 Hz, *C*HCH_2P), 47.24 (*C*HCH_2O), 38.39 (*C*H_2C_{arom}), 32.44 (d, $^3J_{CP}$ = 8.6 Hz, *C*H$(CH_3)_2$), 31.47 (d, $^1J_{CP}$ = 15.0 Hz, CH_2P), 18.78 (CH*C*H_3), 17.82 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.08. IR (ATR): 3297 (N-H st), 1690 (C=O st), 1647 (C=O st), 1528 (N-C=O st) cm^-

[1]. HRMS: Calculated for $[C_{41}H_{42}N_2O_3P]^+$: 641.2933 [(M+H)$^+$]; found: 641.2949. M.p. (petroleum ether/EtOAc): 135-138 °C. $[\alpha]_D^{20}$: +13.34 (*c*=1.3, $CHCl_3$).



33d

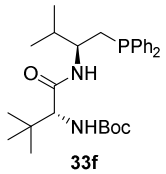
(*R*)-*N*-((*S*)-1-(Diphenylphosphanyl)-3-methylbutan-2-yl)-2-((4-methylphenyl) sulfonamido)-3-phenylpropanamide (**33d**). Following the *General Procedure L*, **33d** (340 mg, 0.59 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (250 mg, 0.92 mmol), tosyl-D-phenylalanine (320 mg, 1.01 mmol), HBTU (380 mg, 1.01 mmol) and NEt_3 (0.26 mL, 1.84 mmol). Yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.25 (m, 12H, C_{arom}-H), 7.25-7.03 (m, 5H, C_{arom}-H), 6.99-6.82 (m, 2H, C_{arom}-H), 6.48 (d, *J* = 9.5 Hz, 1H, TsNH), 4.80 (d, *J* = 6.4 Hz, 1H, CHCON*H*), 4.13-3.96 (m, 1H, CHCO), 3.92-3.72 (m, 1H, C*H*CH_2P), 3.02 (dd, *J* = 14.2, 5.2 Hz, 1H, C$H_a$$H_b$$C_{arom}$), 2.67 (dd, *J* = 14.1, 8.4 Hz, 1H, $CH_aH_bC_{arom}$), 2.35 (s, 3H, C_{arom}-CH_3), 2.22 (d, *J* = 7.2 Hz, 2H, CH_2P), 2.05-1.85 (m, 1H, C*H*$(CH_3)_2$), 0.88 (d, *J* = 6.7 Hz, 6H, CHCH_3 x 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.39 (NHCO), 143.58 (C_{arom}-S), 138.58 (d, $^1J_{CP}$ = 13.6 Hz, C_{arom}-P), 138.49 (d, $^1J_{CP}$ = 12.8 Hz, C_{arom}-P), 135.61 (*C*$_{arom}$-CH_3), 135.52 (*C*$_{arom}$-CH), 132.90 (d, $^2J_{CP}$ = 19.8 Hz, C_{arom}-H), 132.64 (d, $^2J_{CP}$ = 19.9 Hz, C_{arom}-H) 129.71 (C_{arom}-H), 129.12 (C_{arom}-H), 128.78 (C_{arom}-H), 128.74 (C_{arom}-H), 128.68 (C_{arom}-H), 128.59 (C_{arom}-H), 128.56 (C_{arom}-H), 128.47 (C_{arom}-H), 126.99 (C_{arom}-H), 126.94 (C_{arom}-H), 58.05 (*C*HCO), 52.75 (d, $^2J_{CP}$ = 15.0 Hz, *C*HCH_2P), 37.99 (*C*H_2C_{arom}), 32.54 (d, $^3J_{CP}$ = 8.4 Hz, *C*H$(CH_3)_2$), 31.49 (d, $^1J_{CP}$ = 14.7 Hz, CH_2P), 21.46 (C_{arom}-*C*H_3), 18.82 (CH*C*H_3), 17.45 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -22.90. IR (ATR): 1655 (C=O st), 1522 (N-C=O st) cm^{-1}. HRMS: Calculated for $[C_{33}H_{38}N_2O_3PS]^+$: 573.2341 [(M+H)$^+$]; found: 573.2360. M.p. (petroleum ether/EtOAc): 58-60 °C. $[\alpha]_D^{20}$: +54.6 (*c*=1.0, $CHCl_3$).



33e

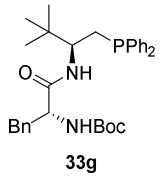
tert-Butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl) carbamate (**33e**). Following the *General Procedure L*, **33e** (370 mg, 0.79 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (330 mg, 1.22 mmol), Boc-D-valine (290 mg, 1.34 mmol), HBTU (510 mg, 1.34 mmol) and NEt_3 (0.35 mL, 2.44 mmol). Yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.29 (m, 10H, C_{arom}-H), 5.78 (d, *J* = 9.3 Hz, 1H, CHCON*H*), 4.86 (s, 1H, BocNH), 4.05-3.91 (m, 1H, C*H*CH_2P), 3.77 (dd, *J* = 8.6, 5.5 Hz, 1H, CHCO), 2.28-2.20 (m, 2H, CH_2P), 2.20-2.08 (m, 1H, C*H*$(CH_3)_2$), 2.06-1.91 (m, 1H, C*H*$(CH_3)_2$), 1.45 (s, 9H, CCH_3 x3), 0.93 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.91-0.79 (m, 9H, CHCH_3 x 3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ

170.83 (NH*C*OCH), 155.82 (COO), 138.52 (d, $^{1}J_{CP}$ = 13.7 Hz, C_{arom}-P), 138.44 (d, $^{1}J_{CP}$ = 12.6 Hz, C_{arom}-P), 133.02 (d, $^{2}J_{CP}$ = 19.4 Hz, C_{arom}-H), 132.62 (d, $^{2}J_{CP}$ = 19.0 Hz, C_{arom}-H), 128.82 (C_{arom}-H), 128.68 (C_{arom}-H), 128.63 (C_{arom}-H), 128.58 (C_{arom}-H), 128.54(C_{arom}-H), 128.48 (C_{arom}-H), 79.72 (*C*$(CH_3)_3$), 60.27 (*C*HCO), 52.14 (d, $^{2}J_{CP}$ = 14.5 Hz, *C*HCH_2P), 32.08 (d, $^{3}J_{CP}$ = 8.3 Hz, $PCH_2CHCH(CH_3)_2$), 31.81 (d, $^{1}J_{CP}$ = 14.8 Hz, *C*H_2P), 30.45 (*C*HCHCO), 28.37 (C*C*H_3 x 3), 19.48 (CH*C*H_3), 19.06 (CH*C*H_3), 17.75 (CH*C*H_3), 17.46 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.74. IR (ATR): 3318 (N-H st), 1686 (C=O st), 1649 (C=O st), 1517 (N-C=O st) cm^{-1}. HRMS: Calculated for $[C_{27}H_{40}N_2O_3P]^+$: 471.2777 [$(M+H)^+$]; found: 471.2798. M.p. (petroleum ether/EtOAc): 76-79 ºC. $[\alpha]_D^{20}$: +28.8 (*c*=1.0, $CHCl_3$).



33f

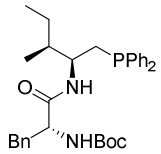
tert-Butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (**33f**). Following the *General Procedure L*, **33f** (400 mg, 0.83 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 7:3) as a white solid starting from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine (300 mg, 1.10 mmol), Boc-D-*tert*-leucine (280 mg, 1.21 mmol), HBTU (459 mg, 1.21 mmol) and NEt_3 (0.31 mL, 2.2 mmol). Yield: 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.28 (m, 10H, C_{arom}-H), 5.65 (d, *J* = 9.0 Hz, 1H, CHCON*H*), 5.24 (d, *J* = 9.1 Hz, 1H, BocNH), 4.02-3.84 (m, 1H, C*H*CH_2P), 3.71 (d, *J* = 9.1 Hz, 1H, CHCO), 2.32-2.16 (m, 2H, CH_2P), 2.10-1.90 (m, 1H, C*H*$(CH_3)_2$), 1.45 (s, 9H, $OCCH_3$ x3), 0.98 (s, 9H, $CHCCH_3$ x3), 0.87 (d, *J* = 6.8 Hz, 6H, CHC*H*$_3$ x 2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.42 (NH*C*OCH), 155.90 (COO), 138.52 (d, $^{1}J_{CP}$ = 12.5 Hz, C_{arom}-P), 138.46 (d, $^{1}J_{CP}$ = 13.6 Hz, C_{arom}-P), 133.14 (d, $^{2}J_{CP}$ = 19.6 Hz, C_{arom}-H), 132.72 (d, $^{2}J_{CP}$ = 18.9 Hz, C_{arom}-H), 128.94 (C_{arom}-H), 128.71 (C_{arom}-H), 128.66 (C_{arom}-H), 128.62 (C_{arom}-H), 128.57 (C_{arom}-H), 79.68 (O*C*$(CH_3)_3$), 62.97 (*C*HCO), 52.28 (d, $^{2}J_{CP}$ = 14.7 Hz, *C*HCH_2P), 34.49 (CH*C*$(CH_3)_3$), 31.92 (d, $^{1}J_{CP}$ = 14.9 Hz, *C*H_2P), 31.79 (d, $^{3}J_{CP}$ = 8.3 Hz, *C*H$(CH_3)_2$), 28.49 (OC*C*H_3 x 3), 26.82 (CHC*C*H_3 x 3), 19.19 (CH*C*H_3), 17.49 (CH*C*H_3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.68. IR (ATR): 1700 (C=O st), 1661 (C=O st), 1506 (N-C=O st) cm^{-1}. HRMS: Calculated for $[C_{28}H_{42}N_2O_3P]^+$: 485.2933 [$(M+H)^+$]; found: 485.2957. M.p. (petroleum ether/EtOAc): 58-60 ºC. $[\alpha]_D^{20}$: +6.90 (*c*=0.8, $CHCl_3$).



33g

tert-Butyl ((R)-1-(((S)-1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**33g**). Following the *General Procedure L*, **33g** (245 mg, 0.46 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (*S*)-1-(diphenylphosphino)-3,3-dimethylbutan-2-

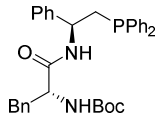
amine (235 mg, 0.82 mmol), Boc-D-phenylalanine (240 mg, 0.90 mmol), HBTU (340 mg, 0.90 mmol) and NEt_3 (0.29 mL, 1.64 mmol). Yield: 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.15 (m, 15H, C_{arom}-H), 5.87 (d, *J* = 10.4 Hz, 1H, CHCON*H*), 4.66 (s, 1H, BocNH), 4.24 (q, *J* = 6.9 Hz, 1H, CHCO), 3.98 (q, *J* = 10.6 Hz, 1H, C*H*CH_2P), 3.24-3.09 (m, 1H, C*H*$_a$H$_b$C$_{arom}$), 3.03-2.83 (m, 1H, CH$_a$*H*$_b$C$_{arom}$), 2.39-2.25 (m, 1H, C*H*$_a$H$_b$P), 2.13-1.95 (m, 1H, CH$_a$*H*$_b$P), 1.40 (s, 9H, OCC*H*$_3$ x 3), 0.80 (s, 9H, CHCC*H*$_3$ x 3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.38 (NH*C*OCH), 155.34 (COO), 139.16 (d, $^1J_{CP}$ = 14.0 Hz, C_{arom}-P), 138.53 (d, $^1J_{CP}$ = 14.5 Hz, C_{arom}-P), 137.18 (*C*$_{arom}$-C), 132.99 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-H), 132.60 (d, $^2J_{CP}$ = 19.2 Hz, C_{arom}-H), 129.26 (C_{arom}-H), 128.70 (C_{arom}-H), 128.66 (C_{arom}-H), 128.62 (C_{arom}-H), 128.57 (C_{arom}-H), 128.47 (C_{arom}-H), 128.38 (C_{arom}-H), 126.72 (C_{arom}-H), 79.97 (O*C*(CH$_3$)$_3$), 56.05 (*C*HCO), 55.06 (d, $^2J_{CP}$ = 14.5 Hz, *C*HCH$_2$P), 37.85 (*C*H$_2$C$_{arom}$), 35.41 (d, $^3J_{CP}$ = 6.9 Hz, CH*C*(CH$_3$)$_3$), 30.34 (d, $^1J_{CP}$ = 13.9 Hz, *C*H$_2$P), 28.25 (OC*C*H$_3$ x 3), 26.02 (CHC*C*H$_3$ x 3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -21.38. IR (ATR): 3300 (N-H st), 1685 (C=O st), 1652 (C=O st) cm^{-1}. HRMS: Calculated for [$C_{32}H_{42}N_2O_3P$]$^+$: 533.2933 [(M+H)$^+$]; found: 533.2939. M.p. (petroleum ether/EtOAc): 108-110 °C. [α]$_D^{20}$: +29.6 (*c*=1.0, $CHCl_3$).



33h

tert-Butyl ((*R*)-1-(((2*S*, 3*S*)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**33h**). Following the *General Procedure L*, **33h** (340 mg, 0.64 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (2*S*,3*S*)-1-(diphenylphosphino)-3-methylpentan-2-amine (225 mg, 0.79 mmol), Boc-D-phenylalanine (230 mg, 0.87 mmol), HBTU (330 mg, 0.87 mmol) and NEt_3 (0.22 mL, 1.58 mmol). Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.14 (m, 15H, C_{arom}-H), 5.79 (d, *J* = 9.3 Hz, 1H, CHCON*H*), 4.78 (s, 1H, BocNH), 4.18 (q, *J* = 7.3 Hz, 1H, CHCO), 4.14-3.97 (m, 1H, C*H*CH_2P), 3.12-2.99 (m, 1H, C*H*$_a$H$_b$C$_{arom}$), 2.99-2.86 (m, 1H, CH$_a$*H*$_b$C$_{arom}$), 2.36-2.05 (m, 2H, CH_2P), 1.67-1.53 (m, 1H, C*H*CH_3), 1.41 (s, 9H, CCH_3 x 3), 1.36-1.22 (m, 1H, C*H*$_a$H$_b$CH$_3$), 1.01-0.85 (m, 1H, CH$_a$*H*$_b$CH$_3$), 0.85-0.66 (m, 6H, CHC*H*$_3$, CH$_2$C*H*$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.17 (NH*C*OCH), 155.24 (COO), 138.69 (d, $^1J_{CP}$ = 10.4 Hz, C_{arom}-P), 138.51 (d, $^1J_{CP}$ = 11.1 Hz, C_{arom}-P), 137.03 (*C*$_{arom}$-C), 132.95 (d, $^2J_{CP}$ = 19.3 Hz, C_{arom}-H), 132.67 (d, $^2J_{CP}$ = 19.1 Hz, C_{arom}-H), 129.26 (C_{arom}-H), 128.78 (C_{arom}-H), 128.71 (C_{arom}-H), 128.63 (C_{arom}-H), 128.55 (C_{arom}-H), 128.46 (C_{arom}-H), 126.77 (C_{arom}-H), 79.93 (*C*(CH$_3$)$_3$), 56.05 (*C*HCO), 51.46 (d, $^2J_{CP}$ = 14.8 Hz, *C*HCH$_2$P), 38.85 (d, $^3J_{CP}$ = 7.8 Hz, C*H*CH_3), 38.30 (*C*H$_2$C$_{arom}$), 30.61 (d, $^1J_{CP}$ = 14.9 Hz, *C*H$_2$P), 28.26 (C*C*H$_3$ x 3), 24.81 (*C*H$_2$CH$_3$), 14.80 (CHC*H*$_3$), 11.54 (CH$_2$*C*H$_3$). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.03. IR (ATR): 3270 (N-H st), 1645 (C=O st) cm^{-1}. HRMS: Calculated for [$C_{32}H_{42}N_2O_3P$]$^+$:

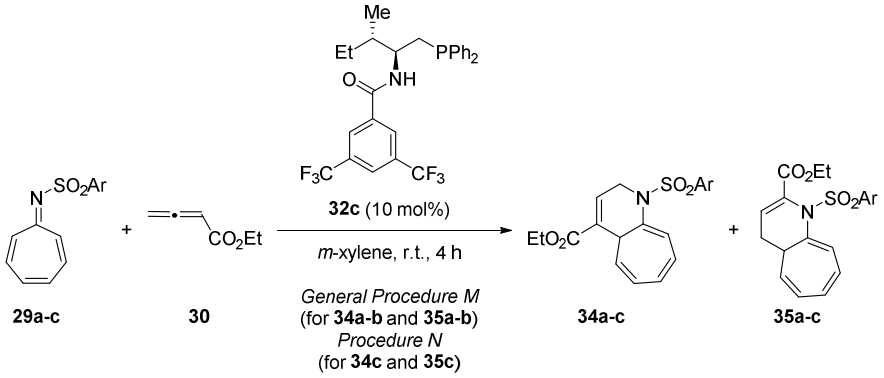
533.2933 [(M+H)$^+$]; found: 533.2952. M.p. (petroleum ether/EtOAc): 133-135 ^{o}C. $[\alpha]_D^{20}$**:** +25.4 (*c*=1.0, $CHCl_3$).

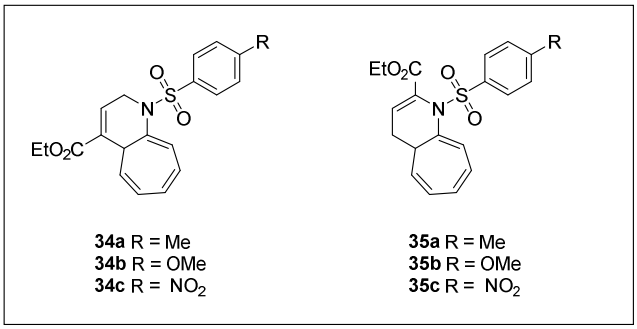


33i

tert-Butyl ((R)-1-(((S)-1-(diphenylphosphanyl)-1-phenylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**33i**). Following the *General Procedure L*, **33i** (214 mg, 0.39 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 7:3 to 1:1) as a white solid starting from (*S*)-2-diphenylphosphino-1-phenylethylamine (165 mg, 0.54 mmol), Boc-D-phenylalanine (155 mg, 0.59 mmol), HBTU (225 mg, 0.59 mmol) and NEt_3 (0.15 mL, 1.08 mmol). Yield: 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.00 (m, 20H, C_{arom}-H), 6.28 (d, *J* = 7.9 Hz, 1H, CHCON*H*), 5.18-5.03 (m, 1H, CHC_{arom}), 4.94 (s, 1H, BocNH), 4.25 (q, *J* = 7.3 Hz, 1H, CHCO), 2.10-2.89 (m, 2H, CH_2C_{arom}), 2.64 (dd, *J* = 13.9, 8.5 Hz, 1H, CH_aH_bP), 2.50 (dd, *J* = 13.9, 6.4 Hz, 1H, CH_aH_bP), 1.43 (s, 9H, CH_3 x 3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.17 (NH*C*OCH), 155.41 (COO), 141.89 (d, $^3J_{CP}$ = 5.6 Hz, C_{arom}-C), 138.27 (d, $^1J_{CP}$ = 13.1 Hz, C_{arom}-P), 137.87 (d, $^1J_{CP}$ = 12.9 Hz, C_{arom}-P), 136.82 (C_{arom}-C), 133.05 (d, $^2J_{CP}$ = 20.0 Hz, C_{arom}-H), 132.79 (d, $^2J_{CP}$ = 19.7 Hz, C_{arom}-H), 129.40 (C_{arom}-H), 129.07 (C_{arom}-H), 128.84 (C_{arom}-H), 128.81 (C_{arom}-H), 128.74 (C_{arom}-H), 128.66 (C_{arom}-H), 128.58 (C_{arom}-H), 127.63 (C_{arom}-H), 126.92 (C_{arom}-H), 126.48 (C_{arom}-H), 80.21 (*C*$(CH_3)_3$), 56.04 (*C*HCO), 51.88 (d, $^2J_{CP}$ = 18.0 Hz, *C*HC_{arom}), 38.51 (*C*H_2C_{arom}), 36.41 (d, $^1J_{CP}$ = 16.0 Hz, *C*H_2P), 28.38 (CH_3 x 3). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -23.40. IR (ATR): 3278 (N-H st), 1688 (C=O st), 1651 (C=O st) cm^{-1}. HRMS: Calculated for $[C_{34}H_{38}N_2O_3P]^+$: 553.2620 [(M+H)$^+$]; found: 553.2635. M.p. (petroleum ether/EtOAc): 140-142 ^{o}C. $[\alpha]_D^{20}$: +24.8 (*c*=0.8, $CHCl_3$).

4.3. Synthesis of bicyclic compounds 34a-c and 35a-c

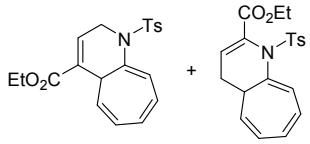




Scheme 4.3. General overview of the synthesis of bicyclic compounds **34a-c** and **35a-c**.

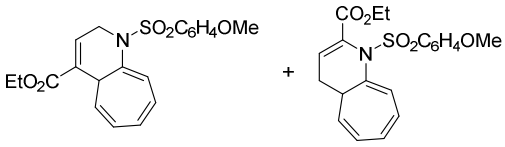
General Procedure M for the synthesis of bicyclic compounds **34a-b** and **35a-b**. Ethyl-2,3-butadientoate **30** (0.05 mmol, 1 equiv.) was added to a solution of *N*-((2*S*,3*S*)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)-3,5-bis(trifluoromethyl)benzamide **32c** (0.005 mmol, 10 mol%) and azaheptafulvene **29a-b** (0.05 mmol, 1 equiv.) in dry *m*-xylene (500 µL, 0.1 *M*) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 4 hours. Then the solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding bicyclic compounds **34a-b** and **35a-b**. Racemic standards for HPLC separation of stereoisomers were prepared using P*n*Bu$_3$ as catalyst.

Procedure N for the synthesis of bicyclic compounds **34c** and **35c**. See below.



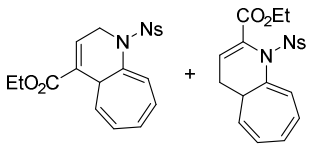
34a **35a**

Ethyl 1-tosyl-2,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-4-carboxylate (**34a**) and Ethyl 1-tosyl-4,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-2-carboxylate (**35a**). Following the *General Procedure M*, **34a** (8.5 mg, 0.02 mmol) was isolated as a brown oil and **35a** (2.4 mg, 0.007 mmol) was isolated as a brown oil, starting from azaheptafulvene **29a** (13.0 mg, 0.05 mmol) and allene **30** (5.6 mg, 0.05 mmol) in the presence of catalyst **32c** (2.6 mg, 0.005 mmol). Data for **34a**: Yield: 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 2H, SC_{arom}-C_{arom}-H), 7.14 (d, *J* = 8.1 Hz, 2H, CH_3C_{arom}-C_{arom}-*H*), 6.99 (dt, *J* = 4.7, 2.1 Hz, 1H, C_3-H), 6.70-6.62 (m, 3H, C_7-H, C_8-H, C_9-H), 6.07-6.02 (m, 1H, C_6-H), 4.80 (ddd, *J* = 20.1, 5.0, 2.0 Hz, 1H, C_2-*H*$_a$H$_b$), 4.32-4.06 (m, 4H, C_2-H$_a$*H*$_b$, C_5-H, C*H*$_2$CH$_3$), 2.36 (s, 3H, C_{arom}-CH_3), 1.94 (ddd, *J* = 6.7, 3.6, 1.8 Hz, 1H, C_{4a}-H), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.44 (COO), 143.91 (*C*$_{arom}$-CH_3), 134.71 (C_{arom}-S), 132.66 (C_3), 129.23 (CH_3C_{arom}-*C*$_{arom}$-H), 129.08 (C_{9a}), 128.82 (C_7), 128.18 (C_8), 127.98 (SC_{arom}-*C*$_{arom}$-H), 124.69 (C_6), 123.19 (C_5), 117.82 (C_4), 116.81 (C_9), 60.95 (*C*H$_2$CH$_3$), 45.50 (C_2), 38.20 (C_{4a}), 21.65 (C_{arom}-*C*H$_3$), 14.24 (CH$_2$*C*H$_3$). IR (ATR): 1716 (C=O st), 1164 (S=O) cm^{-1}. MS (EI) m/z (%): 144 (17), 117 (100), 116 (32), 115 (92), 92 (20), 91 (58), 65 (17). HRMS: Calculated for $[C_{20}H_{22}NO_4S]^+$: 372.1270 [(M+H)$^+$]; found: 372.1272. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_1 = 20.9 min, τ_2 = 26.1 min (53%). Data for **35a**: Yield: 13%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 2H, SC_{arom}-C_{arom}-H), 7.18 (d, *J* = 8.1 Hz, 2H, CH_3C_{arom}-C_{arom}-*H*), 6.70-6.62 (m, 2H, C_8-H, C_9-H), 6.49 (ddd, *J* = 9.8, 5.9, 1.6 Hz, 1H, C_7-H), 6.41 (t, *J* = 2.3 Hz, 1H, C_3-H), 6.06-5.99 (m, 1H, C_6-H), 4.36 (dd, *J* = 9.0, 4,7 Hz, 1H, C_5-H), 4.23-4.08 (m, 2H, C*H*$_2$CH$_3$), 3.47 (ddd, *J* = 19.5, 10.2, 2.2 Hz, 1H, C_4-*H*$_a$H$_b$), 2.96 (ddd, *J* = 19.5, 4.0, 2.4 Hz, 1H, C_4-H$_a$*H*$_b$), 2.37 (s, 3H, C_{arom}-CH_3), 2.11-2.02 (m, 1H, C_{4a}-H), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.41 (COO), 157.69 (C_2), 145.17 (*C*$_{arom}$-CH_3), 133.60 (C_{arom}-S), 131.04 (C_{9a}), 129.83 (C_9), 129.43 (CH_3C_{arom}-*C*$_{arom}$-H), 127.87 (C_7), 127.87 (SC_{arom}-*C*$_{arom}$-H), 126.58 (C_6), 123.22 (C_5), 107.76 (C_8), 102.21 (C_3), 60.11 (*C*H$_2$CH$_3$), 38.09 (C_{4a}), 35.37 (C_4), 21.77 (C_{arom}-*C*H$_3$), 14.50 (CH$_2$*C*H$_3$). IR (ATR): 1706 (C=O st), 1171 (S=O) cm^{-1}. HRMS: Calculated for $[C_{20}H_{22}NO_4S]^+$: 372.1270 [(M+H)$^+$]; found: 372.1273.



34b **35b**

Ethyl 1-((4-methoxyphenyl)sulfonyl)-2,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-4-carboxylate (**34b**) and Ethyl 1-((4-methoxyphenyl)sulfonyl)-4,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-2-carboxylate (**35a**). Following the *General Procedure M*, **34b** (10.8 mg, 0.03 mmol) was isolated as a brown oil and **35b** (4.3 mg, 0.01 mmol) was isolated as a brown oil, starting from azaheptafulvene **29b** (13.8 mg, 0.05 mmol) and allene **30** (5.6 mg, 0.05 mmol) in the presence of catalyst **32c** (2.6 mg, 0.005 mmol). Data for **34b**: Yield: 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, SC_{arom}-C_{arom}-H), 7.00 (dt, *J* = 4.5, 2.1 Hz, 1H, C_3-H), 6.86-6.75 (m, 2H, OC_{arom}-C_{arom}-H), 6.76-6.61 (m, 3H, C_7-H, C_8-H, C_9-H), 6.12-5.98 (m, 1H, C_6-H), 4.80 (ddd, *J* = 20.2, 5.0, 1.9 Hz, 1H, C_2-H_aH_b), 4.35-4.04 (m, 4H, C_2-H_aH_b, C_5-H, CH_2CH_3), 3.81 (s, 3H, OCH_3), 2.02-1.85 (m, 1H, C_{4a}-H), 1.22 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.41 (COO), 163.20 (C_{arom}-O), 132.72 (C_3), 130.06 (SC_{arom}-C_{arom}-H), 129.39 (C_{arom}-S), 129.05 (C_{9a}), 128.70 (C_7), 128.16 (C_8), 124.61 (C_6), 123.30 (C_5), 117.93 (C_4), 116.72 (C_9), 113.73 (OC_{arom}-C_{arom}-H), 60.93 (CH_2CH_3), 55.71 (OCH_3), 45.45 (C_2), 38.17 (C_{4a}), 14.22 (CH_2CH_3). The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_1 = 24.0 min, τ_2 = 30.5 min (32%). Data for **35b**: Yield: 22%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.44 (m, 2H, SC_{arom}-C_{arom}-H), 6.89-6.80 (m, 2H, OC_{arom}-C_{arom}-H), 6.73-6.62 (m, 2H, C_8-H, C_9-H), 6.57-6.46 (m, 1H, C_7-H), 6.43 (t, *J* = 2.3 Hz, 1H, C_3-H), 6.08-5.98 (m, 1H, C_6-H), 4.38 (dd, *J* = 9.0, 4,7 Hz, 1H, C_5-H), 4.26-4.09 (m, 2H, CH_2CH_3), 3.84 (s, 3H, OCH_3), 3.49 (ddd, *J* = 19.6, 10.1, 2.2 Hz, 1H, C_4-H_aH_b), 3.00 (ddd, *J* = 19.6, 3.9, 2.4 Hz, 1H, C_4-H_aH_b), 2.13-1.99 (m, 1H, C_{4a}-H), 1.38-1.21 (m, 3H, CH_2CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.46 (COO), 164.05 (C_{arom}-O), 157.80 (C_2), 131.11 (C_{9a}), 129.96 (SC_{arom}-C_{arom}-H), 129.87 (C_9), 128.24 (C_{arom}-S), 127.80 (C_7), 126.57 (C_6), 123.29 (C_5), 113.98 (OC_{arom}-C_{arom}-H), 107.72 (C_8), 102.11 (C_3), 60.10 (CH_2CH_3), 55.81 (OCH_3), 38.13 (C_{4a}), 35.42 (C_4), 14.51 (CH_2CH_3).



34c **35c**

Ethyl 1-((4-nitrophenyl)sulfonyl)-2,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-4-carboxylate (**34c**) and Ethyl 1-((4-nitrophenyl)sulfonyl)-4,4a-dihydro-1*H*-cyclohepta[*b*]pyridine-2-carboxylate (**35c**). To a solution of *N*-(cyclohepta-2,4,6-trien-1-ylidene)-4-nitrobenzenesulfonamide **29c** (14.5 mg, 0.05 mmol) and *N*-((2*S*,3*S*)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)-3,5-bis(trifluorome-

thyl)benzamide **32c** (2.6 mg, 0.005 mmol) in dry toluene (1 mL, 0.05 *M*) was added a solution of 3thyl-2,3-butadientoate **30** (16.8 mg, 0.15 mmol) in dry toluene (0.5 mL, 0.3 *M*) over 14 h (0.6 µL/min) at room temperature. Then the solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc gradient from 9:1 to 7:3) to afford the corresponding bicyclic compounds **34c** (9.3 mg, 0.02 mmol) as brown oil and **35c** (3.2 mg, 0.008 mmol) as brown oil. Data for **34c**: Yield: 46%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26-8.14 (m, 2H, NO_2C_{arom}-C_{arom}-H), 7.66-7.51 (m, 2H, SC_{arom}-C_{arom}-*H*), 7.00 (dt, *J* = 5.1, 2.1 Hz, 1H, C_3-H), 6.80-6.66 (m, 3H, C_7-H, C_8-H, C_9-H), 6.13-5.99 (m, 1H, C_6-H), 4.84 (ddd, *J* = 20.1, 5.0, 2.0 Hz, 1H, C_2-H_aH_b), 4.33 (ddd, *J* = 20.1, 3.8, 2.2, 1H, C_2-H_aH_b), 4.24-4.08 (m, 3H, C_5-H, CH_2CH$_3$), 2.11-1.87 (m, 1H, C_{4a}-H), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.07 (COO), 150.27 (C_{arom}-NO_2), 143.08 (C_{arom}-S), 132.06 (C_3), 129.69 (C_{9a}), 129.33 (SC_{arom}-C_{arom}-H), 129.23 (C_7), 128.35 (C_8), 125.21 (NO_2C_{arom}-C_{arom}-H), 123.88 (C_6), 123.13 (C_5), 117.73 (C_4), 117.03 (C_9), 61.21 (CH_2CH_3), 45.73 (C_2), 38.09 (C_{4a}), 14.23 (CH_2CH_3). The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_1 = 24.5 min, τ_2 = 29.8 min (90%). Data for **35c**: Yield: 16%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29-8.21 (m, 2H, NO_2C_{arom}-C_{arom}-H), 7.75-7.67 (m, 2H, SC_{arom}-C_{arom}-*H*), 6.75-6.67 (m, 2H, C_8-H, C_9-H), 6.57 (ddd, *J* = 8.7, 5.8, 2.6 Hz, 1H, C_7-H), 6.47 (t, *J* = 2.4 Hz, 1H, C_3-H), 6.15-5.96 (m, 1H, C_6-H), 4.31 (dd, *J* = 9.0, 4,7 Hz, 1H, C_5-H), 4.26-4.12 (m, 2H, CH_2CH$_3$), 3.52 (ddd, *J* = 19.7, 10.1, 2.2 Hz, 1H, C_4-H_aH_b), 2.94 (ddd, *J* = 19.7, 3.9, 2.5 Hz, 1H, C_4-H_aH_b), 2.18-2.02 (m, 1H, C_{4a}-H), 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

Appendix

Abbreviations, acronyms and symbols[1]

9-BBN	9-Borabicyclo[3.3.1]nonane
AD	Asymmetric dihydroxylation
Ad	Adamanthyl
Ar	Aryl group
ATR	Attenuated total reflectance
bipy	2,2´-Bipyridine
Boc	*tert*-Butyloxycarbonyl
BOX	Bisoxazoline
BTM	Benzotetramisole
c	Concentration (measured in g/100 mL)
C_{arom}	Aromatic carbon
Cat.	Catalyst
Conv.	Conversion
COD	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
CSA	10-Camphorsulfonic acid
Cy	Cyclohexyl group
D-A	Donor-Acceptor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
E	Electrophile
EDG	Electron-donating group
e.e.	Enantiomeric excess
ELF	Electron localization function
Ent.	Enantiomer
Equiv.	Equivalent
EWG	Electron-withdrawing group
FC	Flash column chromatography
FMO	Frontier molecular orbital
Fmoc	9-Fluorenylmethoxycarbonyl
HOMO	Highest occupied molecular orbital
Ile	Isoleucine
J	Coupling constant

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

L	Ligand
LA	Lewis acid
Leu	Leucine
LUMO	Lowest occupied molecular orbital
MBH	Morita-Baylis-Hillman reaction
M.p.	Melting point
MS	Mass spectrometry
NAHDMS	Sodium bis(trimethylsilyl)amide
n.d.	Not determined
Ns	Nosyl
Nu	Nucleophile
PG	Protecting group
Phe	Phenylalanine
Phg	Phenylglycine
QTOF	Quadrupole-time of flight
R	Alkyl group or substituent
SOMO	Single occupied molecular orbital
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Thr	Threonine
TMS	Trimethylsilyl
TOX	Trisoxazoline
Ts	Tosyl
Val	Valine
vs	Versus
X	Halogen or heteroatom
δ	Chemical shift
τ_1	Retention time for first enantiomer
τ_2	Retention time for second enantiomer

Resumen Extendido

El empleo de aminas primarias y secundarias quirales como catalizadores covalentes en la activación de aldehídos y cetonas se ha convertido en un área de la química de gran interés a la hora de desarrollar reacciones estereocontroladas. La metodología implica la formación de cantidades subestequiométricas de intermedios de azometino activados (enamina e ion iminio) a partir de la condensación reversible del organocatalizador y el compuesto carbonílico. La capacidad de las aminas primarias y secundarias quirales para promover reacciones en las que el producto final se consigue altamente enantioenriquecido ha sido demostrada por el gran número de transformaciones publicadas al respecto. Simultáneamente, el empleo de fosfinas quirales nucleófilas como catalizadores covalentes ha ido ganando interés en el área de la organocatálisis, debido a su capacidad para promover transformaciones que no se han podido llevar a cabo en presencia de otros catalizadores nucleófilos. El carácter nucleofílico de las fosfinas las convierte en excelentes candidatas para la activación de alquenos, alquinos y alenos pobres en electrones a través de una adición y ampliando así la variedad de substratos que pueden participar en reacciones activadas mediante organocatalizadores.

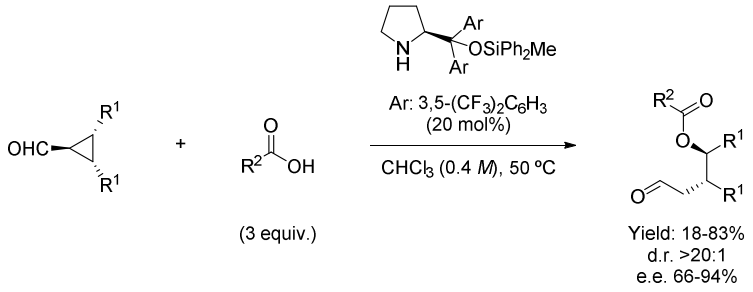
Siguiendo la línea de investigación del grupo en el campo de la organocatálisis asimétrica, la memoria recoge el estudio de diversas metodologías basadas en el empleo de organocatalizadores covalentes. En este sentido, la selección de reactivos que difieren de los comúnmente usados en la bibliografía posibilita el desarrollo de nuevas transformaciones, las cuales a su vez son llevadas a cabo de manera enantioselectiva en presencia de catalizadores que son capaces de proporcionar el entorno asimétrico adecuado.

En un primer capítulo, se muestra un resumen con perspectiva histórica de las características más generales de la organocatálisis asimétrica, haciendo especial mención a los avances en los diferentes modos de activación de compuestos carbonílicos empleando catalizadores tipo amina primaria y secundaria, y describiendo las reacciones que cursan a través de la formación de intermedios tipo enamina, ion iminio y especies vinílogas. Por otro lado, se detallan las transformaciones en las que el empleo de fosfinas nucleófilas quirales ha demostrado ser de gran utilidad consiguiendo productos finales altamente enantioenriquecidos, en transformaciones en las que participan alquenos, alquinos y alenos pobres en electrones.

En un segundo capítulo, se presenta la investigación dirigida a explorar la reacción de apertura de anillo de *meso*-formilciclopropanos promovida por nucleófilos externos en presencia de aminas secundarias quirales como catalizadores. La formación del intermedio de ion iminio aumenta la reactividad del ciclopropano facilitando la escisión del enlace C-C y a su vez, provee a la transformación de un entorno quiral necesario para controlar la estereoquímica del producto final.

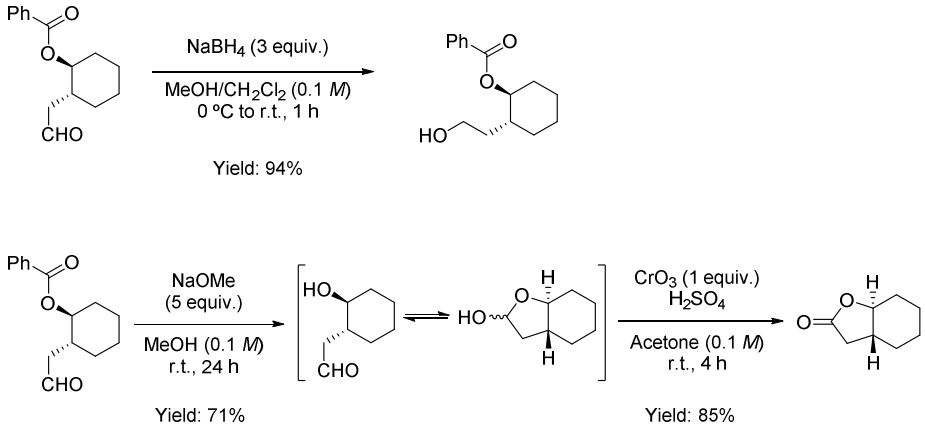
En una fase inicial del estudio se ha demuestrado que los ácidos carboxílicos son capaces de participar en la reacción como nucleófilos externos, consiguiendo aldehídos γ-aciloxi substituidos tras la apertura de anillo. Seguidamente, se ha llevado a cabo un extenso proceso de exploración de las variables de reacción, determinando que el empleo de metildifenilsilil 2-(bis(3,5-bis(trifluorometil)fenilprolinol como aminocatalizador en cloroformo a 50 ºC, en presencia de 3 equivalentes del acido carboxílico correspondiente y un equivalente del ciclopropano conducen a la formación de aldehídos γ-aciloxi substituidos en alto rendimiento y con excelente diastereo- y enantioselectividad (Esquema 1). La

metodología se ha extendido a derivados del ácido benzoico, ácidos carboxílicos alifáticos y amino ácidos *N*-protegidos. Por otro lado, la substitución del ciclopropano también ha podido ser alterada, consiguiendo resultados excelentes con anillos fusionados de varios tamaños y sustituyentes alquílicos y aromáticos.



Esquema 1

Los aldehídos finales se han sometido a transformaciones selectivas, en las cuales solo reacciona el grupo funcional seleccionado manteniendo el otro intacto sin necesidad de grupos protectores adicionales (Esquema 2). En este sentido, el grupo formilo se ha reducido al correspondiente alcohol primario en presencia de $NaBH_4$. A su vez, el ester también se ha conviertido al correspondiente alcohol mediante una hidrólisis consiguiendo γ-hidroxi aldehídos, que dan acceso a γ-lactonas a través de un paso adicional de oxidación.



Esquema 2

Por otro lado, también se ha llevado a cabo un estudio del mecanismo de la reacción llegando a la conclusión de que el proceso de apertura de anillo debe considerarse concertado pero asíncrono, ya que se pueden localizar dos eventos diferentes en las coordenadas de reacción, pero solo se pude identificar un único paso de reacción. A su vez, la completa diastereoselectividad del proceso es debida a que el ataque del nucleófilo solo se da por una de las caras y la selección de uno u otro carbono genera los dos posibles enantiomeros. Respecto a la alta enantioselectividad de la transformación, los cálculos llevados a cabo demuestran una clara preferencia hacia el estado de transición que deriva en el enantiomero que se observa como mayoritario experimentalmente (Figure 1).

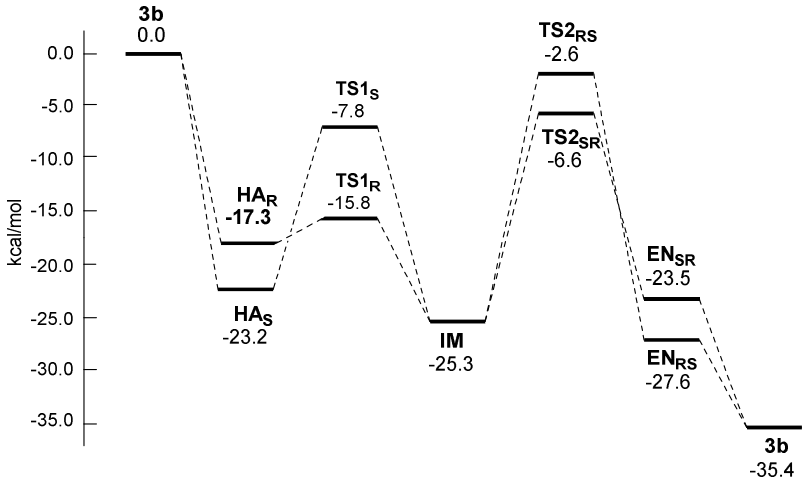
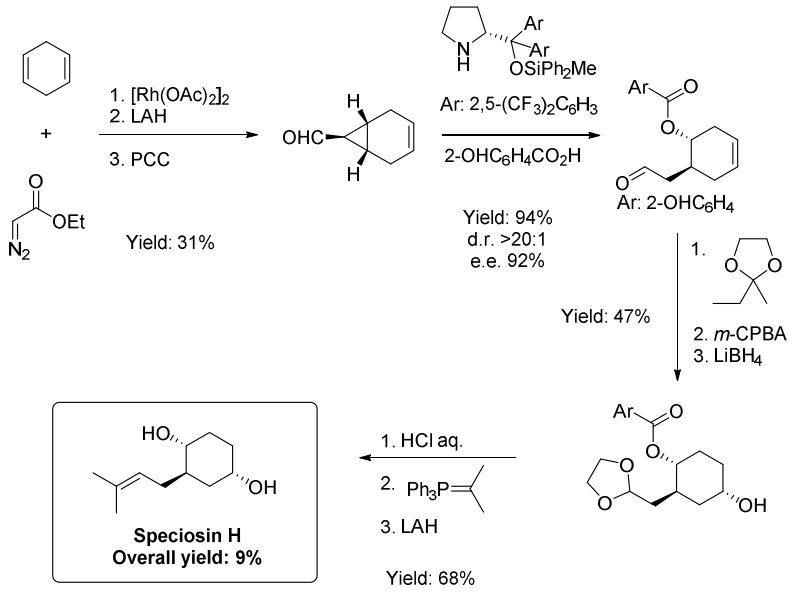


Figure 1

En un tercer capítulo, con el fin de demostrar la utilidad de la reacción de apertura de anillo, se presenta la primera síntesis total de (-)-speciosin H empleando dicha reacción como paso clave (Esquema 3). La hidrólisis del ester daría lugar al grupo hidroxilo presente en la estructura final y una olefinacion sobre el grupo formilo daría acceso al alqueno deseado, a su vez los sustituyentes se encuentran en *trans* al igual que en el producto natural. Por otro lado, la presencia de un doble enlace en el ciclohexano daría acceso al grupo hidroxilo unido al carbono C4 mediante una oxidación.

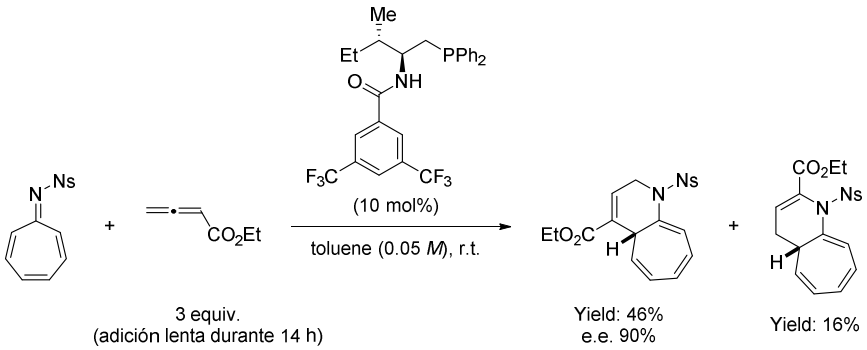


Esquema 3

Primero se sintetizó el biciclo[4.1.0]hept-3-ene-7-carbaldehído como producto de partida para la reacción de apertura de anillo. La epoxidación del doble enlace C-C, seguida de la apertura del epóxido regio- y diastereoselectiva da lugar al grupo hidroxilo en la posición adecuada. Por último, la olefinación del grupo formilo seguida de la reducción del ester dan acceso al producto natural.

Finalmente, el capítulo cuarto trata del desarrollo de una cicloadición de alto orden [8+4] enantioselectiva. En este sentido los 1,3-dipolos generados a partir de la adición nucleofílica de fosfinas a alenoatos se emplean como componentes-4π y por otro lado, los azaheptafulvenos como componentes-8π. En un primer estudio se decide que los substratos más apropiados para llevar a cabo la transformación son el alenoato de etilo y el azaheptafulveno de *N*-nosilo. Seguido, la evaluación de condiciones de reacción lleva al empleo de la fosfina derivada de aminoácido *N*-1-

(difenilfosfanil)-3-metilpenatl-2-il)-3,5-bis(trifluorometil)benzamida como catalizador en tolueno a temperatura ambiente, añadiendo 3 equivalentes de alenoato durante 14 horas para la formación de los productos de cicloadición esperados (Esquema 4). En las mejores condiciones conseguidas hasta el momento el producto final se obtiene con un rendimiento moderado, como mezcla de regioisomeros y con una enantioselectivad excelente.



Esquema 4