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Unconventional Reactivity Patterns in Asymmetric Organocatalytic Cycloaddition Reactions

MEMORIA PRESENTADA POR

Liher Prieto Aretxabaleta

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Summary

The use of chiral primary and secondary amines as covalent catalysts for the activation of aldehydes and ketones toward stereocontrolled chemical transformations is flourishing as a field of increasing interest. This methodology implies the reversible formation of substoichiometric azometine intermediate (enamine or iminium ion) as an activated species. Currently, the implementation of the vinylogy concept to this activation mode inspired the discovery of dienamines and trienamines as fascinating and versatile synthetic strategies to achieve the respective γ-and ε-functionalization of carbonyl compounds. Simultaneously, the use of *N*-Heterocyclic Carbenes (NHC) as covalent catalyst is a rapidly growing field, which is explained by the ability of carbene catalysts to generate intermediates in which the natural reactivity of carbonyl compounds is reversed.

The present manuscript compiles the study and development of diverse enantioselective organocatalytic cycloaddition reactions. In this context, investigations were directed to the use of nitrone ylides as dipoles in [3+2] cycloaddition with enals under a chiral secondary amine triggered iminium activation that lead to unconventional regioselectivity compared to the standard behavior of the parent nitrones as 1,3-dipoles, furnishing densely functionalized *N*-hydroxypyrrolidines in high yields and excellent stereoselectivity.

Additionally, vinylogous enamine concept was also explored selecting dienals with interrupted conjugation as model substrates to generate trienamine intermediates in a catalytic fashion using a chiral secondary amine as catalyst and their application in Diels-Alder cycloaddition chemistry with nitroolefins, affording highly substituted cyclohexenes in high yields, excellent diastereo- and enantioselectivities.

Moreover, the ability of NHC catalysts to reverse the reactivity of carbonyl compounds (*umpolung*) was employed to achieve the chiral NHC-catalyzed enantioselective cycloaddition between formylcyclopropane-derived azolium enolates and

alkylideneoxindoles as Michael acceptors in inverse electron-demand Diels-Alder cycloaddition chemistry. Adducts were obtained as single diastereomer with moderate to excellent yield and high enantioselectivity.

Finally and as a part of a short stay in the laboratories of Prof. Phil S. Baran, the use of ring strain release as the driving force to achieve unprecedented synthetic transformations was studied, motivating the discovery of a new methodology which implied the use of small strained bicyclic rings, such as [1.1.1]propellane, 1-azabicyclo[1.1.0]butane and 1-(arylsulfonyl)bicyclo[1.1.0]butane, substrates with noteworthy propensity to experience reactions with amine nucleophiles, in a transformation that resembles hydroamination reaction and leading to the formation of products of great interest for pharmaceutical industry, since the reaction is a powerful synthetic tool for late stage funtionalization of amine compounds.

Resumen

El empleo de aminas primarias y secundarias como catalizadores covalentes en la activación respectiva de cetonas y aldehídos para llevar a cabo transformaciones estereocontroladas está asentándose como área de la química de creciente interés. La metodología implica la formación reversible de cantidades subestequiometricas de intermedios tipo azometino (enamina o ion iminio) como especies activas. Recientemente, la aplicación del principio de vinilogía a este modo de activación inspiró el descubrimiento de la dienamina y trienamina como nuevas estrategias sintéticas para alcanzar la funcionalización de compuestos carbonílicos en γ y ε respectivamente. Simultáneamente, la utilización de Carbenos *N*-Heterociclicos (NHC) como catalizadores se presenta como un área de rápida expansión, sustentada en la habilidad de las especies tipo carbeno para generar intermedios que invierten la reactividad inherente de compuestos carbonílicos.

La memoria recoge el estudio y desarrollo de diversas reacciones organocatalíticas enantioselectivas. En primer lugar, se presenta la investigación dirigida a explorar la reactividad de iluros de nitrona como 1,3-dipolos en la cicloaddición [3+2] con aldehídos α-β-insaturados activados mediante aminas secundarias quirales *via* ión iminio, que presenta regioselectividad poco convencional comparada con el comportamiento habitual de nitronas como 1,3-dipolos, conduciendo a la formación de *N*-hidroxipirrolidinas densamente funcionalizadas con altos rendimientos y estereoselectividad excelente.

Adicionalmente, el concepto de enamina vinílogа fue aplicado seleccionando como sustrato modelo dienales que presenten conjugación interrumpida para la generación catalítica de intermedios tipo trienamina, empleando para ello catalizadores de amina secundaria quirales, y su aplicación en química de cicloaddición tipo Diels-Alder con nitroolefinas, rindiendo ciclohexenos polisustituidos con altos rendimientos y de manera altamente diastereo- y enantioselectiva.

Además, la capacidad que presentan los catalizadores NHC para invertir la polaridad (*umpolung*) de compuestos carbonílicos fue empleada para desarrollar la cicloadición enantioselectiva catalizadad por NHC quirales entre enolatos de azolio provenientes de formilciclopropanos y alquilideneoxindoles como aceptores de Michael, en una reacción que se corresponde con cicloaddiciones de Diels-Alder de demanda electrónica inversa. Los aductos se obtuvieron como únicos diastereoisomeros en moderado hasta alto rendimiento y enantioselectividad excelente.

Finalmente, como parte de una estancia breve en los laboratorios dirigidos por el Prof. Phil S. Baran, haciendo uso de la tensión de anillo como fuerza impulsora y motivando el desarrollo de transformaciones sintéticas sin precedentes, se estudió una metodología que implica el uso de anillos bicíclicos tensionados, *i.e.* [1.1.1]propelano, 1-azabiciclo[1.1.0]butano y 1-(arilsulfonil)biciclo[1.1.0]butano, como sustratos propensos a experimentar adición de aminas como nucleófilos, en una transformación que se asemeja a la reacción de hidroaminación, y como potente herramienta sintética para la funcionalización en etapa tardía de compuestos tipo amina, llevando a la formación de productos de elevado interés para la industria farmacéutica

Laburpena

Amina primario eta sekundario kiralen erabilera katalizatzaile kobalente gisa konposatu karbonilikoak aktibatzeko erreakzio kimiko estereokontrolatuetan hedatzen ari den esparru kimikoa da. Metodologia honek, azometino bitartekarien (enamina eta iminio ioia) sorrera katalitikoan oinarritzen da. Egun, binilogia kontzeptuaren ezarpena dienaminen eta trienaminen aktibazio moten aurkikuntza sustatu du komposatu karbonilikoen γ- eta ε-funtzionalizasioa lortuz. Era berean, Karbeno *N*-Heteroziklikoen (NHC) erabilera katalizatzaile kobalente moduan komposatu karbonilikoen erreaktibitate naturala aldatzen denez, azkar hazten doan arloa da.

Eskuizkribu honetan zikloadizio enantioselektibo orrganokatalitiko desberdinen garapena bilatzen da. Horren inguruan, ikerketak bideratu dira nitrona iluroen erabilera 1,3-dipolo gisa [3+2] zikloadizioan amina sekundario kiralen bitartez eratutako iminio ioiaz aktibatutako enalekin, ezohiko erregioselektivitatea garatuz eta *N*-hidroxipyrrolidinen ekoizpenera zuzenduz etekin eta enantioselektibitate altuekin.

Gainera, enamina binilogo kontzeptua ikertu zen konjugazio etendako dienalak substratu eredu gisa hautatuz, trienamina bitartekarien sorrera katalitikoa lortzeko katalizatzaile amina sekundario kiralen bitartez, Diels-Alder zikloadizioan nitroalkenoekin ziklohexenoak emanez etekin, diastereo- eta enantioselektibitate bikainekin.

Horretaz gain, NHC-en gaitasuna konposatu karbonilikoen erreaktibitatea alderantzikatzeko (*umpolung*) erabili zen, zikloadizio enantioselektiboa azolio enolatoen eta alkilideneoxindolen arteko alderantzizkako elektro-eskari Diels-Alder erreakzioa lortuz. Produktuak diastereoisomero bakarra moduan, etekin ertainetik bikainetara eta enantioselektibitate altuan lortu ziren.

Azkenik, egonaldi motz baten emaitzaz, Prof. Phil S. Baranen laborategian, eraztun tentsio askapena erabili zen indar bultzatzaile bezala transformazio ezezagunak lortzeko. Horretarako biziklo eraztunak, [1.1.1]propelano, 1-azabiziklo[1.1.0]butano eta 1-

(arilsulfonil)biziklo[1.1.0]butano bezala erabili ziren. Hauek amina nukleofiloekin erreakzionatzeko joera aurkeztu zuten hidroaminazioa gogorarazten duen erreakzioan, industria farmazeutikorako konposatu interesgarriak eraikiz.

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Chapter 1

1

Introduction

1. ASYMMETRIC ORGANOCATALYSIS: A MODERN SYNTHETIC TOOL

Among the different synthetic strategies available for the preparation of chiral compounds in a stereoselective manner, asymmetric catalysis is probably the most efficient and versatile methodology in terms of efficacy and atom economy. Although the field of asymmetric catalysis has been traditionally governed by enzymatic catalysis[1] and metal catalysis,[2] the use of small organic molecules without metal atoms in their active site as catalyst in a wide variety of transformations is becoming increasingly important during the last two decades,. Therefore, this field, known today as *organocatalysis*[3] has become a well established area in asymmetric catalysis, that often provides a complementary approach to synthetic problems not easily faced through enzymatic and metal catalysis. A clear evidence of the relevance gathered by this field is represented by the increasing amount of contributions to the field.[4]

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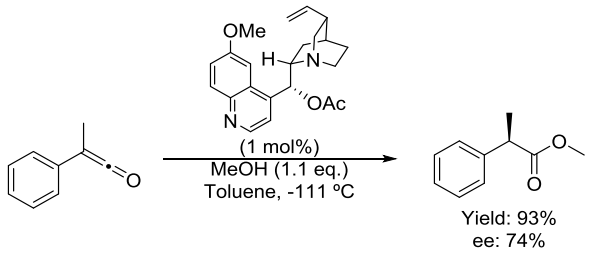
1 Enzymatic catalysis: (a) Callender, R.; Dyer, B. *Acc. Chem. Res.* **2015**, *48*, 407. (b) Drauz, K.; Gröger, H.; May, O. *Enzyme Catalysis in Organic Chemistry*; 3rd ed.; Wiley-VCH: Weinheim, 2012. (c) Moniruzzaman, M.; Kamiya, N.; Goto, M. *Org. Biomol. Chem.* **2010**, *8*, 2887. (d) Tao, J.; Zhao,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

2 Metal catalysis: (a) 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) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; 3rd ed.;Wiley-VCH: Weinheim, 2004. (d) Ojima, I. *Catalytic Asymmetric Synthesis*; 2nd ed.; Wiley-VCH: New York, 2010.

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

4 General reviews on organocatalysis: (a) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (b) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (d) Marson, C. M. *Chem. Rev.* **2012**, *41*, 7712. (e) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618. (f) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138. (g) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (h) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304. (i) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413. (j) Yang, J. W.; List, B. *Science* **2006**, *313*, 1584. Books and chapters: (k) Rios Torres, R. *Stereoselective Organocatalysis. Bond Formation and Activation Modes*; Wiley-VCH: Weinheim, 2013. (l) Waser, M. *Asymmetric Organocatalysis in Natural Product Syntheses*; 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.

Although the first steps on asymmetric organocatalytic reactions were taken at the beginning of 20th century with the works of Marckwald for the enantioselective decarboxylation of a malonic acid derivative in the presence of brucine,[5] and the quinine-catalyzed enantioselective addition of cyanide to benzaldehyde reported by Bredig and Fiske,[6] it was in 1960 when Pracejus reported the first enantioselective organocatalytic transformation providing synthetically useful enantioselectivities in the context of the addition of methanol to methyl phenyl ketene catalyzed by quinine (Scheme 1.1).[7]



Scheme 1.1

An additional remarkable contribution on asymmetric organocatalysis was the development of the L-proline-catalyzed intramolecular aldol reaction used in the preparation of chiral precursors in the synthesis of steroids, a reaction named today as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, recognizing the key contribution of the discoverers (Scheme 1.2).[8,9]

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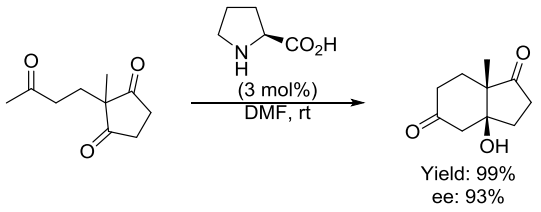
5 Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349.

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

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

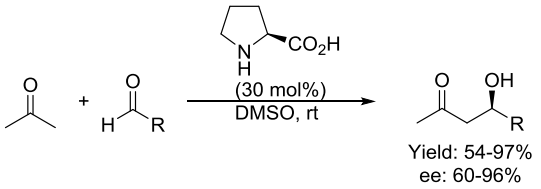
8 (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Hajos, Z. G.; Parrish, D. R. *Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds*. German Patent DE 2102623, **1971**.

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



Scheme 1.2

Perhaps one of the landmarks on organocatalysis was established in 2000 when the L-proline-catalyzed asymmetric intermolecular aldol reaction between acetone and a number of aldehydes was reported in a process that resembled an enzymatic reaction triggered by aldolase antibodies (Scheme 1.3). Experimental and mechanistic insights pointed to the formation of enamine intermediate, after condensation of L-proline aminoacid and acetone, which acts as a nucleophile in the reaction.[10]



Scheme 1.3

In the same year, the *iminium ion activation* concept was introduced with the first asymmetric organocatalytic Diels-Alder cycloaddition between α,β-unsaturated aldehydes and various electron-rich dienes. In this example, an imidazolidinone based catalyst activated the enal *via* condensation of the chiral amine, thus lowering the energy of its LUMO and enhancing its reactivity towards the [4+2] cycloaddition process with an electron-rich diene (Scheme 1.4).[11]

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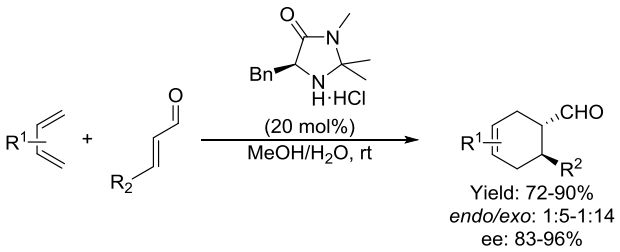
[10] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[11] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.



Scheme 1.4

Besides these two seminal works, which are nowadays considered as the initial point for the renaissance of the field of organocatalysis, other methodologies were discovered, among which phase-transfer catalysis,[12] and H-bonding catalysis[13] stand out for their relevance in early stages of the rebirth of the field.

In general, the diverse manifolds for substrate activation in organocatalytic reactions can be classified in two groups according to the nature of the interactions between catalyst and substrate in the transition state; these are *covalent* and *non-covalent catalysis*. The first group, *covalent catalysis*, represents reactions in which substrate and catalyst form covalent adducts, like azomethine species generated employing aminocatalysts (enamine, iminium ion, SOMO),[14] *N*-heterocyclic carbene activated intermediates,[15] and others, such as ylides and phosphines[16] which undergo a wide variety of transformations. The second group (*non-covalent catalysis*) encompasses the situations where the substrate-catalyst interactions are

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

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

[14] A section of this Chapter is dedicated to discuss aminocatalysis, see: Chapter 1. Section 2. AMINOCATALYSIS.

[15] A section of this Chapter is dedicated to discuss *N*-heterocyclic carbene catalysis, see: Chapter 1. Section 3. *N-HETEROCYCLIC* CARBENE CATALYSIS.

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

weak; this is the case for H-bonding[17] and electrostatic (PTC)[18] interactions. Chiral Brønsted base catalysis[19] is also included in the *non-covalent catalysis* (Figure 1.1).

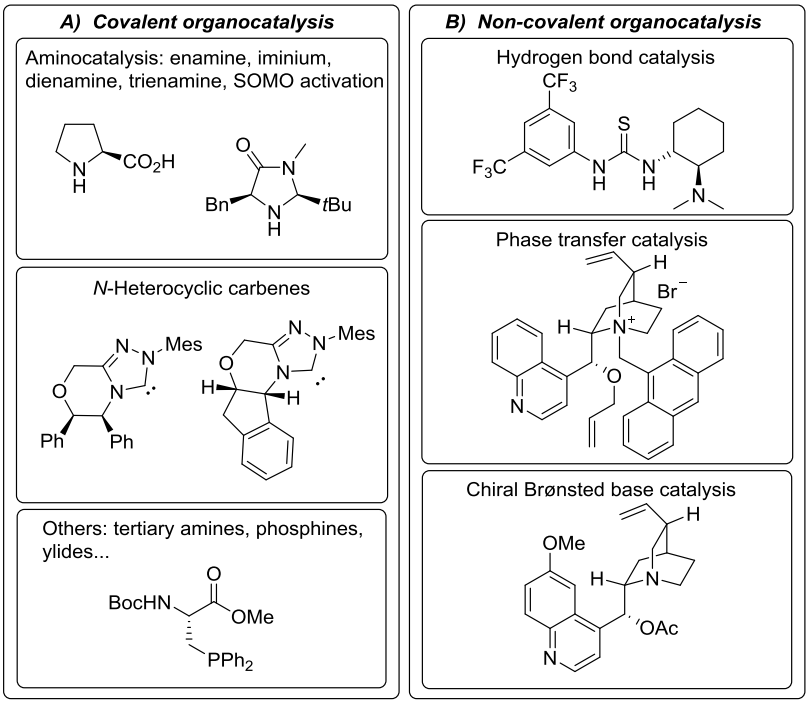

Figure 1.1

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

[18] For recent 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.

[19] For a selected review on Brønsted base catalysis, see: Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

2. AMINOCATALYSIS

The use of chiral primary or secondary amines as covalent catalysts for the activation of aldehydes and ketones toward stereocontrolled chemical transformations is flourishing as a field of increasing interest.[20] This approach implies the reversible formation of a substoichiometric azometine intermediate as activated reactive species. Regarding the nature of the azometine intermediate, the aminocatalysis can be categorized into two activation modes: *enamine*[21] or *iminium ion*[22] catalysis, that have recently found a broadening of the concept through the implementation of the vinylogy principle[23] to these two general activation modes, inspiring the discovery of *dienamine*, *trienamine* and *vinylogous iminium ion*[24] as fascinating and versatile synthetic strategies. These manifolds, together with other varieties of aminocatalytic activation, such as *SOMO* catalysis,[25] allow the α, β, γ, δ and/or ε functionalization of carbonyl compounds in a selective and efficient manner.

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[20] For some reviews on aminocatalysis, see: (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (c) List, B. *Chem. Commun.* **2006**, 819. (d) List, B. *Tetrahedron* **2002**, *58*, 5573.

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

[22] For some 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, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

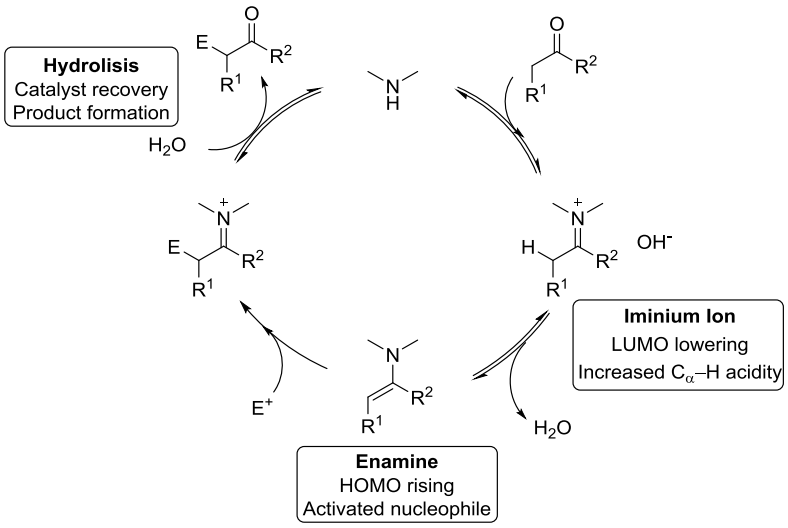
[23] Vinylogy principle: Fuson, R. C. *Chem. Rev*., **1935**, *16*, 1.

[24] For some 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.

[25] For some 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, 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.

2.1 Enamine and Iminium ion catalysis

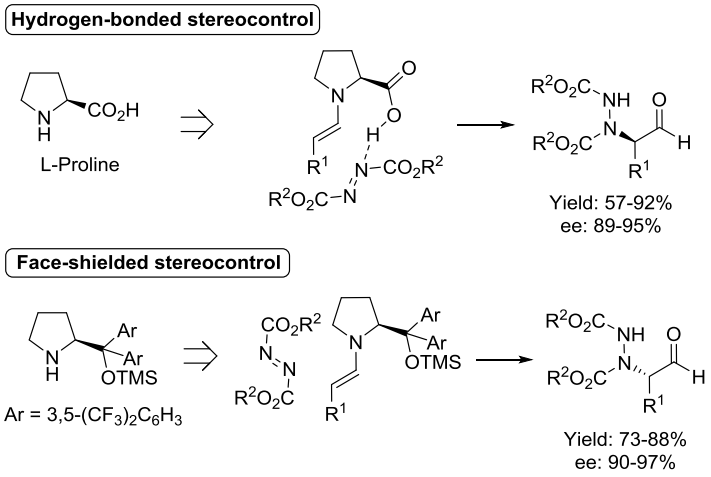
The reversible condensation of a primary or secondary amine catalyst with an enolizable ketone or aldehyde leads to the generation of substoichiometric amounts of the *enamine* intermediate that gives name to this activation mode. The catalytic cycle starts with the condensation of the aminocatalyst with the carbonyl compound yielding an iminium ion. In this process, the energy of the LUMO compared to the parent carbonyl derivative has decreased and, consequently, the acidity of the α-CH increases, giving the opportunity to the enamine intermediate to be formed. At this point, the enamine intermediate presents raised-HOMO energy, making it more prone to react with electrophiles. A final hydrolysis step follows, releasing the aminocatalyst and the α-functionalized aldehyde or ketone (Scheme 2.1).



Scheme 2.1

The use of a chiral aminocatalyst enables access to diastereomeric transition states showing differences in their activation barriers and, therefore, gives the opportunity to control the stereoselectivity of the process. In this context, extensive efforts have been

made to understand the source of enantioselectivity of the reactions catalyzed by chiral amines. There are two possibilities to describe the trajectory of the electrophile depending on the nature of the aminocatalyst: the incorporation of a stereodirecting element (*e.g.* H-bond donor, proline),[26] or by using a bulky substituent that shields one of the diastereotopic faces of the enamine. [27] This second strategy is the most widely applied being the *O*-trimethylsilyl protected α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-prolinol derivative the archetypical example of this behavior (Scheme 2.2).[28]



Scheme 2.2

Considering the most frequently used stereocontrol through face-shielding, in addition to the capacity of the bulky substituent to impede the accession of the electrophile to one of the diastereotopic sides, there are two important issues to be considered: the ability of the catalyst to control the *Z/E* geometry of the enamine intermediate and the

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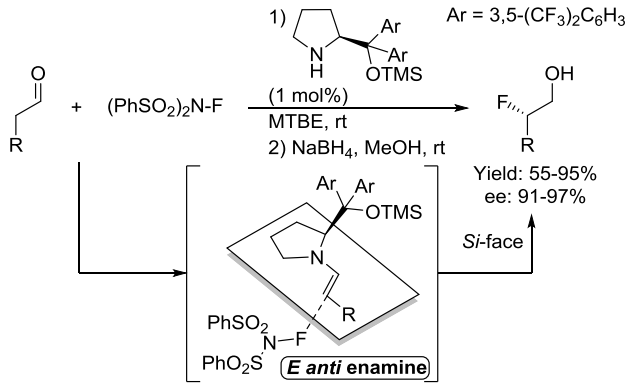
[26] (a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (c) For mechanistic insights, see: Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc*. **2001**, *123*, 11273.

[27] Franzén, J.; Marigo, M. Fielencah, D.; Wabnitz, T. C.; Kjaersgaard. A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

[28] (a) For a general review, see: Halskov, K. S.; Donslund, B. S.; Paz, B. M.; Jørgensen, K. A. *Acc. Chem. Res.* **2016**, *49*, 974. (b) For mechanistic insights, see: Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632.

conformational orientation of the double bond (*syn* or *anti*) relative to the 2-substituent, when considering a pyrrolidine based catalyst, both vital issues as the addition of the electrophile takes place through the less hindered face, thus different isomers of the enamine lead to the formation of opposite enantiomers of the product. Mechanistic studies have settled that *E* enamine is favored over the *Z* enamine due to the repulsive steric interactions between the enamine substituents and the protons adjacent to the nitrogen atom in the pyrrolidine ring when *Z* geometry is considered. As the *E* enamine can be oriented *syn* or *anti* relative to the 2-subtituent in the pyrrolidine, the enantiomeric excess of the synthetic transformation results from the ability of the catalyst to accelerate the reaction of one of the conformers over the other.[29] The aforementioned selectivity is illustrated in Scheme 2.3, where the absolute configuration of the product can be explained by the fluorination taking place from the *Si*-face of the most stable *E*-*anti* conformer of the enamine.[30]

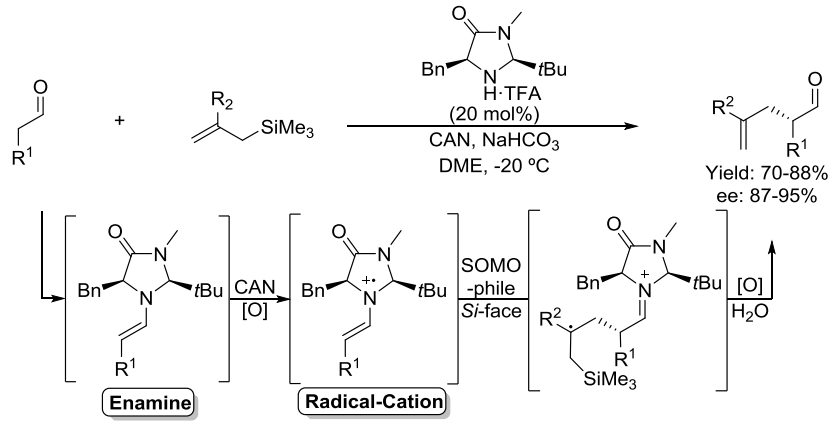


Scheme 2.3

A conceptually different approach for the α-functionalization of carbonyl compounds aroused with the SOMO catalysis (Scheme 2.4).[25b] Making use of the highly

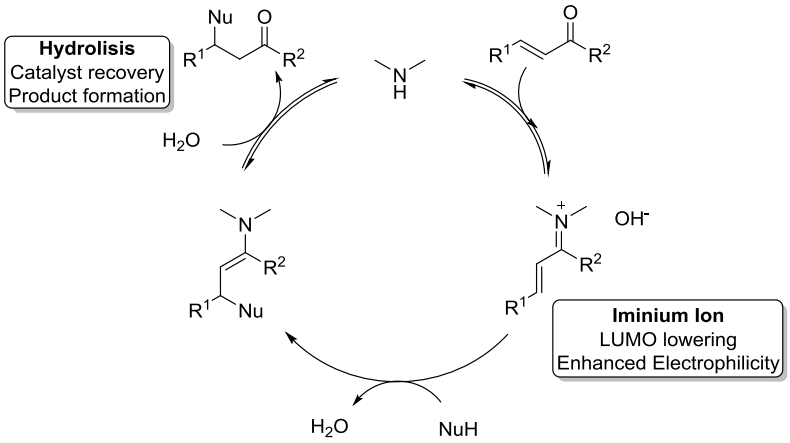
[29] Dinér, P.; Kjaersgaard, A.; Lie, M. A.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 122.
[30] Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703.

energetic HOMO of the enamine intermediate, in the presence of an oxidant, the enamine undergoes electron abstraction, leading to the formation of a radical-cation with tendency to react with SOMO-philes in α-position, and enabling an unprecedented transformation. The formation of the iminium ion occurs after an additional SET oxidative process, which is followed by hydrolysis, rendering the α-functionalized carbonyl compound and releasing the aminocatalyst.



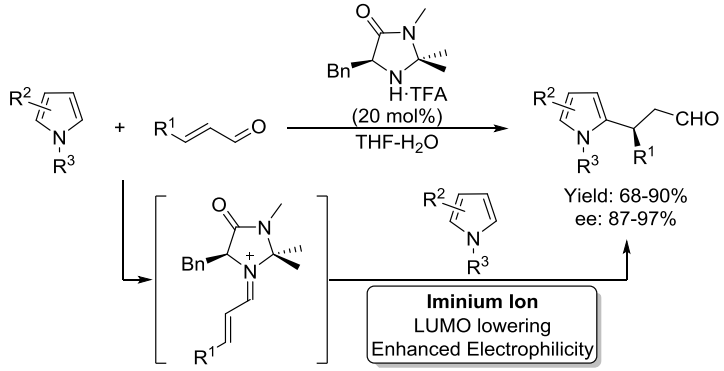
Scheme 2.4

On the other hand, iminium ion catalysis, as the other main aminocatalytic activation mode, comprises the use of chiral secondary or primary amines to enhance the inherent reactivity of α,β-unsaturated carbonyl compounds as Michael acceptors. Over the years, a large number of applications for this activation mode have been reported, aiding to understand the role of the catalyst and the nature of the catalytic cycle (Scheme 2.5).[22] The catalytic cycle starts with the reversible formation of an the iminium ion after condensation of the amine catalyst and the α,β-unsaturated aldehyde or ketone. The main feature of this intermediate is the lowered energy of its LUMO compared to the original enal or enone substrate, which leads to an increased electrophilicity and, therefore to higher reactivity towards nucleophiles that undergo addition on β-position . As final step, hydrolysis occurs releasing the catalyst and the β-substituted carbonyl product.



Scheme 2.5

The enantioselective organocatalytic Friedel-Crafts[31] alkylation of enals with pyrroles is a fine example to illustrate the potential of this strategy for the stereoselective introduction of a new bond on the β-position of enals (Scheme 2.6).[32] In this example, an oxazolidinone-type compound is used as catalyst to promote the reaction that proceeds under very mild conditions with excellent yields and enantioselectivities.



Scheme 2.6

[31] Friedel, C.; Crafts, J. M. *Bull. Soc. Chim. Fr.* **1877**, *27*, 530.
[32] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

As in the previous case, the use of an a chiral catalyst leads to the formation of diastereomeric reaction intermediates, that allow differentiating between the two diastereotopic faces of the Michael-acceptor and favoring one trajectory of the nucleophile during the 1,4-addition reaction. Two strategies may be considered to achieve a successful stereo-differentiation between diastereotopic sides: the use of a catalyst that hinders the approach of the nucleophile through one of the two faces (face shield), represented inFigure 2.1A,[33] or a stereodirecting element guiding the nucleophile through secondary interactions (*e.g.* electrostatic or H-bonding interactions) (Figure 2.1B).[34] Additionally, and as it occurs in enamine catalysis, the ability of the chiral catalyst to produce an iminium ion with a well defined geometry (*Z*/*E*) is a relevant issue to be considered in catalyst design.

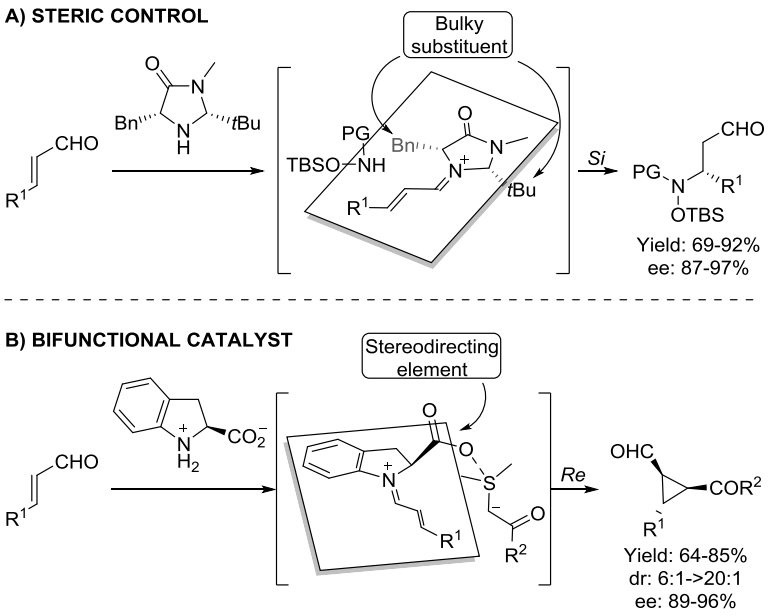


Figure 2.1

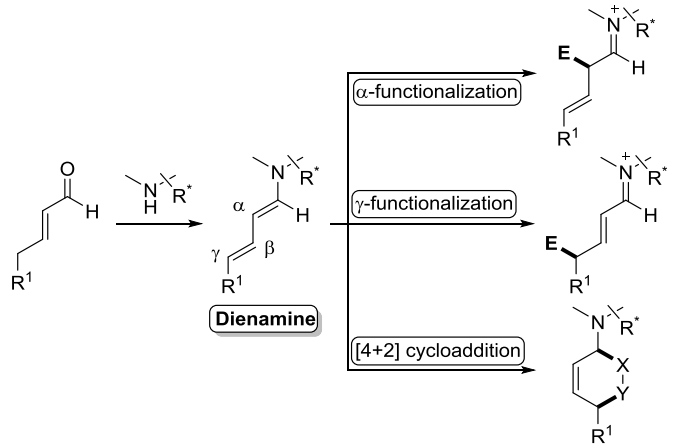
[33] Chen, Y. K.; Toshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.
[34] Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

2.2 Vinylogous Enamine and Iminium ion catalysis

The application of the principle of vinylogy in aminocatalysis has greatly extended the variety of transformations that can be addressed by simply studying the reactivity of substrates with elongated conjugated unsaturated systems.[24b] Closely related to enamine catalysis, dienamine catalysis[35] arises from the use of γ-enolizable α,β-unsaturated carbonyl compounds in combination with a primary or secondary amine catalyst that, after condensation, generates the iminium ion that follows γ-deprotonation rendering a dienamine intermediate. This dienamine intermediate, the same as a vinilogous enamine, exhibits nucleophilic reactivity in γ-position as consequence of the HOMO-raising effect along the conjugated π-system.

It should be pointed out that, regarding the extended conjugation of the electron-rich system in dienamines, the regioselectivity might be an issue, since multiple nucleophilic positions are present in dienamine intermediates (Scheme 2.7). The α-functionalization may take place, in a similar way as enamines would react. Remote γ-functionalization can also happen when the extended conjugate system reacts *via* the γ-terminus as previously discussed. Lastly, the dienamine can be considered as an electron-rich diene suitable to react with dienophiles in a classical [4+2] cycloaddition reaction, yielding an intermediate that has the hydrolysis step forbidden.

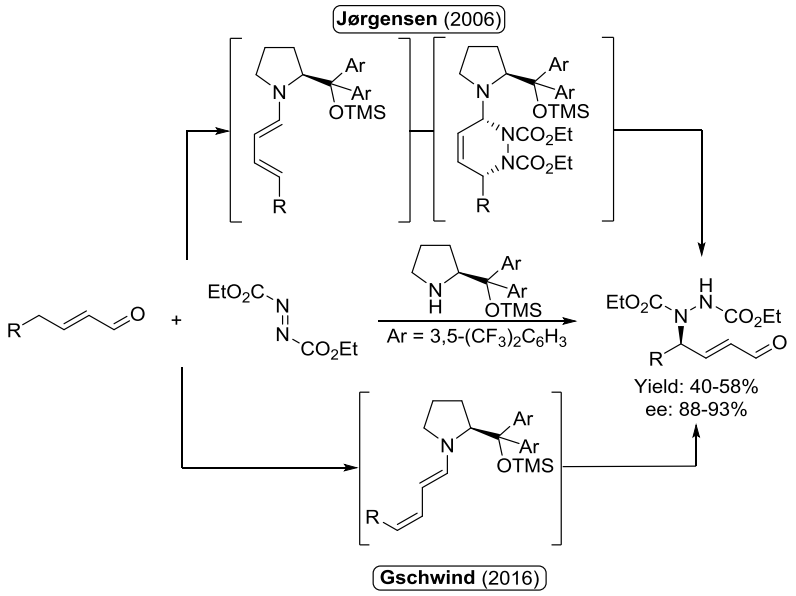
[35] For a selected review, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.



Scheme 2.7

The pioneering work on dienamine catalysis was the γ-functionalization of γ-enolizable α,β-unsaturated aldehydes in the presence of a chiral secondary amine with diethyl azodicarboxylate (Scheme 2.8).[36] The reasoning for the observed stereochemical outcome was firstly based on mechanistic and experimental studies that pointed to the formal Diels-Alder type reaction between the dienamine, as electron-rich diene, with the azodicarboxylate. Later investigations suggested that the reaction was under kinetic control, explaining the outcome of the reaction with the participation of the *E*,s-*trans*,*Z* conformer as the most reactive dienamine geometry (Scheme 2.8). Steric shielding exerted by the bulky substituent on the aminocatalyst led to the stereoselective formation of the observed product.[37]

[36] Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.
[37] Seegerer, A.; Hioe, J.; Hammer, M. M.; Morana, F.; Fuchs, P. J. W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 9864.



Scheme 2.8

In a similar way to enamine catalysis, in case an asymmetric catalyst is employed, the aminocatalysts function in not only to activate the pronucleophilic carbonyl compound *via* HOMO-rising, but also to perform a facial discrimination between the diastereotopic sites of the dienamine intermediate. The most widely employed strategy to achieve facial stereo-discrimination is the aforementioned steric-shielding approach (Scheme 2.8). However H-bonding directing strategies have also been successfully applied.[38] The first bifunctional H-bond directed dienamine catalysis reported made use of a squaramide-based pyrrolidine catalyst to simultaneously generate the dienamine intermediate and to direct the approach of the electrophile trough H-bonding interactions to react in a stereocontroled manner (Figure 2.2).[39] In this, case a nitroalkene was used as useful reagent which

[38] For reviews, see: (a) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.*, **2011**, *40*, 2330. (b) Alemán, J.; Parra, A.; Jiang, H.; Jorgensen, K. A. *Chem. Eur. J.*, **2011**, 17, 6890. (c) Chauhan, P.; Mahan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253.

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

undergoes formal [2+2] cycloaddition with the electron-rich dienamine to generate the corresponding cyclobutane with remarkable yields and enantioselectivities.

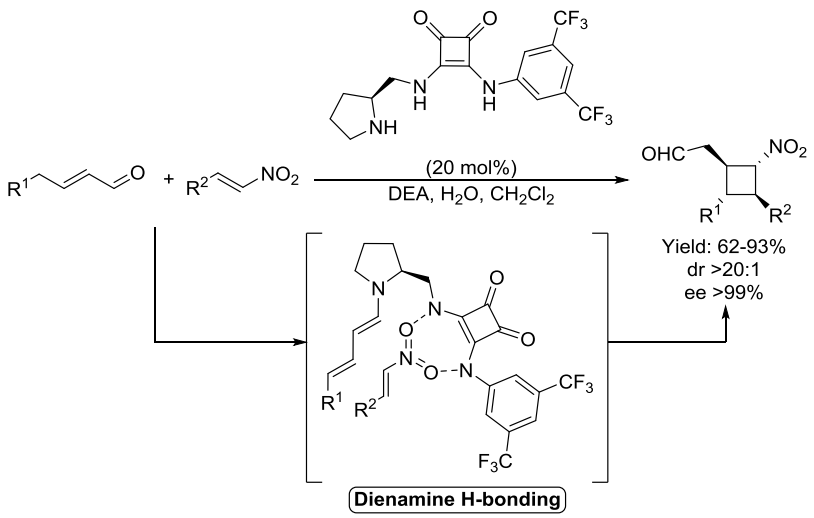


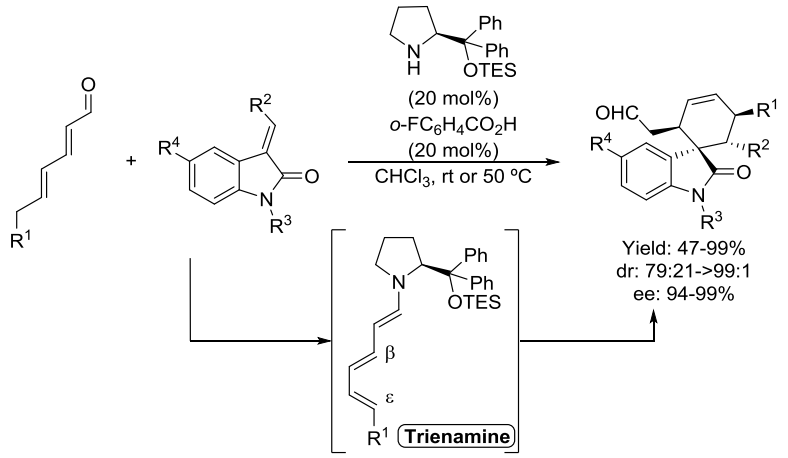
Figure 2.2

More recently, the further propagation of the HOMO-raising electronic effect in polyunsaturated carbonyl compounds, *i.e.* trienamine[40] and tetraenamine[41] catalysis, has demonstrated to be a powerful platform to perform enantioselective transformations on remote positions of carbonyl compounds. Achieving high levels stereoselectivity in transformations on the distant end of polyunsaturated carbonyl compounds is a challenge, considering the remoteness of the chiral inductor from the reactive site. Trienamine intermediates, due to the HOMO-raising effect and their polyunsaturated structure, take part in Diels-Alder type reactions as chiral dienes prone to react with various electron-deficient dienophiles. In fact, the first report on trienamine catalysis was a Diels-Alder reaction

[40] For pioneering 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 reviews, see: (b) Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5290. (c) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.*, **2013**, *11*, 709.

[41] For 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.; Yuan, X.; Chen, Y.-C. *Asian J. Org. Chem.* **2014**, *3*, 545.

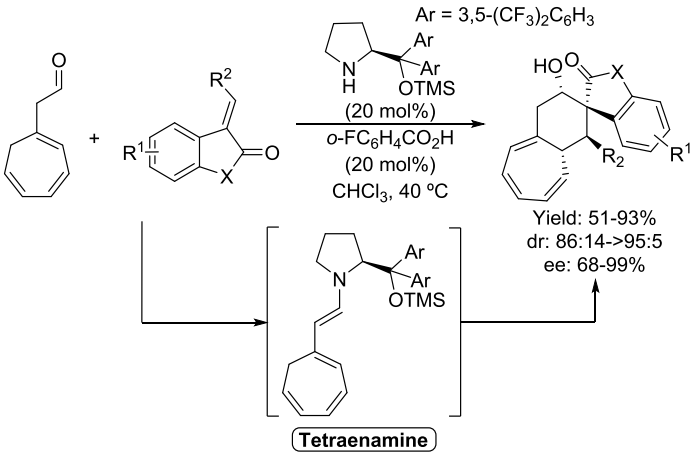
between 2,4-dienals and 3-olefinic oxindoles where a chiral secondary amine transformed the aldehydes into electron-rich dienes able to react with electron-deficient alkenes (Scheme 2.9).[40a,42]



Scheme 2.9

Application of the same strategy to substrates presenting additional unsaturations conduced to the tetraenamine catalysis. This methodology, regarding the limited number of reports, is restricted to configurationally restricted carbonyl systems, which do not achieve remote functionalization, entailing important boundaries for the method. Tetraenamines, as polyunsaturated highly energetic HOMO species show tendency to react with electron-deficient olefins as shown on Scheme 2.10, where a conformationally rigid cycloheptatriene acetaldehyde in the presence of a chiral secondary amine reacts on γ-position with olefinic oxindole, as electron poor alkene, in a formal [4+2] fashion with outstanding yields and stereoselectivities [41a]

[42] Further insights in trienamine catalysis see Chapter 3.



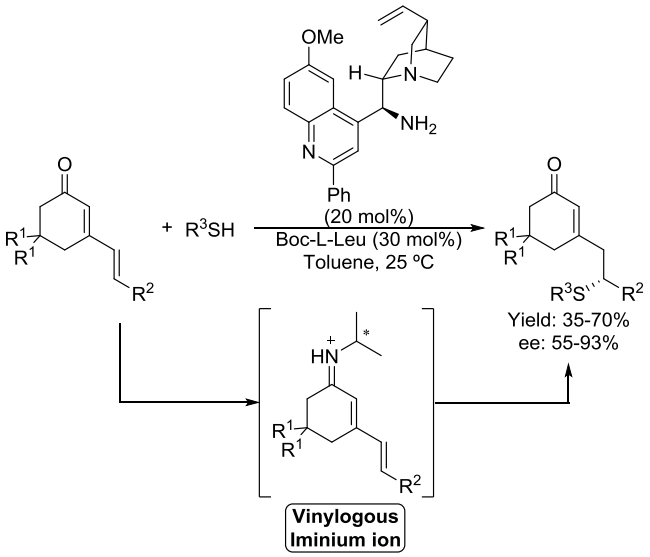
Scheme 2.10

The vinylogous enamine strategies (*i.e.* di- tri- and tetraenamine) allows the remote functionalization of (poly)unsaturated carbonyl compounds. For trienamine catalysis, the methodology gives access to densely substituted cyclohexene products with remarkable regioselectivity, the reaction occurring specifically with β,ε-selectivity for the two new bonds formation, and the noteworthy capacity of the chiral catalyst to transfer the chiral information along the system to the reactive points, six atoms apart from the catalyst binding site.

Finally, it should also be pointed out that the iminium ion activation has also found its corresponding extension in the vinylogous iminium ion catalysis, although to a much less extent compared to di- and trienamine catalysis, presumably due to their reduced.[43] The LUMO-lowering effect associated to the iminium ion activation can be transmitted through the conjugate system of 2,4-diunsaturated aldehydes or ketones enabling the direct and stereoselective functionalization of carbonyl compounds on the δ-position with a suitable

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

nucleophile, as illustrated on Scheme 2.11. In this example, the 1,6-addition of alkylthiols catalyzed by a cinchona-based primary amine in the presence of *N*-Boc protected L-leucine as co-catalyst was carried out leading to the δ-sulfur functionalized carbonyl compounds with excellent yields and high level of enantiocontrol.[43a]



Scheme 2.11

3. *N*-HETEROCYCLIC CARBENE CATALYSIS

N-Heterocyclic carbenes (NHC) constitute qualitatively the next most prevalent group of organocatalyst that participate in the activation of substrates trough covalent interactions. In a similar way to the aminocatalysis, *N*-heterocyclic carbenes have demonstrated their ability to circumvent traditionally challenging transformations when used as catalysts in a variety of synthetically relevant transformations[44,45,46]

NHCs are heterocyclic species composed of a carbene carbon and one or more nitrogen atoms adjacent to the carbene carbon.[47] Frequently, these nitrogen-atoms bear bulky substituents with the role of increasing the kinetic stability of the carbene species by hindering their spontaneous dimerization into olefins.[48] Additionally, nitrogen atoms contiguous to the carbene carbon also produce an electronic stabilization that greatly extends the lifetime of carbene species in solution. Since carbene carbons in NHCs present a singlet ground-state electronic-configuration with a lone electron pair in a formally sp^2-hybridized orbital (HOMO) and an unoccupied *p*-orbital (LUMO), the adjacent nitrogen atoms perform a simultaneous σ-electron-withdrawing and π-electron-donating "push-pull"

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

[45] For the use of NHCs as metal ligands, see: (a) Ritleng, V.; Henrion, M.; Chetcuti, M. J. *ACS Catal*. **2016**, *6*, 890. (b) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *ACS Catal.* **2016**, *6*, 5978. (c) Visbal, R.; Concepción Gimeno, M. *Chem.* Soc. Rev. **2014**, *43*, 355. (d) Schaper, L.-A.; Hock, S. J.; Hermann, W. A.; Kühn, F. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 270. (e) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (f) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122. (g) Nolan, S. *N-Heterocyclic Carbenes in Synthesis*; Wileye-VCH: Weinheim, 2006.

[46] For selected reviews on the use of NHC as organocatalyst, see: (a) Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14912. (b) Walden, D. M.; Ogba, O. M.; Johnston, R. C.; Cheong, P. H. *Acc. Chem. Res.* **2016**, *49*, 1279. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (d) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (d) Chen, X. Y.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 7991. (e) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (f) Biju, A. K.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (g) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichim. Acta* **2009**, *42*, 55. (h) Marion, N.; Díez-González, S.; Nolan, S. P.; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (i) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

[47] (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862.

[48] (a) Wanzlick, H.-W. *Angew. Chem. Int. Ed.* **1962**, *76*, 571. (b) Wanzlick, H.-W.; Kleiner, H.-J. *Angew. Chem. Int. Ed.* **1964**, *3*, 65.

synergistic effect that greatly increases carbenes stability, the former by lowering the energy of the HOMO and the latter by contributing with electon-density to the empty LUMO, respectively (Figure 3.1).[49]

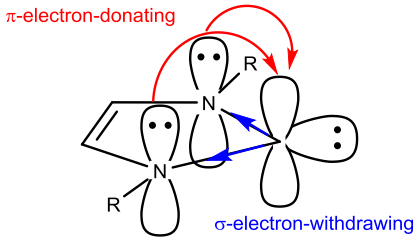

Figure 3.1

The electronic σ-donor nature of NHCs predicts their properties and reactivity as excellent ligands for metallic and non-metallic species, resulting in tunable adducts where the *N*-heterocyclic carbene properties greatly influence the structure and reactivity of the resultant complexes. However, singlet NHCs can be used as Lewis bases (σ-donor) with empty π-orbitals which show features that grant them with the capacity to react with aldehydes forming intermediates with very interesting reactivity. In fact, the potential use of NHCs to promote organic reactions for themselves began in 1943 with the observation of the thiamine-catalyzed coupling of two molecules of benzaldehyde rendering benzoin.[50,51] Fifteen years had to be waited for the accepted mechanistic proposal of this reaction, when R. Breslow suggested the presence of an *in situ* generated enaminol species, resulting from the reaction of the deprotonated thiazolium salt (*i.e.* the carbene) and benzaldehyde (Scheme 3.1).[52]

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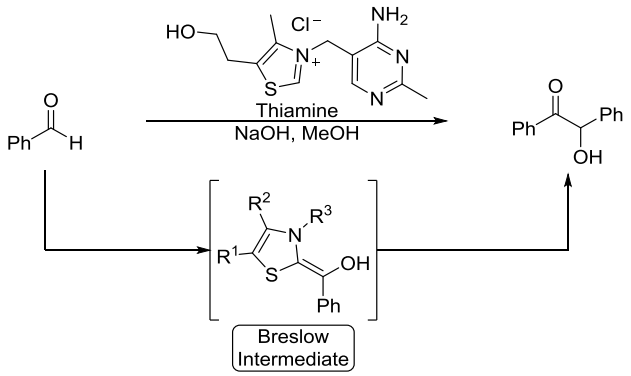
49 (a) Dixon, D. A.; Arduengo, A. J., III. *J. Phys. Chem.* **1991**, *95*, 4180. (b) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913.
50 Wöhler, F.; Liebig, J. *Ann. Der. Pharm.* **1832**, *3*, 249.
51 Ugai, T.; Tanaka, R.; Dokawa, T. *J. Pharma. Soc. Jpn.* **1943**, *63*, 296.
52 Breslow, R. J. *Am. Chem. Soc.* **1958**, *80*, 3719.

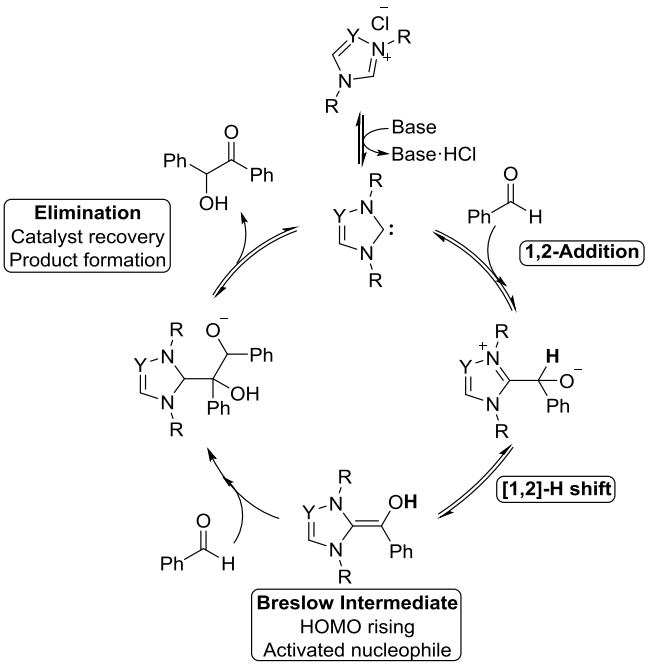


Scheme 3.1

Breslows proposal was based on the nucleophilic character of the carbene, which shows high affinity for aldehydes and tend to undergo 1,2-addition on the carbonyl group. As a result, the acidity of the *ipso* hydrogen is dramatically increased and a 1,2-proton shift occurs from the *ipso*-position to the alcoxide yielding an enaminol, known as the Breslow intermediate.[53] The high electron density on the π-orbitals of the heteroaromatic ring increases the nucleophilic character of the conjugated enaminol species becoming suited to react with electrophiles, like a carbonyl compound. Finally, the nature of the thiazolium moiety as a good leaving group provides the ability to follow elimination rendering the final benzoin product and releasing the carbene catalyst (Scheme 3.2). As a result, the typical reactivity of aldehydes is inverted in the course of the reaction from the electrophilic carbonyl compound to acyl anion type reactivity, in a typical example of an *umpolung* process.[54]

[53] He, Y.; Xue, Y. *J. Phys. Chem. A* **2011**, *115*, 1408.

[54] (a) Wittig, G.; Davis, P.; Koenig, G. *Chem. Ber*., **1951**, *84*, 627. (b) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.



Scheme 3.2

Elucidation of the benzoin reaction mechanism[52] and isolation and characterization of the Breslow intermediate[55] established the basis for the understanding of NHC-catalyzed reactions. Moreover, the participation of a covalently bonded carbene-substrate intermediate (*i.e.* Breslow intermediate) disclosed the possibility to achieve enantiocontrol on the product formation through the use of chiral NHC catalysts. This possibility relies on the ability to successfully differentiate the diastereotopic sides of the enaminol of the reacting intermediate, typically by hindering the approach of the external reactant to one of its faces by steric bias. Additionally, control on the geometry of the double bond of the enaminol is also a matter to be considered in order to achieve high enantioselectivity. The C=C double bond geometry is frequently directed by steric interactions with bulky substituents on adjacent position to carbene carbon atom (Figure 3.2).

[55] Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, L.-M. *Angew. Chem. Int. Ed.* **2012**, *52*, 11158.

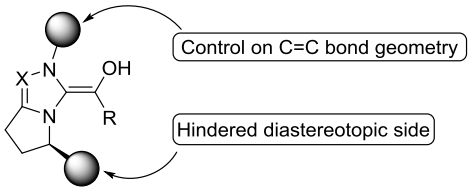
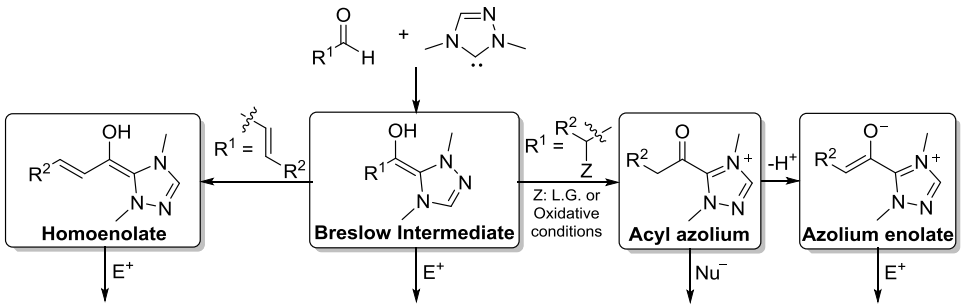


Figure 3.2

Furthermore, the reactivity of *N*-heterocyclic carbenes as organocatalysts is not limited to the acyl anion reactivity displayed by Breslow intermediate, commonly generated in the reaction between *N*-heterocyclic carbenes and aromatic aldehydes, which shows reactivity with electrophilic species as an *acyl anion* equivalent. Reaction between NHCs and structurally different aldehydes has given rise to a number of diverse reactivity patterns. Indeed, when using α,β-unsaturated aldehydes, a Breslow intermediate with extended conjugation is formed: *homoenolate*, which reacts with electrophiles on β-position. Aldehydes with leaving groups on α-position or aliphatic aldehydes in oxidative conditions under NHC catalysis, give rise to *acyl azolium* species, which exhibit tendency to react with nucleophiles or undergo deprotonation in basic environment, delivering *azolium enolates*, intermediates with disposition to react with electrophiles (Scheme 3.3).



Scheme 3.3

Each group represents a selective transformation of carbonyl compound into diverse reactive intermediates with unique reactivity enabling, in most cases, stereocontrol on a subsequent reaction. Over the last decades, the study of NHCs as catalysts to perform

unprecedented reactions has been in the focus of the scientific community with noteworthy achievements in the development of new activation modes.. An overview of the synthetic applications of carbenes as organocatalyst introducing each of the activation modes presented on Scheme 3.3 and the characteristic reactivity of the intermediates is presented in the following paragraphs.

The previously presented acyl anion reactivity, useful to perform nucleophilic addition on carbonyl compounds in *(aza)benzoin condensation*.[56] The synthetic problem of developing an efficient asymmetric version of the benzoin condensation[57] was successfully addressed with the nowadays most effective chiral carbene catalyst precursors, triazolium salts, yielding homo-benzoin products with excellent enantioselectivities (Scheme 3.4).[58,59,60] Additionally, the Breslow intermediate is also able to react with activated alkenes in a 1,4-addition fashion, the *Stetter reaction*.[61] The Stetter reaction has found application in a number of either intra- and intermolecular[62] reactions with various Michael acceptors electron-deficient alkenes. The following example represents an intramolecular Stetter reaction where the substrates bear a formyl group as acyl anion precursor linked to a α,β-unsaturated ester.(Scheme 3.4).[63,64]

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56 Menon, R, S.; Biju, A. T.; Nair, V. *Beilstein J. Org. Chem.* **2016**, *12*, 444.

57 For the first asymmetric benzoin condensation, obtaining ee up to 22% employing chiral thiazolium salts, see: Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666.

58 Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.

59 For computational studies on the asymmetric benzoin condensation, see: Dudding, T.; Houk, K. N. *PNAS*, **2004**, 5770.

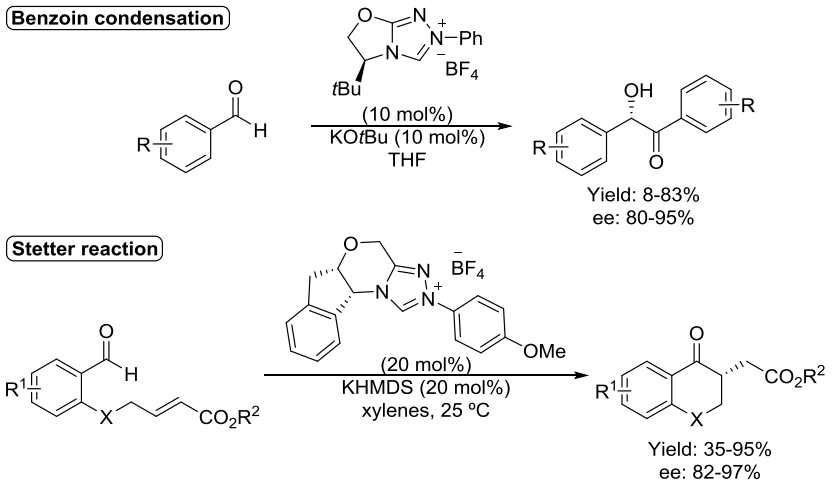
60 For insights on the influence of *N*-mesityl group on NHC-catalyzed reactions, see: Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192.

61 Original report: (a) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639. For a review on Stetter reaction, see: (b) De Alaniz, J. R.; Rovis, T. *Synlett* **2009**, *8*, 1189.

62 For a selected example of intermolecular Stetter reaction, see: Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066.

63 Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

64 For discussion on counterion effect, see Wei, S.; Wei, X.-G.; Su, X.; You, J.; Ren, Y. *Chem. Eur. J.* **2011**, *17*, 5965.



Scheme 3.4

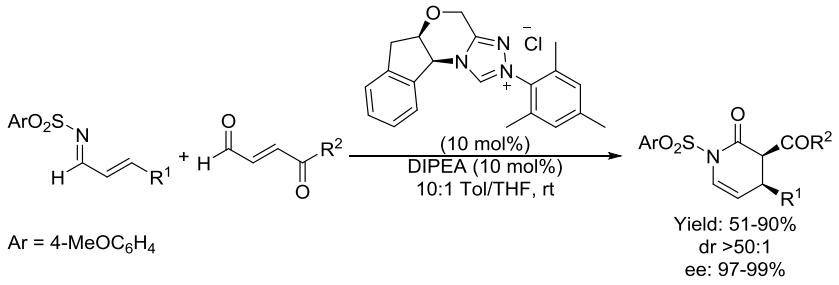
Both benzoin and Stetter reactions are based on the reactivity of the acyl anion (*i.e.* Breslow intermediate), generated through an *umpolung* process triggered by the carbene catalyst on formyl groups.

Aldehydes with good leaving groups (*e.g.* halogen) in α-position, among others, undergo, in a process catalyzed by carbenes, the formation of acyl azolium and azolium enolate species. The *acyl azolium*, as activated carbonyl compound with an extraordinary leaving group, reacts with nucleophiles producing azolium substitution products.[65]

On the other hand, *azolium enolate*,[66] due to the enhanced nucleophilicity of the α-carbon atom, reacts with electrophiles in α-position following the traditional enolate reactivity with electron-deficient dienes in inverse electron-demand Diels-Alder reaction, where the azolium enolate takes part as activated alkene with high affinity for heterodienes as α,β-unsaturated imines (Scheme 3.5).[67] These reactions enable the enantioselective synthesis of six membered heterocycles, such as δ-lactams and δ-lactones under mild

[65] Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8126.
[66] Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617.
[67] He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

conditions. Azolium enolate reactivity, unlike acyl azolium, gives the opportunity for the development of enatioselective methodologies through the use of chiral catalysts.[68]



Scheme 3.5

The last group represents the *homoenolate*[69] reactivity, arising from the use of α,β-unsaturated aldehydes with NHC catalysis. Homoenolates are extended Breslow intermediates with the HOMO-raising effect affecting all the π-system and reversing the reactivity of the β-position, making it nucleophilic, thus, the *umpoled* nucleophile reacts with electrophiles in β-position.[70] The following example illustrates the formal [3+2] cycloaddition of homoenolates generated from α,β-unsaturated aldehydes with isatins, employing a chiral triazolium salt as carbene precursor, to form spyrocyclic adducts. In this case, it is assumed that the H-bond donor present on the catalyst structure plays an important role on the stereocontrol of the reaction (Scheme 3.6).[71]

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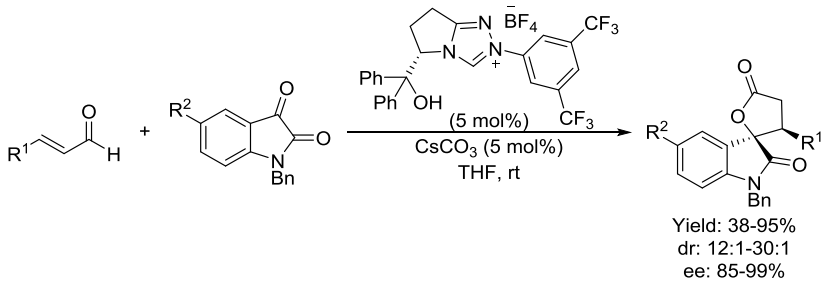
[68] Reactivity of azolium enolates will be further discussed in Chapter 4. Section 1. NHC-Catalyzed [4+2] Cycloadditions of Azolium Enolates.

[69] Nickon, A.; Lambert, J. L. S. J. *J. Am. Chem. Soc.* **1962**, *84*, 4604.

[70] Menon, R. S.; Akkattu, T. B.; Nair, V. *Chem. Soc. Rev.* **2012**, *44*, 5040.

[71] Sun, L.-H.; Shen, L.-T.; Ye, S. *Chem. Commun.* **2011**, *47*, 10136.



Scheme 3.6

In summary, the diverse activation strategies accessible using NHCs have been developed in the last decades, enabling the selective activation on *ipso*-, α- or β-positions of suitable aldehydes controlling the stereochemical outcome of the reaction when possible.

4. PRECEDENTS OF THE GROUP

The group has been traditionally involved in the development of methodologies in asymmetric synthesis, originally employing the chiral auxiliary strategy with the β-aminoalcohol (*S*,*S*)-(+)-pseudoephedrine with a number of contributions to enolate chemistry,[72] and conjugate additions.[73] However, in the last decade the interest of the research group moved to the asymmetric organocatalysis. For this purpose, a number of different methods for the activation of carbonyl compounds have been explored, covering in the following examples the use of cinchona- or proline-derived catalysts, NHC and H-bond catalysis.

The first work reported on the field of organocatalysis was an enamine catalyzed Michael reaction of α-enolizable aldehydes activated by prolinol derivatives with β-nitroacrolein dimethyl acetal.[74] The obtained Michael adducts were straightforwardly transformed into densely functionalized enantioenriched pyrrolidines (Scheme 4.1).[75]

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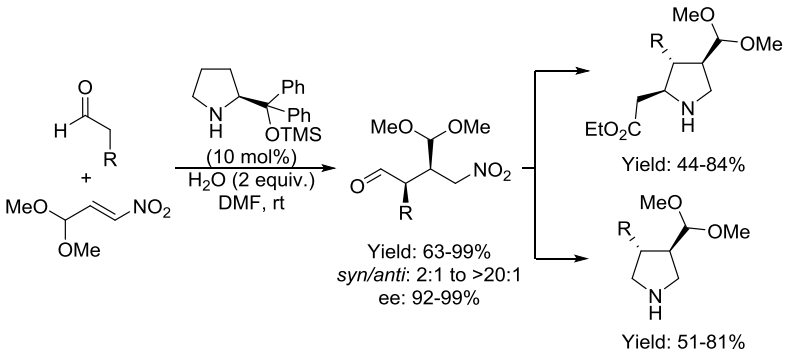
[72] Latest aldol reaction: (a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460 Latest Mannich reaction: (b) Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, 4065. Latest electrophilic amination reaction: (c) Vicario, J. L.; Badía,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

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

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

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



Scheme 4.1

Iminium ion catalysis was also investigated using chiral secondary amines as catalyst to activate α,β-unsaturated aldehydes. Iminium ion approach was applied for the β-functionalization of enals in a reaction with hydrazones, as *umpolung* acyl anion equivalents, for the enantioselective synthesis, after oxidation/[1,3]-H shift, of 1,4-dicarbonyl compounds.[76] Furthermore, iminium ion activation afforded the successful activation of enals as dipolarophiles to undergo [3+2] cycloaddition reaction with azomethine ylides to render polysubstituted pyrrolidines of high enantiopurity (Scheme 4.2).[77,78]

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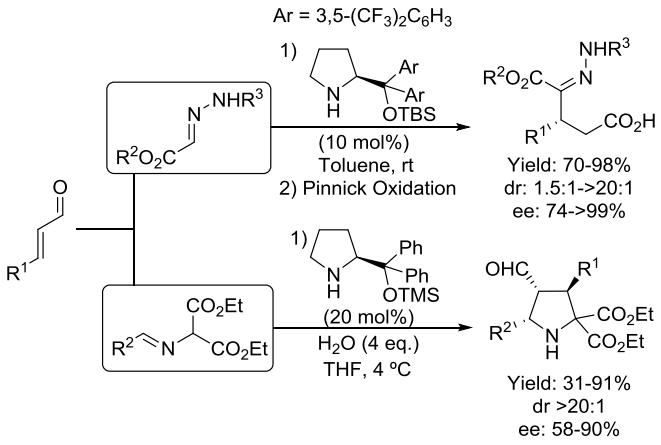
[76] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc*. **2012**, *134*, 11872.

[77] (a) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. (b) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal*. **2011**, *353*, 3307. (c) Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. *Chem. Eur. J*. **2012**, *18*, 7179,. (d) Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* 2013, *45*, 2669. For other works on iminium ion catalyzed [3+2] cycloaddition reaction, see: (e) Iza, A.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E.; Martínez, J. I. *Org. Biomol. Chem.* **2010**, *8*, 2238. (f) Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313. (g) Iza, A.; Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2013**, *69*, 8878. (h) Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Asymmetric Catal.* **2015**, *2*, 26.

[78] For other works on iminium ion activation, see (a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509. (b) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701. (c) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, 701. (d) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336. (e) Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048. (f) Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092. (g) Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal*. **2012**, *354*, 371. (h) Martínez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240. (i) Martínez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.;

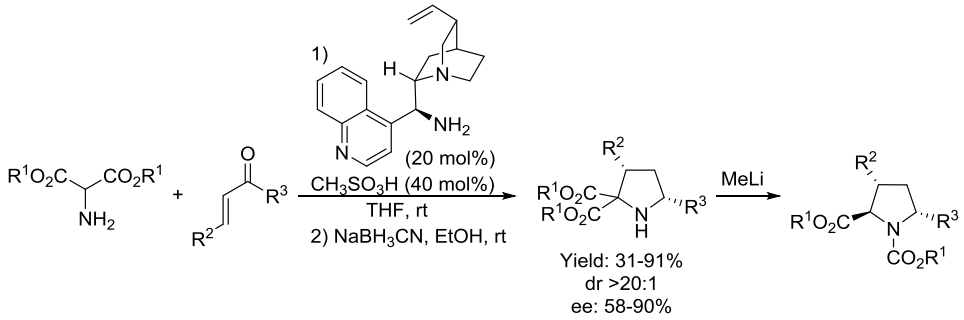


Scheme 4.2

Additionally, cinchona-based chiral primary amines were employed for the iminium ion activation of α,β-unsaturated ketones to react with aminomalonates that, after *in situ* reduction, delivered diastereo- and enantioselective synthesis of 3,5-disubstituted pyrrolidines (Scheme 4.3).[79] The products could be straightforwardly transformed into the corresponding *N*-protected prolines after base promoted C-N acyl transfer.

Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240. (j) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653. (k) Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.* **2015**, *2*, 206. (l) Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.

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

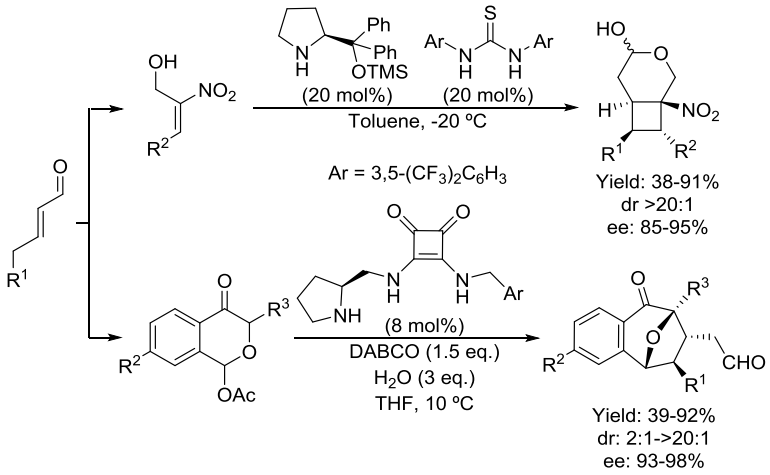


Scheme 4.3

The vinylogous enamine activation was surveyed in cycloaddition reactions where γ-enolizable enals, upon activation with chiral secondary amines, generated dienamine type intermediates, which reacted as HOMO-activated alkenes with suitable electron-deficient species. On one hand, α-hydroxymethylnitrostyrene in the presence of thiourea co-catalyst reacted in a formal [2+2] fashion with dienamine intermediate for the diastereo- and enantioselective formation of densely substituted cyclobutanes.[80] On the other hand, the *in situ* generated oxidopyrylium ylide, from conveniently substituted acetoxypyranone, participated in a formal [5+2] reaction with dienamine intermediate catalyzed by a squaramide based bifunctional chiral amine rendering 8-oxabicyclo[3.2.1]octane (Scheme 4.4).[81]

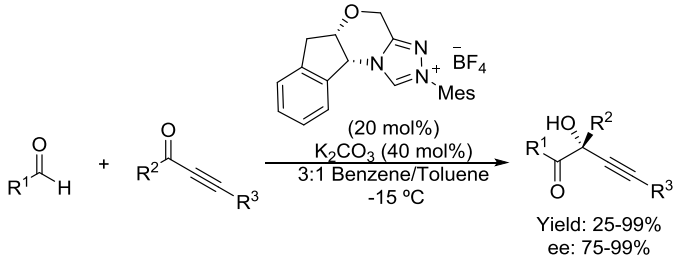
[80] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

[81] (a) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3043. (b) Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L.; Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 884. For other works on dienamine catalysis, see: (c) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.



Scheme 4.4

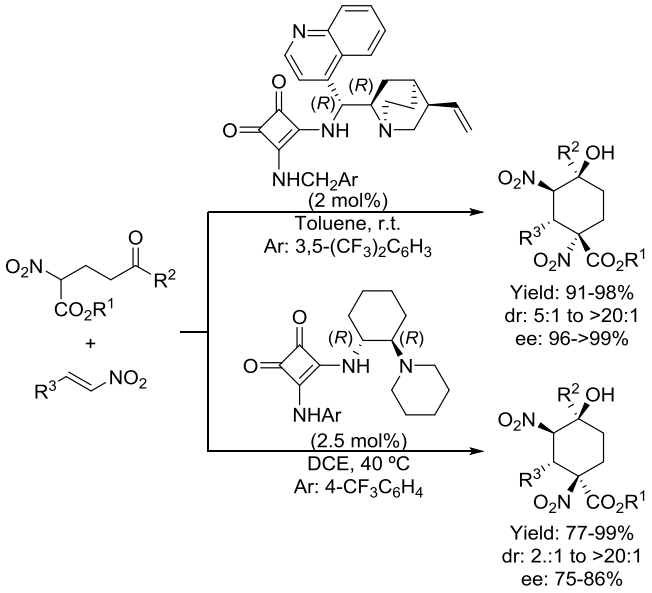
An additional covalent mode of activation of carbonyl compounds was explored using *N*-heterocyclic carbene catalysis for the cross-benzoin reaction between aldehydes and ynones resulting in the highly enantioselective formation of tertiary propargylic alcohols (Scheme 4.5).[82]



Scheme 4.5

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

Moving on to non-covalent activation mechanism, hydrogen-bond catalysis was investigated, leading to the development of a diastereodivergent strategy for the enantioselective synthesis of densely substituted cyclohexanes from nitroalkenes and α-nitro-δ-oxo esters in a Michael/Henry cascade process using squramide-based bifunctional catalysts. The catalyst interacted *via* hydron-bonding with the substrate directing the stereoselectivity of the reaction. (Scheme 4.6).[83]



Scheme 4.6

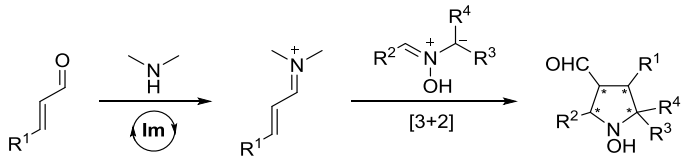
The selected examples illustrate different ways to achieve stereocontrol on different reactions over carbonyl compounds employing diverse activation mechanisms, including, catalysts which perform covalent and non-covalent interactions with substrates

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

5. GENERAL OBJECTIVES OF THE PRESENT WORK

The work presented in this manuscript was developed within the general research activities of the group, more specifically, on the *search for unconventional reactivity patterns in enantioselective reactions under organocatalytic activation*. The research was divided in three parts as follows:

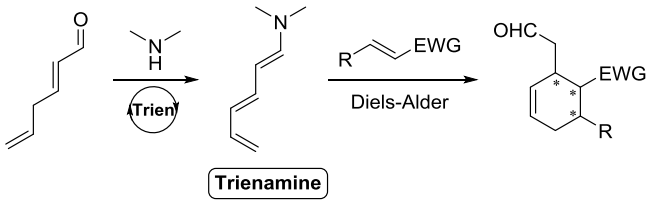
1. Iminium activation: Nitrone ylides as unconventional 1,3-dipoles in [3+2] cycloaddition. Taking advantage of the rather unexplored reactivity of nitrone ylides in asymmetric synthesis, an enantioselective formal [3+2] cycloaddition between nitrone ylides, as 1,3-dipoles, and enals as dipolarophiles under iminium ion activation was investigated. The key point of the reaction would be the effective production of nitrone ylide intermediates able to react with activated α,β-unsaturated iminium ion intermediates displaying a regioselectivity change from the typical C,O-1,3 reactivity of nitrones to an less conventional C,C-1,3 reactivity, which would provide enantioenriched *N*-hydroxypyrrolidines (Scheme 5.1).



Scheme 5.1

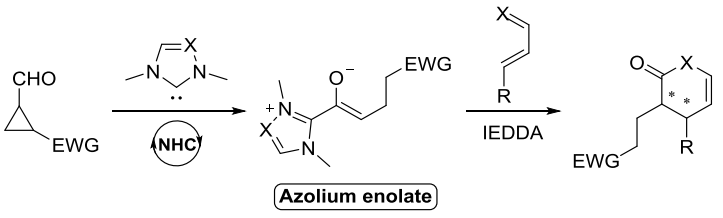
2. Unconjugated dienals as reactive substrates for Diels-Alder reaction under trienamine activation: The increasing conjugation level of the starting carbonyl compounds in order to perform dienamine or trienamine catalysis entails depletion in reactivity toward the condensation with the aminocatalyst, turning into a loss of reactivity and critically affecting these strategies implementation. The high efficacy shown by trienamine catalysis to achieve highly complex structures in a single Diels-Alder type [4+2] cycloaddition step from relatively simple starting materials encouraged the search to

increase the reactivity and the scope of the reaction, regarding the polyunsaturated aldehyde, employing polyunsaturated non-conjugated carbonyl compounds to circumvent the loss in reactivity associated with the employment of substrates with increasing number of unsaturations (Scheme 5.2).



Scheme 5.2

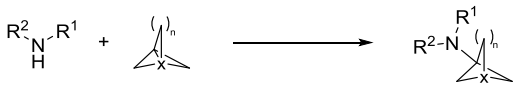
3. Organocatalytic generation of Donor-Acceptor cyclopropanes under NHC activation: Donor-Acceptor cyclopropanes are particularly exciting substrates since the synergistic electronic nature of their substituents strongly favors the release of the strain energy associated to the cyclopropane ring through ring-opening process, generating a zwitterionic intermediate. In this context, a methodology for the *in situ* generation of synthetically interesting D-A cyclopropanes from easily accessible and stable precursors triggered by an organocatalyst, in a diastereo- and enantioselective inverse electron-demand Diels-Alder reaction with adequate reacting partners was studied (Scheme 5.3).



Scheme 5.3

4. Finally, the most relevant results obtained during a short stay carried out in The Scripps Research Institute (La Jolla) under the supervision of Prof. Phil S. Baran is

presented. This project describes the synthesis and use of highly strained carbo- and heterocycles in amination reaction to access structurally elusive and pharmaceutically interesting compounds (Scheme 5.4).



Scheme 5.4

The reaction represents a novel strategy for the late functionalization of pharmaceutically interesting compounds, giving access to previously elusive bioisosteric forms, while retrieving known but underexploited reactivity of polycyclic molecule.

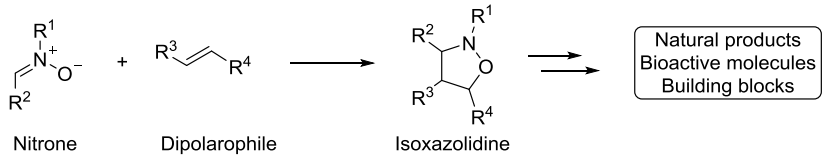
Chapter 2

2

Organocatalytic Enantioselective [3+2] Cycloaddition of Nitrone Ylides

1. NITRONES IN 1,3-DIPOLAR CYCLOADDITION REACTIONS

1,3-Dipolar cycloadditions[1] are considered a powerful synthetic tool to access five-membered heterocycles through direct reaction between 1,3-dipolar compounds and dipolarophiles.[2] Nitrones are probably one of the most extensively studied type of 1,3-dipoles, as they are easy to obtain, handle, and also isoxazolidine products obtained after the cycloaddition process, are of high utility since these heterocycles are present in natural products,[3] and bioactive synthetic molecules (Scheme 1.1).[4] Moreover, isoxazolidines can also be straightforwardly transformed into interesting skeletons such as β-aminoacids,[5] β-lactams[6] and β-aminoalcohols.[7]



Scheme 1.1

Additionally, nitrones exhibit multifaceted reactivity since they are capable to take part in 1,3-dipolar cycloaddition reactions with dipolarophiles of opposite electronic properties, a phenomenon attributed to the propensity of both FMOs of nitrones to

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1 (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *10*, 565. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *10*, 633.

2 (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry*; John Wiley & sons: New York, USA, 2003. For selected reviews on 1,3-Dipolar cycloaddition, see: (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Kanemasa, S. *Synlett* **2002**, 1371. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (e) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (f) Kanemasa, S. *Heterocycles* **2010**, *82*, 87. (g) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366.

3 (a) Wilson, M. S.; Padwa, A. *J. Org. Chem*. **2008**, *73*, 9601. (b) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem*. **2005**, *70*, 6884. (c) Akai, S.; Tanimoto, K.; Kanao, Y.; Omura, S.; Kita, Y. *Chem. Commun.* **2005**, 2369.

4 (a) Piotrowska, D. G.; Balzarini, J.; Głowacka, I. E. *Eur. J. Med. Chem*. **2012**, *47*, 501. (b) Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc*. **2004**, *126*, 10504.

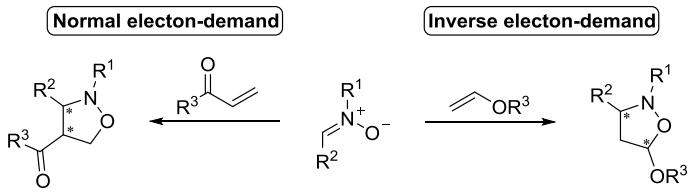
5 Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett*. **1996**, 37, 5947.

6 Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999,** 64, 5017.

7 (a) Hoogenboom, J.; Zuilhof, H.; Wennekes, T. *Org. Lett*. **2015**, *17*, 5550. (b) Yao, C.-Z.; Xiao, Z.-F.; Ning, X.-S.; Liu, J.; Zhang, X.-W.; Kang, Y.-B. *Org. Lett*. **2014**, *16*, 5824. (c) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, 603, 6.

participate in the cycloaddition reaction with dipolarophiles showing opposite electronic properties.[8]

In view of their versatile reactivity, the vast number of 1,3-dipolar cycloadditions reported in the literature that use nitrones can be divided in two different groups, according to the FMO energies of the reacting species: normal electron-demand and inverse electron-demand reactions (Scheme 1.2). For normal electron-demand 1,3-dipolar cycloadditions, the reaction is controlled by interaction between the HOMO of the nitrone and the LUMO of the alkene. In this case, the most common alkenes to take part as dipolarophiles in this type of 1,3-dipolar cycloaddition are electron-deficient olefins, such as α,β-unsaturated carbonyl compounds. On the other hand, inverse electron-demand 1,3-dipolar cycloaddition reactions are those in which, due to a higher energy of the FMOs of the alkene, as vinyl ethers, the prevailing interaction is between the LUMO of the nitrone and the HOMO of the alkene.[9]



Scheme 1.2

In order to develop a catalytic process, the main factor to be considered is the relative FMO energies of the reagents given that the transition state of concerted 1,3-dipolar cycloaddition reactions is controlled by FMO of the substrates. Thus, a catalyst apt to alter the FMOs energies causing a LUMO-lowering effect on either the nitrone or the

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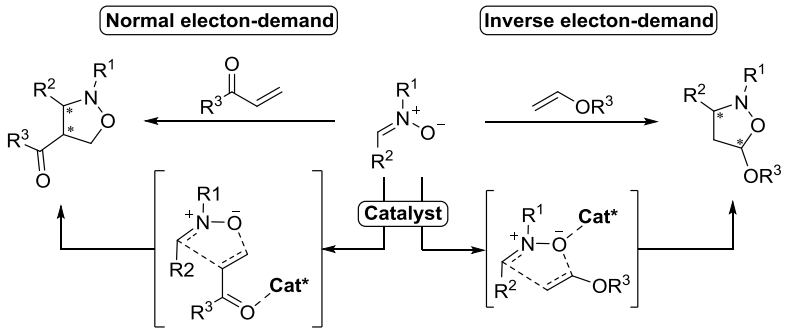
8 (a) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (b) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 407.

9 Gothelf, K V. Asymmetric Metal-Catalyzed 1,3-Dipolar Cycloaddition Reactions. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2001, Chapter 6; pp 211-247.

dipolarophile, such as a Lewis acid, is required. Following the previously presented classification, normal electron-demand catalyzed reactions cover the situations when the catalyst activates the dipolarophile, usually α,β-unsaturated carbonyl compounds, which can be easily activated with a wide variety of catalysts, from Brønsted or Lewis acids to aminocatalysts. These catalysts present the common feature of enhancing the electron-withdrawing effect of the dipolarophile, thus lowering the energy of the LUMO, while meeting requirements for the selective binding on the dipolarophile and producing sufficient stabilization of the LUMO of the alkene to achieve accelerated reaction rates enabling the catalytic control of the reaction (Scheme 1.3 Left).

Divergently, for inverse electron-demand 1,3-dipolar cycloadditions between nitrones and electron-rich alkenes (*e.g.* vinyl ethers) as dipolarophiles, in order to design a catalytic process, the catalyst needs to be able to selectively lower the energy of the LUMO of the nitrone. Therefore, the catalyst, usually a Lewis acid, must exhibit superior affinity for nitrone than for other reaction partners and, when coordinated with nitrones *N*-oxide needs to cause a satisfactory LUMO-lowering effect to bring closer the reacting FMOs and expediting the catalytic pathway of the reaction (Scheme 1.3 Right).

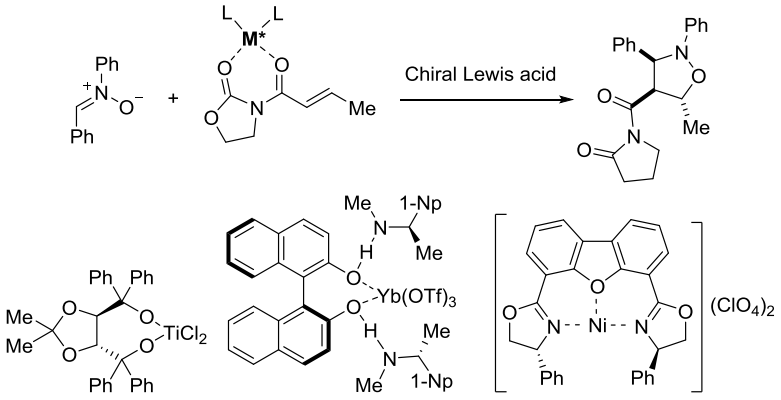


Scheme 1.3

For either normal or inverse electron-demand dipolar cycloadditions, both situations lead to the formation of products presenting one or more stereogenic centers. With the

purpose of designing an enantioselective process, and considering either normal or inverse electron-demand dipolar cycloadditions, the enantiocontrol of the reaction implies the use of chiral catalysts bearing suitable chiral environment to provide diastereomeric transition states, to selectively activate either the dipolarophile or the nitrone could lead to the formation of enantiomerically enriched adducts.[10]

Chiral Lewis acids have demonstrated their talent to achieve excellent results activating a range of α,β-unsaturated carbonyl compounds as dipolarophiles in enantioselective normal electron-demand 1,3-dipolar cycloaddition reactions with nitrones.[11] It is necessary to highlight the need to use bidentate dipolarophiles to ensure a successful implementation of the reaction, as the Lewis basic nitrone competes with the dipolarophile for coordinating the chiral Lewis acid. In these sense, the use of a bidentate dipolarophiles results in almost exclusive formation of the catalyst-dipolarophile complex, benefiting the stereoselective control of the reaction (Scheme 1.4).

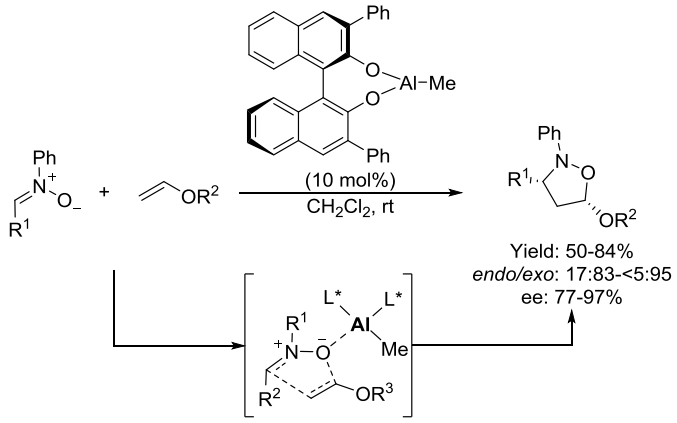


Scheme 1.4

[10] Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449.

[11] (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.*, **1994**, *59*, 5687. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

The catalytic activation of nitrones in inverse electron-demand reaction with enol ethers was achieved employing Lewis acids with one single available coordination site that displayed superior affinity to interact with the more Lewis basic nitrone oxygen's lone pair compared to enol ethers oxygen atom. This is the case of the Al (III) complex incorporating 3,3'-disubstituted BINOL ligand represented on Scheme 1.5, which gave access to a range of substituted isoxazolidine products with remarkable diastereo- and enantioselectivities.[12]

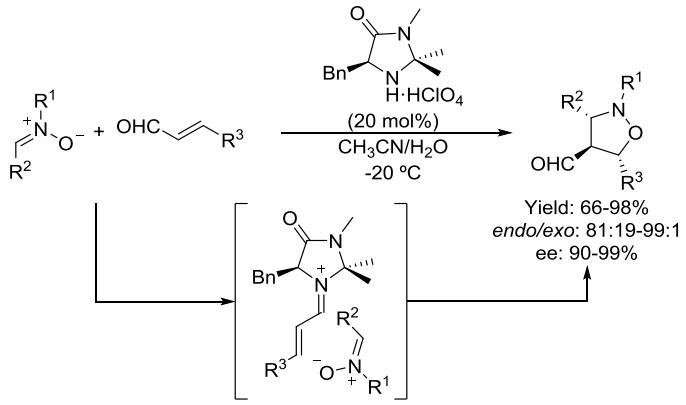


Scheme 1.5

With the arise of organocatalysis, opportunities for the development of new enantioselective 1,3-dipolar cycloaddition reactions appeared. The LUMO-lowering effect accessed by aminocatalysts on α,β-unsaturated aldehydes, *i.e.* iminium ion activation, improves substrates properties as a dipolarophile and turn them perfectly suited to take part in normal electron-demand dipolar cycloaddition with nitrones. MacMillan *et al.*, turned to a chiral imidazolidinone based catalyst, able to activate α,β-unsaturated aldehydes *via* iminium catalysis, to lower the LUMO of enals as dipolarophiles. The reaction covered the use of the chiral aminocatalyst to promote the reaction of acrolein or crotonaldehyde with nitrones rendering *endo* cycloadducts with high enantioselectivities, circumventing

[12] Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845.

problems associated with the employment of Lewis acids, like the lack of regioselectivity when using enals as dipolarophiles or the need of bidentate dipolarophiles to get high enantioselectivities (Scheme 1.6).[13]



Scheme 1.6

Afterwards, several methods were described to catalytically activate α,β-unsaturated aldehydes as dienophiles using chiral secondary amines, introducing modifications on the structure of the chiral catalysts,[14] broadening the scope of nitrones,[15] or ynals.[16] One-pot approaches were also studied, avoiding the synthetic step of nitrone synthesis and isolation in a three-component reaction of aldehyde, hydroxylamine and the unsaturated aldehyde.[17]

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13 (a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem, Soc.* **2000**, *122*, 9874. For extension of the method, see: (b) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923. (c) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782. (d) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2016**, *138*, 6412.

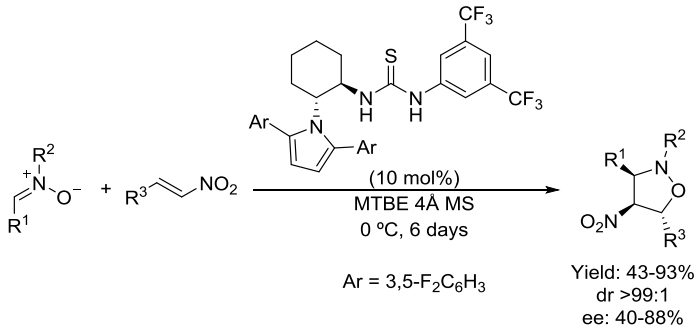
14 (a) Lemay, M.; Trant, J.; Ogilvie, W. W. *Tetrahedron* **2007**, *63*, 11644. (b) Chow, S. S.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. *Tetrahedron Lett.* **2007**, *48*, 277. (c) Weselinski, L.; Stepniak, P.; Jurczak, J. *Synlett*, **2009**, *14*, 2261. (d) Weselinski, L.; Slyk, E.; Jurczak, J. *Tetrahedron Lett*. **2011**, *52*, 381.

15 (a) Wesselinski, L.; Kalinowska, E.; Jurczak, J. *Tetrahedron: Asymmetry*, **2012**, *23*, 264. (b) Selim, K. B.; Beauchard, A.; Lhoste, J.; Martel, A.; Laurent, M. Y.; Dujardin, G. *Tetrahedron: Asymmetry* **2012**, *23*, 1670.

16 (a) Cai, X.; Wang, C.; Sun, J. *Adv. Synth. Catal*. **2012**, *354*, 359. (b) Alemán, J.; Fraile, A.; Marzo, L.; García-Ruano, J. L.; Izquierdo, C.; Díaz-Tendero, S. *Adv. Synth. Catal.* **2012**, *354*, 1665.

17 (a) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5701. (b) Vesely, J.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 2693. (c) Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614. (d) Chua. P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Commun*. **2010**, *46*, 7611.

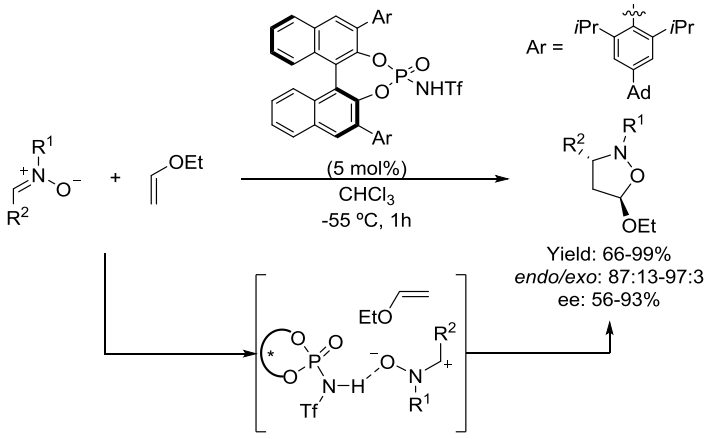
Representing an alternative strategy, H-bonding interactions were successfully implemented to achieve a LUMO-lowering effect on dipolarophiles. For this purpose, chiral thioureas were employed as organocatalysts to activate nitroolefins as dipolarophiles, in a normal electron-demand 1,3-dipolar cycloaddition reaction, through H-bond interactions, achieving LUMO-lowering of the dipolarophile and facilitating the cycloaddition reaction with nitrones rendering nitro-substituted isoxazolidines achieving excellent levels of diastereo- and enantioselectivity (Scheme 1.7).[18]



Scheme 1.7

Alternatively, and introducing the organocatalytic enantioselective version of the inverse electron-demand 1,3-dipolar cycloaddition reaction with nitrones, a BINOL-derived Brønsted acid was found to successfully activate nitrones to induce the reaction with ethyl vinyl ether as electron rich dipolarophile (Scheme 1.8).[19] The Brønsted acid catalyzed-reaction showed *endo*-selectivity, opposite to the previously presented analogous reaction catalyzed by Lewis acids which exhibited *exo*-selectivity. The reaction performed satisfactorily with a wide variety of aromatic nitrones, with excellent levels of diastereo-and enantioselectivity.[12]

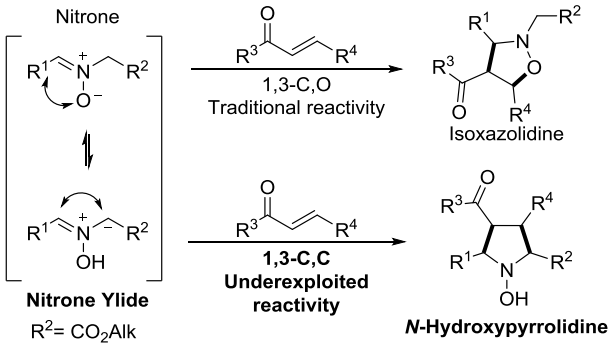
[18] Du, W.; Liu, Y.-K.; Yue, L.; Chen, Y.-C. *Synlett* **2008**, *19*, 2997.
[19] Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411.


Ar
O
P
O
O
NHTf
Ar
Ar =
iPr
iPr
Ad
R1
R2
N
O
OEt
(5 mol%)
CHCl3
-55 ºC, 1h
Yield: 66-99%
endo/exo: 87:13-97:3
ee: 56-93%
EtO
R2
O
P
O
O
N–H
O
N
R1
Tf

Scheme 1.8

2. SPECIFIC OBJECTIVES AND WORK PLAN

Although many studies were centered on the development of 1,3-dipolar cycloadditions of nitrones that react on the C- and O-*termini*, little focus was drawn to the possibility of switching the classical 1,3-C,O reactivity of nitrones to a much less exploited 1,3-C,C reactivity. A number of non-catalytic strategies employing nitrone ylides were reported where the basis for the electronic and structural requirements of the nitrone to develop 1,3-C,C reactivity were outlined.[20] The electronic properties of nitrone ylides, as highly energetic HOMO species, make them adequate to react with electron-deficient dipolarophiles in a normal electron-demand reaction. Considering the structure, access to nitrone ylides is restricted to pro-1,3-dipoles with acidic protons next to the nitrogen atom, a feature provided by an ester group adjacent to the methylene in glycinate-based nitrones, promoting the 1,3-C,C-selectivity in the reaction (Scheme 2.1).



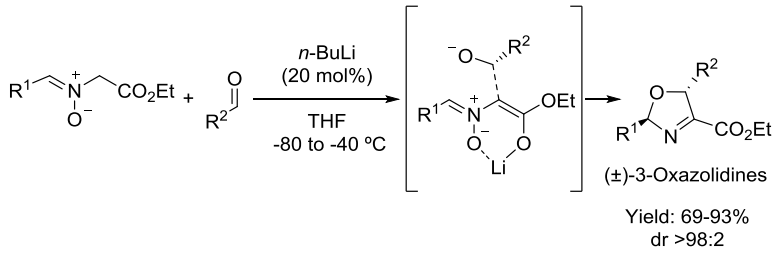
Scheme 2.1

The reactivity of nitrone ylides under *n*-BuLi catalytic conditions has been tested in a formal [3+2] reaction with aldehydes, as electron-deficient dipolarophiles, to access 3-oxazolidines providing excellent yields and diastereoselectivities(Scheme 2.2).[21].

[20] (a) Hanessian, S.; Bayrakdarian, M. *Tetrahedron Lett.* **2002**, *43*, 967. (b) Hanessian, S.; Bayrakdarian, M. *Tetrahedron Lett.* **2002**, *43*, 9441. (c) Merino, P.; Tejero, T.; Díez-Martínez, A. *J. Org. Chem.* **2014**, *79*, 2189.

[21] Juste-Navarro, V.; Delso, I.; Tejero, T.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 11527.

Computational and experimental studies, which pointed to an stepwise mechanism for the overall [3+2] process, disclosed that the role of the lithium was to facilitate the deprotonation and enolate formation on the α-position to the ester group, enhancing its nucleophilicity to effect the 1,2-addition.[22] The key point for the successful formation of the 1,3-C,C dipole and satisfactory outcome of the reaction was the fact that the lithium cation, assisted by chelation with the ester group, remained coordinated with the nitrone ylide. A particular feature of this reaction lied on the dehydration step concomitant with the N-O bond cleavage, which was the driving force of the reaction. Nitrones with C-aromatic substituents were unable to perform the reaction, unless bearing strong electron-withdrawing groups, due to their decreased reactivity compared to the more reactive C-alkyl substituted nitrones, for the second step of the reaction



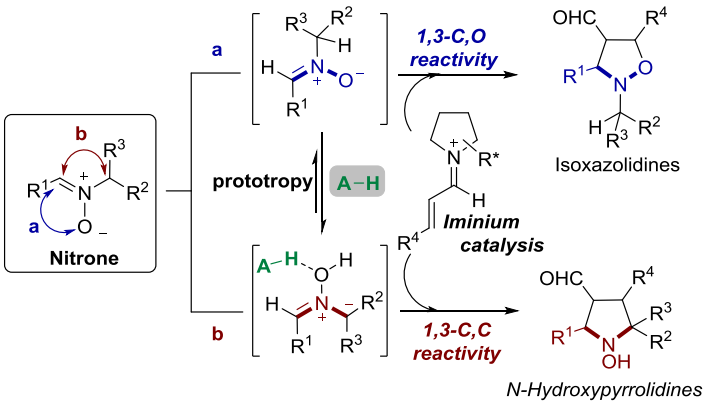
Scheme 2.2

However, up to date, no *enantioselective* 1,3-dipolar cycloaddition involving nitrone ylides has yet been reported. In this context, the need to cover the only partially explored reactivity of nitrone ylides and the lack of a catalytic enantioselective processes to access *N*-hydroxypyrrolidines, encourages the development of new research on this topic and fully exploit the synthetic possibilities of nitrone ylides in 1,3-dipolar cycloaddition reactions.

Taking into account the need to expand the research on nitrone ylide chemistry, and the proven ability of chiral secondary aminocatalysts to perform a LUMO-lowering effect on α,β-unsaturated carbonyl compounds, their effectiveness to induce enantioselectivity to

[22] Merino, P.; Tejero, T.; Díez-Martínez, A.; Gültekin, Z. *Eur. J. Org. Chem.* **2011**, 6567.

the process and in particular, their success catalyzing the previously presented primal 1,3-dipolar cycloaddition with classical nitrones,[13] the second aim of this project is to develop an **organocatalytic enantioselective [3+2] normal electron-demand cycloaddition exploring the C-N-C reactivity of nitrone ylides with enals as dipolarophiles under iminium activation directed to the synthesis of enantioenriched *N*-hydroxypyrrolidines**. In contrast to previously described asymmetric [3+2] reactions using nitrones as 1,3-dipoles, this strategy involves the use of the less conventional 1,3-C,C reactivity (Scheme 2.3b) rather than the well established 1,3-C,O reactivity (Scheme 2.3a) of these dipoles in a reaction with α,β-unsaturated aldehydes as electron-deficient dipolarophiles in a normal electron-demand [3+2] cycloaddition catalyzed by chiral secondary amines.[23]



Scheme 2.3

[23] During the completion of this project, nitrone ylides were used in an asymmetric [3+2] cycloaddition: Chen, Y.-R.; Zhan, G.; Du, W.; Chen, Y.-C. *Adc. Synth. Catal.* **2016**, *358*, 3759.

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

1. *Proof of concept:* Initially, in order to demonstrate the possibility to generate nitrone ylides in conditions compatible with iminium activation approach, and the viability of the process will be studied. For this purpose structural requirements of the nitrone will be addressed, evaluating, in particular, nitrones bearing acidic α-protons, together with the identification of suitable additives to achieve a successful formation of the nitrone ylide intermediate that enables the [3+2] cycloaddition reaction (Figure 2.1).

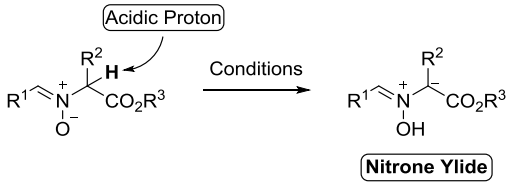
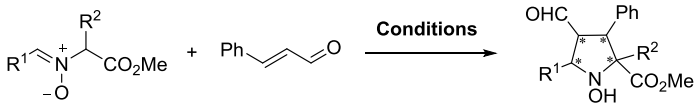


Figure 2.1

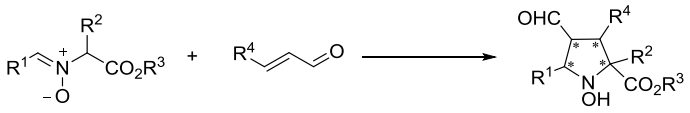
2. *Optimization of the reaction conditions*: Using cinnamaldehyde and the selected nitrone as model reaction, search for the best reaction conditions will be undertaken, assessing diverse aminocatalysts looking for optimal results of enantio- and diastereoselectivity, and appraising variations on experimental conditions, such as solvent, temperature and additives, in order to attain satisfactory results on yield and stereoselectivity (Scheme 2.4).



Scheme 2.4

3. *Scope of the reaction*: Once optimal conditions for the reaction are settled, the method will be expanded to the use of different α,β-unsaturated aldehydes and diverse

nitrones, evaluating the influence of the substitution pattern of these reagents on the stereoselectivity and yield of the reaction (Scheme 2.5).



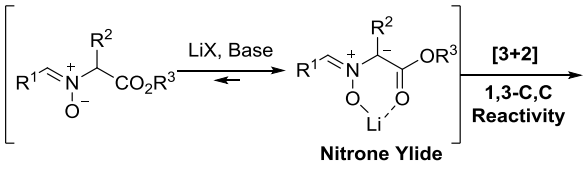
Scheme 2.5

3. RESULTS AND DISCUSSION

With the overall objectives of the project already defined, the most relevant results obtained during the research will be disclosed in the following paragraphs, according to the previously defined working plan.

3.1 Proof of concept

As previously mentioned, literature precedents suggest the need to carefully design the structure of the nitrone to access the desired 1,3-C-C reactivity. Literature examples point out that electron-withdrawing groups on the aliphatic *N*-substituent of the nitrone, such as an alcoxycarbonyl group, were required to increase the acidity of the protons next to the nitrogen atom, hence favoring the nitrone ylide intermediate formation. In addition, literature precedents indicate that, in most cases, an additive is needed in order to assist the formation of the nitrone ylide species, namely the use of chelation of lithium salts in basic environment (Scheme 3.1).[20,22,21]



Scheme 3.1

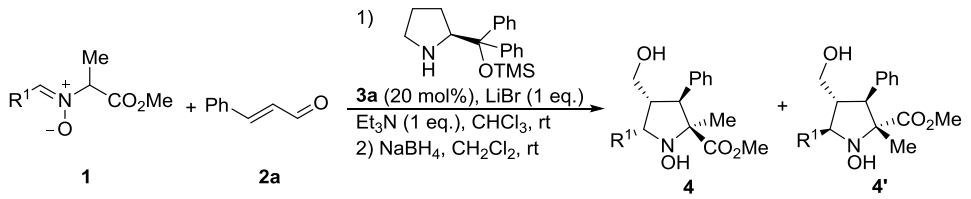
Due to the electronic nature of nitrone ylides, as high-energy HOMO species, these should show affinity for low-energy LUMO dipolarophiles, like α,β-unsaturated carbonyl compounds. In this sense, enals stand out for their capacity to be activated by chiral secondary amines through iminium ion activation.

Therefore, the work began evaluating the potential of nitrones with the general structure shown in Figure 2.1, bearing the required alcoxycarbonyl group at the α-carbon attached to the *N*-atom. Initially, and for prospective reasons, a series of four nitrones

incorporating alkyl and aryl substituents with different electronic properties as substituents at the azomethine carbon-atom, were tested.

All reactions were carried out in chloroform using cinnamaldehyde (**2a**) as dipolarophile, stoichiometric amounts of LiBr and triethylamine, as additives that, according to literature precedents, favor the nitrone ylide formation.[20,22,21] Diphenylprolinol trimethylsilyl ether (**3a**) was selected as catalyst,[24] which has a proven ability to catalyze reactions *via* iminium ion with excellent stereocontrol (Table 3.1).[25]

Table 3.1: Evaluation of various nitrones.[a]



Entry	R^1	Yield (%)[b]	dr[c]	ee (%)[d]
1	*i*-Pr	<5	n.d.[e]	n.d.[e]
2	4-$MeOC_6H_4$	<5	n.d.[e]	n.d.[e]
3	Ph	17	5:1	14
4	4-$NO_2C_6H_4$	45	5:1	16
5[f]	4-$NO_2C_6H_4$	41	5:1	-

[a] Reactions performed in 0.2 mmol scale of **1** and **2a** in 0.4 mL of $CHCl_3$. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d] Enantiomeric excess determined by HPLC analysis. [e] n.d.: Not determined. [f] Reaction performed in absence of **3a**.

[24] (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[25] For some 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, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

As outlined in Table 3.1, the reaction with alkyl-substituted nitrones did not deliver the desired product (entry 1) resulting instead on the formation of 3-oxazolidines in low yield in a reaction of the nitrone ylide with the carbonyl group of the α,β-unsaturated aldehyde.[26] Electron-rich aromatic substituents were unreactive for the [3+2] cycloaddition and followed hydrolysis or transimination with cinnamaldehyde (entry 2). Using phenyl substituted nitrones provided the desired *N*-hydroxypirrolidine in low yield and poor enantioselectivity (entry 3), confirming the formation of the desired adduct. Electron-withdrawing aromatic substituents performed better, reaching moderate yield with similar results of stereoselectivity (entry 4).

During these experiments, it was observed that the products presented stereochemical instability upon manipulation. For this reason, adducts were subjected to various transformations among which the *in situ* reduction successfully circumvented the spontaneous epimerization on C-4. The reduction of the formyl group was carried out evaporating the solvent of the reaction under reduced pressure, redissolving it in dry dichloromethane and using $NaBH_4$ as reducing agent at room temperature. This transformation afforded stereochemically stable adducts.

The ability of the lithium salt/triethylamine system to promote the reaction was clearly settled performing the reaction in absence of chiral amine (Table 3.1 entry 5). This trial evidenced that fast background proceeded in the presence of lithium salts with no need to activate the dipolarophile through iminium ion formation, thus explaining the deficient enantioselectivity of the reactions presented on Table 3.1

The determination of the enantiomeric excess of the products was performed using racemic standards of **(±)-4**, which were obtained using racemic mixtures of catalyst **(±)-3a** under the reaction conditions shown on Table 3.1. The products were isolated as diastereomeric mixtures. Enantiomers were chromatographically separated using the

[26] This reaction was already described in the literature under different reaction conditions, see: Ref. 21.

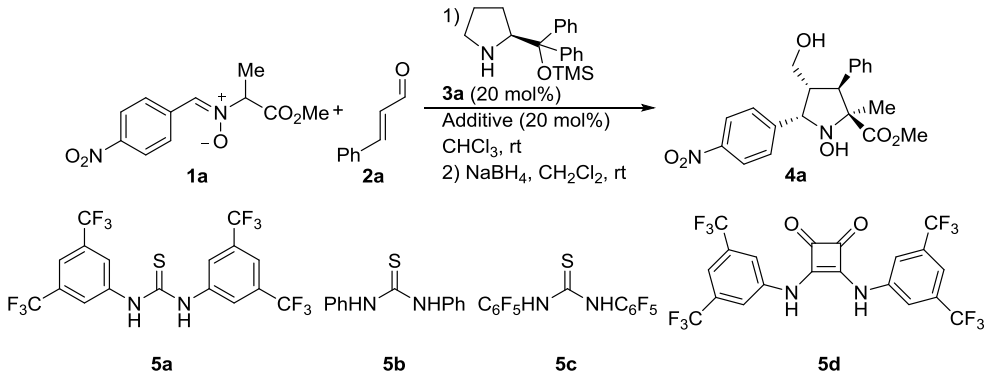
chromatographic chiral stationary phase column *Chiralpak IA* with an eluent mixture of *n*-hexane/*i*-PrOH in 90:10 ratio with 1.0 mL/min of flow.

nOe experiments on both isolated diasteremores of the product, aided to determine the relative configuration of both major (**4**) and minor (**4'**) diastereomers produced in the reaction, which resulted to be the epimers on both C-2 and C-5 positions (see Table 3.1).

3.2 Optimization of the reaction conditions

Once the possibility to obtain the *N*-hydroxypyrrolidine adducts **4** from nitrones of type **1** was verified, and with the aim of improving the reaction, the influence of additives of different nature was evaluated. The additives evaluated covered reagents of basic and acidic nature. The reactions were performed with nitrone **1a**, cinnamaldehyde **2a** and catalyst **3a**, in chloroform as solvent and at room temperature (Table 3.2).

Table 3.2: Study of additives of diverse nature.[a]



Entry	Additive	Yield (%)[b]	dr[c]	ee (%)[d]
1	none	<5	n.d.[e]	n.d.[e]
2	$PhCO_2H$	<5	n.d.[e]	n.d.[e]
3	Et_3N	9	2:1	98
4	**5a**	47	5:1	97
5	**5b**	<5	n.d.[e]	n.d.[e]
6	**5c**	41	3:1	92
7	**5d**	52	2:1	86

[a] Reactions performed in 0.2 mmol scale of **1a**, 0.24 mmol of **2a** and 20 mol% of **3a** in 0.4 mL of $CHCl_3$ at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d] Enantiomeric excess determined by HPLC analysis. [e] n.d.: Not determined.

As illustrated on Table 3.2, the catalyst **3a** by itself was not capable to promote the reaction in absence of an additive (entry 2) or with benzoic acid (entry 3).[27] Howerver, under basic conditions a small amount of product was isolated (entry 4), with this experiment the ability of catalyst **3a** to achieve high enantioselectivity was confirmed.

Interestingly, incorporating thiourea **5a** as additive resulted in the formation of **4a** with a promising yield, good diastereoselectivity and keeping the high enantioselectivity of the reaction (entry 5). Although the use of thiourea **5b** led to no product formation, pointing to the need of additives bearing N-H protons with a certain acidity (entry 6),[28] while thiourea **5c** and squramide **5d** rendered the product with moderate yield and with slightly lower diastereo- and enantioselectivity in comparison with the results provided by additive **5a** (entries 7-8). It should be highlighted that, no evidence of isoxazolidine product formation was observed.

Although the enantiocontrol of the reaction was satisfactory, yield and diastereoselectivity remained improvable. A range of aminocatalysts, known for their ability to generate iminium ion intermediates from enals, were then evaluated, including MacMillan-type imidazolidinone based catalysts, pyrrolidine-based secondary amines bearing bulkier silylated groups or substituted aromatic rings and a bifunctional pyrrolidine/squramide catalyst (Table 3.3).

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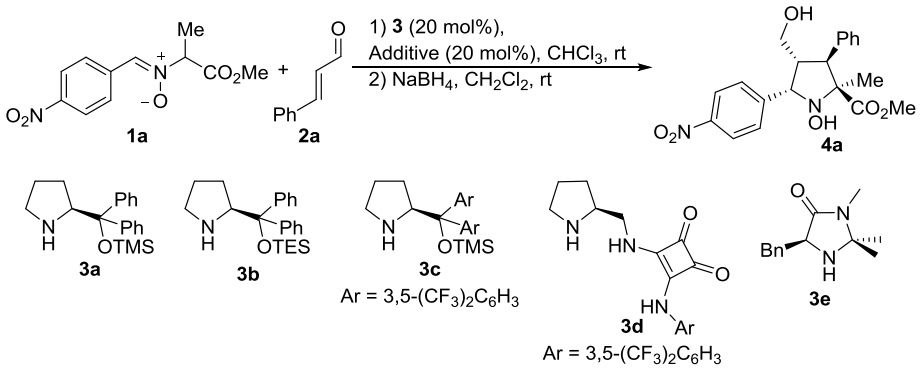
[27] Benzoic acid is a broadly used additive in combination with **3a**.

[28] pKa values for $PhCO_2H$: 4.2; **5a**: 8.5 and **5b**: 13.4. From: Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

Table 3.3: Evaluation of aminocatalysts.[a]



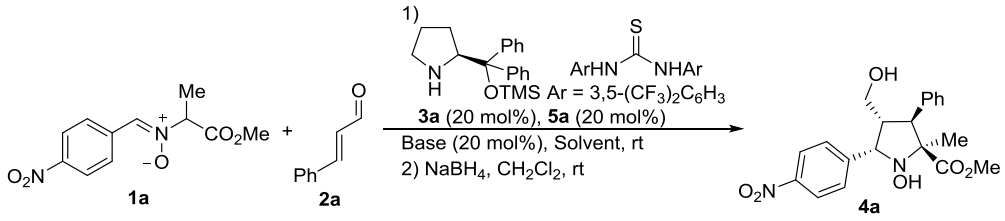
Entry	Catalyst	Additive	Yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	**5a**	47	5:1	97
2	**3b**	**5a**	14	6:1	99
3	**3c**	**5a**	<5	n.d.[e]	n.d.[e]
4[f]	**3d**	none	40	4:1	20
5[g]	**3e**	HCl	<5	n.d.[e]	n.d.[e]

[a] Reactions performed in 0.2 mmol scale of **1a**, 0.24 mmol of **2a** and 20 mol% of **5a** in 0.4 mL of $CHCl_3$ at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis of the reduced adduct **4a**. [e] n.d.: Not determined. [f] 10 mol% of catalyst was used.[g] Nitromethane was used as solvent.

Initially, catalyst **3b**, with a larger silyl protecting group than **3a**, gave access to product **4a** with slightly better diastereomer ratio, but with a remarkable negative effect on the yield (entry 2). Catalyst **3c**, with bulkier aryl substituents, did not provide any cycloaddition produc (entry 3). Alternatively, the bifunctional catalyst **3d** containing both a pyrrolidine moiety to activate the α,β-unsaturated aldehyde and a squaramide scaffold to promote the nitrone ylide formation was tested, resulting in moderate results regarding yield and diastereoselectivity but with poor enantiocontrol (entry 4). Finally, imidazolidinone catalyst **3e** was employed under the reaction conditions reported by MacMillan for the primal organocatalytic [3+2] cycloaddition with nitrones,[13a] where no isoxazolidine formation was either observed. In view of these results, catalyst **3a** was chosen to continue the screening of reaction conditions.

With the need of **3a** as catalyst settled, the use of bases as additives, in combination with the necessary thiourea **5a**, was then considered, as evidences of the benefits of a basic environment for the product formation were shown in the literature.[20] The effect of the solvent was also evaluated trying to find the best compromise between solvent polarity and yield with the stereocontrol (Table 3.4).

Table 3.4: Study of the effect of the base and solvent.[a]



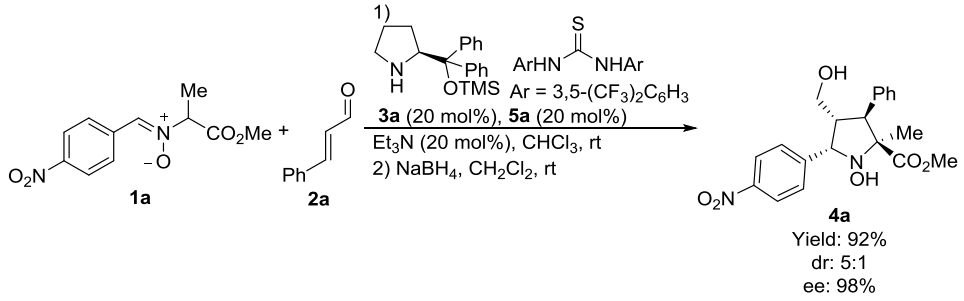
Entry	Base	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	none	$CHCl_3$	47	5:1	97
2	Et_3N	$CHCl_3$	92	5:1	98
3	DIPEA	$CHCl_3$	75	5:1	97
4	DABCO	$CHCl_3$	25	4:1	97
5	DBU	$CHCl_3$	<5	n.d.[e]	n.d.[e]
6	Et_3N	CH_2Cl_2	82	3:1	98
7	Et_3N	Toluene	53	4:1	98
8	Et_3N	THF	28	4:1	98
9	Et_3N	EtOAc	22	4:1	97
10	Et_3N	MeCN	31	2:1	96

[a] Reactions performed in 0.2 mmol scale of **1a**, 0.24 mmol of **2a**, using 20 mol% of **3a**, 20 mol% of **5a** and 20 mol% of base in 0.4 mL of solvent at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis. [e] n.d.: Not determined.

As expected, the presence of substoichiometric amounts of triethylamine, together with thiourea **5a**, strongly benefited the formation of the product **4a** achieving excellent yield and maintaining the high level of stereoselectivity (entry 2). Other related bases were

tested such as the more sterically hindered *N*,*N*-diisopropylethylamine (DIPEA) (entry 3), or the more nucleophilic 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 4-5), obtaining in all cases inferior results. Finally, continuing with the use of triethylamine as basic additive, different solvents were assessed. Dichloromethane led to the product formation with high yield, although with moderate diastereoselectivity (entry 6). Non-polar solvents like toluene delivered the product with moderate yield, not observing improvement on diastereoseletivity (entry 7), while polar solvents like tetrahydrofuran, ethyl acetate and acetonitrile rendered the adduct with a notable decrease on yield (entries 8-10). Then, the results obtained with other solvents were below the standard in chloroform.

In summary and after evaluating the most influential reaction parameters, the best conditions for the reaction are shown on Scheme 3.2. These comprise the catalyst **3a** with thiourea **5a** and triethylamine in chloroform at room temperature.

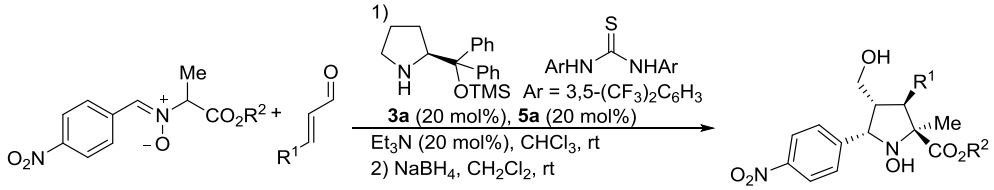


Scheme 3.2

3.3 Scope of the reaction

Having established a robust experimental procedure for the synthesis of the cycloadducts, the method was expanded to the use of various α,β-unsaturated aldehydes with different substitution patterns and nitrones with variability on azomethine carbon-atom. Firstly, the substituents on the ester group and aldehyde were evaluated (Table 3.5).

Table 3.5: Scope of the reaction using esters and β-substituted enals.[a]



Entry	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	Me	92	5:1	98
2	Ph	Et	84	4:1	99
3	Ph	*t*-Bu	<5	n.d.[e]	n.d.[e]
4	4-MeC_6H_4	Me	84	6:1	99
5	4-$MeOC_6H_4$	Me	85	6:1	>99
6	4-$MeOC_6H_4$	Et	82	5:1	98
7	2-$MeOC_6H_4$	Me	72	4:1	94
8	4-$Et_2NC_6H_4$	Me	74	2:1	>99
9	2-furyl	Me	93	9:1	>99
10	2-thienyl	Et	78	7:1	>99
11	3,5-$(MeO)_2C_6H_4$	Et	83	4:1	>99
12	4-BrC_6H_4	Et	81	4:1	99
13	4-ClC_6H_4	Et	94	4:1	98
14	4-IC_6H_4	Et	86	5:1	99
15	4-$CF_3C_6H_4$	Et	85	4:1	99
16	Me	Et	<5	n.d.[e]	n.d.[e]

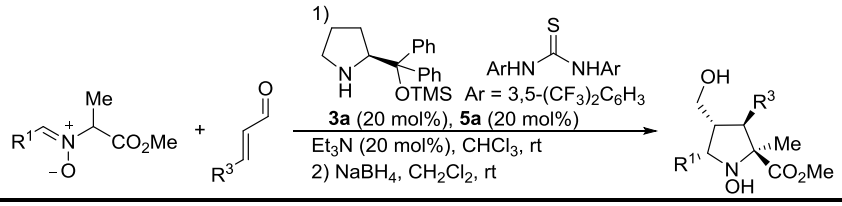
17	*n*-Bu	Et	<5	n.d.[e]	n.d.[e]

[a] Reactions performed in 0.2 mmol scale of **1a-b**, 0.24 mmol of **2a-l**, using 20 mol% of **3a**, 20 mol% of **5a** and 20 mol% of Et_3N in 0.4 mL of $CHCl_3$ at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis.[e] n.d.: Not determined

As illustrated on Table 3.5, nitrones reached high level performance independently if the substituent on the ester moiety is either a methyl or ethyl group (compare entries 1 vs 2 and 5 vs 6), although bulky substituents on this position (*e.g. t*-Bu)completely inhibited the reaction (entry 3). The method resulted efficient with a range of structurally diverse β-aryl substituted enals, including *otho*-, *meta*-, and *para*-substituted aromatic rings in the enal (entries 5, 7 and 11). Satisfactory results were also achieved in spite of the electronic nature of the aryl group. This was the case for electron-donating aromatic rings (entries 4-11), which exhibited excellent reaction outcome in a similar way to enals substituted with electron-withdrawing aromatic substituents (entries 12-15). Additionally, α,β-unsaturated aldehydes with heteroaromatic rings also performed satisfactorily (entries 9-10). It should be mentioned that β-akyl substituted enals did not provide product formation as aldehyde decomposition occurred relatively fast under the described reaction conditions, while nitrones were recovered (entries16-17). In general, the reaction accepts structural modification on the β-aryl substituents of the enals furnishing *N*-hydroxypyrrolidine adducts with excellent yield, good diastereoselectivity and great enantioselectivity.

Subsequently, modifications on the azomethine carbon-atom of the nitrone were evaluated together with variation of the alkyl substituent on glycinate moiety (Table 3.6).

Table 3.6 Scope of the reaction using different nitrones.[a]

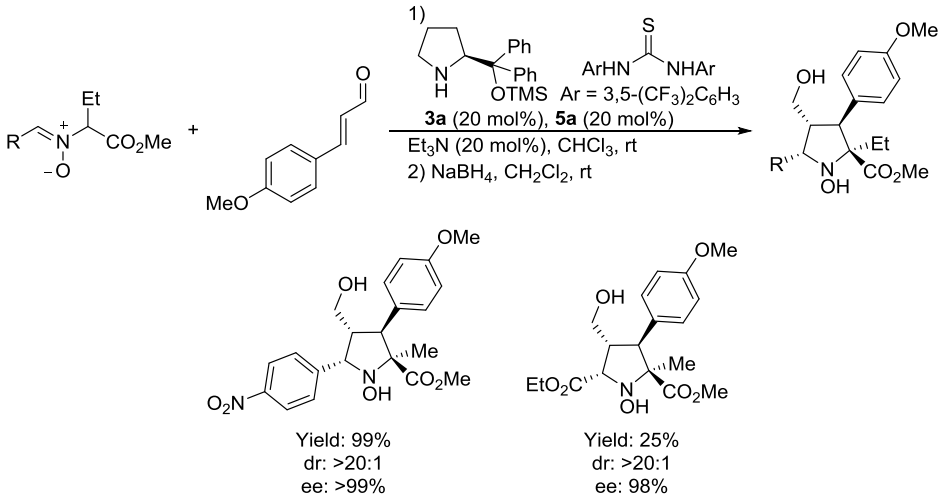


Entry	R^1	R^3	Yield[b]	dr[c]	ee (%)[d]
1	3,5-$(CF_3)_2C_6H_3$	Ph	80	9:1	98
2	4-CNC_6H_4	Ph	82	9:1	96
3	4-CNC_6H_4	4-$MeOC_6H_4$	84	9:1	96
4	4-CNC_6H_4	2-thienyl	82	10:1	99
5[e]	Ph	4-$MeOC_6H_4$	45	1:1	92
6[e]	4-BrC_6H_4	4-$MeOC_6H_4$	46	1:1	90
7	4-$MeOC_6H_4$	4-$MeOC_6H_4$	<5	n.d.[f]	n.d.[f]

[a] Reactions performed in 0.2 mmol scale of **1c-h**, 0.24 mmol of **2a**, **2c**, **2l**, using 20 mol% of **3a**, 20 mol% of **5a** and 20 mol% of Et_3N in 0.4 mL of $CHCl_3$ at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis. [e] 1 Eq. of thiourea **5a** and Et_3N were employed. [f] n.d.: Not determined

As shown on table Table 3.6, a number of diversely substituted aromatic rings on the azomethine carbon-atom of the nitrone were evaluated. In the cases when strong electron-withdrawing groups like nitro, trifluoromethyl (entry 1) or cyano (entries 2-4) were present the reaction proceeded efficiently, whereas phenyl (entry 5) or halogenated aromatics (entry 6) needed of stoichiometric amounts of thiourea **5a** and base in order to get increased reaction rates and achieve isolable amounts of product in manageable reaction times, due to the decreased reactivity of substrates not bearing strong electron-withdrawing groups on the azomethine moiety. Indeed, aromatic substituents bearing electron-donating groups did not afford the product after prolonged reaction times (entry7). Therefore, these results indicated that aromatics with strong electron-withdrawing groups performed considerably better in terms of yield.

Surprisingly, a bulkier group at the α-position of the ester moiety (*i.e.* an ethyl group) showed excellent performance under the same reaction conditions, evidencing the possibility to introduce other substituents in this position of the nitrone (Scheme 3.3). Additionally, to exemplify the possibility to use other groups on the imine site, glyoxylate-derived nitrone was also employed as a *Z/E* mixture from which only one showed reactivity, thus resulting in a lower conversion.



Scheme 3.3

The absolute configuration of the major diastereomer was assigned by X-ray diffraction on monocrystals of adduct **4j** (2*S*,3*S*,4*R*,5*S*) (Figure 3.1). The absolute configuration of the other adducts was established assuming an identical mechanistic pathway for all reactions. The resultant configuration is in accordance with bibliographic examples proceeding through steric facial differentiation promoted by **3a** catalyst *via* iminium activation.[29]

[29] (a) Donslund, B. S.; Johansen, T. K; Poulsen, P. H.; Halskov, K. A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (b) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248 (d) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

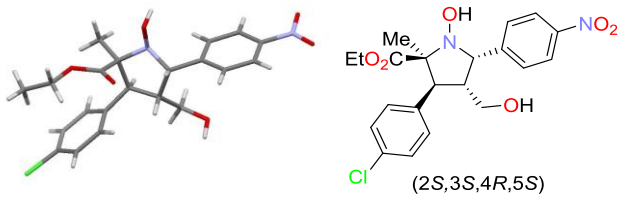
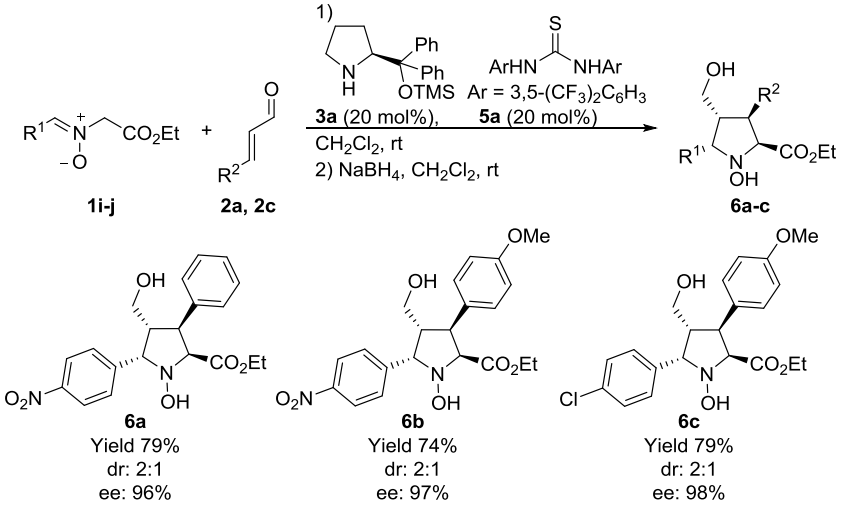


Figure 3.1

The use of glycinate-based nitrones presented an additional opportunity, since the absence of substitution on the α-position of the ester should facilitate the nitrone ylide formation. The reactivity of these nitrones was explored with a number of substrates (Scheme 3.4). In this case, after a short evaluation of reaction conditions, it was noted that performing the reaction in dichloromethane and in absence of any basic additive gave slightly better yields. The reaction progressed satisfactorily rendering cycloadducts **6a-c** in good yields, as a mixture of diastereomers and with excellent enantiocontrol.

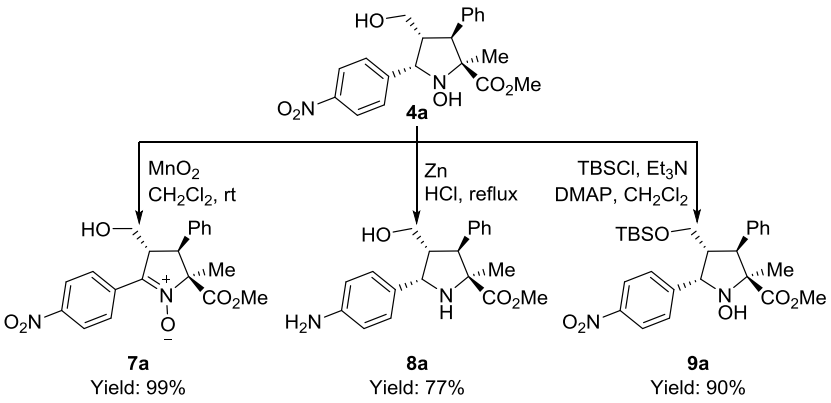


Scheme 3.4

3.4 Transformation of the cycloadducts

Having established a methodology that comprehends the use of a wide variety of precursors that enable the synthesis of a library of *N*-hydroxypyrrolidines and taking advantage of the diverse functional groups present in the prepared adducts, a number of selective transformations were carried out in order to access related interesting structures and to further attest the applicability of the method.[30]

Compound **4a** was chosen as a representative example, on which the following transformations were implemented. First, oxidation of the *N*-hydroxyl functionality in the presence of manganese dioxide was performed, rendering the densely substituted cyclic nitrone **7a** in excellent yield. The *N*-hydroxypyrrolidine adduct **4a** could also be reduced to the corresponding pyrrolidine **8a** using zinc dust in water/HCl upon heating. Both the *N*-hydroxyl group and the nitro group present on the aromatic ring were reduced in this reaction not observing evidences of epimerization. The selective protection of the primary alcohol over the hydroxylamine group was also successfully accomplished yielding product **9a** (Scheme 3.5).

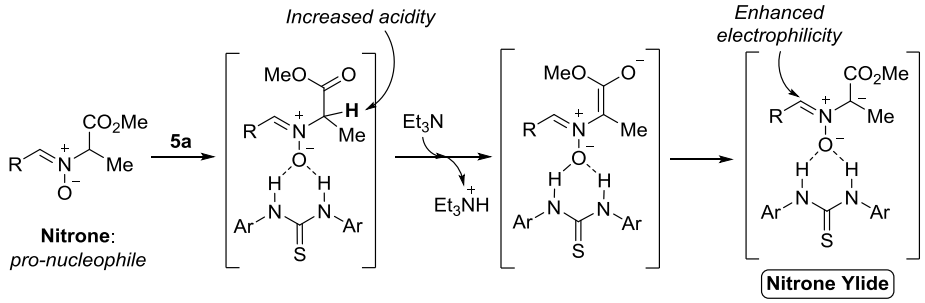


Scheme 3.5

[30] Schreiber, S. L. *Science* **2000**, *287*, 1964.

3.5 Mechanistic insights

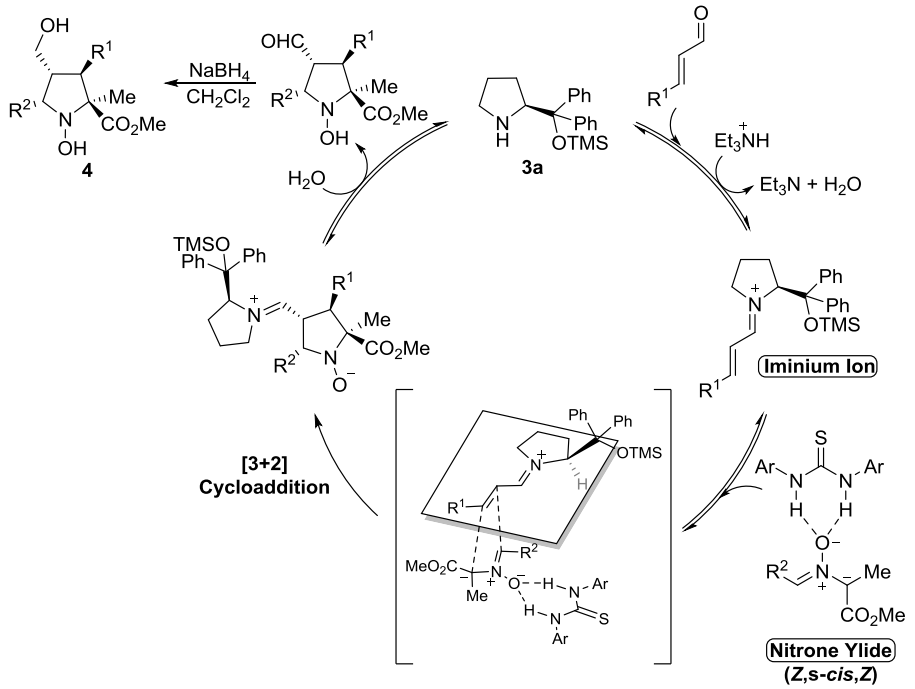
Based on the results obtained and using the current understanding reactions under iminium ion activation provided by the literature background, the following mechanistic proposal was suggested: Experimental evidences point to the need of an activation step of the nitrone, an event that very likely occurs prior to the [3+2] cycloaddition reaction, as the nitrone itself is not capable to undergo cycloaddition in absence of certain additives. Therefore it is suggested, that nitrone, with a α-proton acidic enough to be deprotonated, undergoes deprotonation on the α-position to the ester in the presence of a base, such as triethylamine, generating the nitrone ylide intermediate. Thiourea **5a** might participate in this process interacting with either the *N*-oxide or the alcoxycarbonyl group of the nitrone, increasing the acidity of the α-proton and counteracting a negative charge on the otherwise very unstable double negatively charged zwitterionic intermediate. This hypothesis is supported by the observation of low conversion when only base is used, implying that triethylamine alone is not sufficient to activate the pro-nucleophile, and secondary interactions are required in order to achieve an efficient formation of nitrone ylide. On the contrary, thiourea **5a** is able to promote the reaction with moderate yield in absence of base, suggesting that thiourea **5a** is sufficient to trigger the nitrone ylide formation. An additional role of thiourea **5a** could also be to coordinate the negatively charged oxygen of the nitrone ylide enhancing the electrophilic character of the imine moiety, thus reinforcing the reactivity of the 1,3-dipole (Scheme 3.6).



Scheme 3.6

In spite of all the possible conformers of the nitrone ylide, the observation of the unique formation of final adducts with stereochemistry derived from the (*Z*,s-*cis*,*Z*) nitrone ylide in the reaction suggest that other conformers of the nitrone ylide are not productive under the selected reaction conditions, thus only the (*Z*,s-*cis*,*Z*) nitrone ylide has been considered to take part in the following catalytic cycle. This observation is consistent with the thermodynamic stability of structures containing multiple same sign charges that usually adopt conformations where the charges of the same sign are distant due to electrostatic repulsion.

Considering the discussed nitrone ylide formation mechanism and the background on iminium ion activation, the following catalytic cycle is proposed (Scheme 3.7). The catalytic cycle starts with the condensation of the chiral secondary amine **3a** with an α,β-unsaturated aldehyde, generating an activated dipolarophile, whose LUMO-energy has been lowered through the formation of the iminium ion species. As mentioned before, the nitrone ylide also is generated *in situ* by the combined effects of thiourea **5a** and triethylamine on the nitrone, that leads to the formation of the activated 1,3-dipole. Both active species undergo an *endo*-selective [3+2] cycloaddition. Finally, protonation of the *N*-hydroxyl group takes place followed by hydrolysis rendering the observed *N*-hydroxypyrrolidine product (Scheme 3.7).

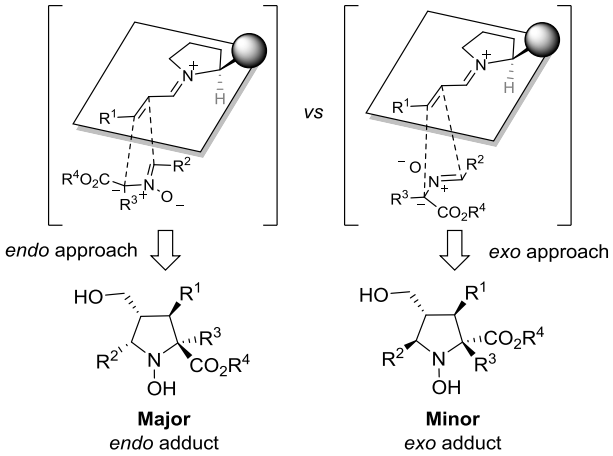


Scheme 3.7

Considering the stereochemical outcome of the reaction, the enantioselectivity of the process is governed by the efficient steric shielding of one diastereotopic face of the iminium ion carried out by the bulky substituent on C-2 of catalyst **3a**, achieving excellent *ee* values (see Scheme 3.7).

However, in some cases, the reaction shows lack of diastereoselectivity. This phenomenon can be explained comparing the different possibilities for the approach of the nitrone ylide to the iminium ion that lead to the two observed diastereomers (Scheme 3.8). The *endo* approach, which results on the formation of the major diastereomer, leaves the R^3 substituent of the nitrone facing the β-proton of the iminium ion, minimizing the steric repulsion compared to the *exo* approach where R^3 substituent of the nitrone encounters the β-aryl substituent of the iminium ion, represented as R^1. This theory is supported by the

experimental observation of an increase in diastereoselectivity when bulkier substituents on α-position to the ester (*i.e.* R^3) are used.[31]



R^3	***endo:exo***[a]
H	2:1
Me	4:1 to 10:1
Et	>20:1

Scheme 3.8[32]

[31] See diastereomeric ratios in Section 3.3 Scope of the reaction.
[32] Thiourea **5a** has been omited for simplicity.

4. CONCLUSION

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

- Nitrones with acidic protons on α-carbon atom can display a less conventional 1,3-C,O reactivity in opposition to the well documented 1,3-C,C reactivity, provided that a careful design of the nitrone and adequate additives are used.

- A complex catalytic system that enables the efficient *in situ* formation of nitrone ylides has been described, which comprises the combined use of substoichiometric amounts of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea **5a** and triethylamine.

- The *in situ* generated nitrone ylides take part in the organocatalyzed asymmetric [3+2] cycloaddition of nitrones with α,β-unsaturated aldehydes under iminium ion activation promoted by the diphenylprolinol-derivative **3a** as the most suitable catalyst

- The described method provides excellent results with high yields and enantioselectivities, with a wide substrate scope, including diverse β-aryl substituted enals, various nitrones observing better performance on those substituted with strong electron-withdrawing aromatic rings on the azomethine carbon, and tolerating substitution on the α-position to the alcoxycarbonyl group, observing increase on the diastereoselectivity of the process as the volume of the substituent augments.

- Taking advantage of the multiple functional groups on the synthesized *N*-hydroxypyrrolidine adducts, successful transformations have been carried out to illustrate the diversity in reactivity that the aforementioned adducts provide.

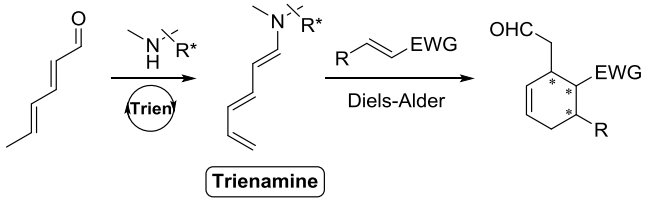
Chapter 3

3

Favoring Trienamine Activation through Unconjugated Dienals

1. TRIENAMINE CATALYSIS IN CYCLOADDITION REACTIONS

Trienamine catalysis has demonstrated to be a powerful synthetic tool to achieve enantioselective transformations in remote positions of α,β,γ,δ-diunsaturated carbonyl compounds. The foundation of this mode of activation lies on the idea of propagating the HOMO-raising effect over the conjugated system of a polyunsaturated aldehyde or ketone. Trienamine intermediates can act as electron-rich dienes in Diels-Alder[1] type reactions befitting to react with a number of electron-deficient alkenes as dienophiles with unique β,ε-selectivity, leading to two new bonds formation with high stereoselectivity, due to the capacity of the chiral catalyst to convey the chiral information to the reactive carbon atoms (Scheme 1.1).



Scheme 1.1

The pioneering work on this field was jointly reported by Jørgensen and Chen in the first example of a trienamine aminocatalytic Diels-Alder reaction between 2,4-hexadienal and 3-alkenyl oxindoles, employing a chiral proline derivative as catalyst and a Brønsted acid as co-catalyst. The reaction provided oxindol-derived spirocyclic products (Scheme 1.2).[2] Regarding the scope of the reaction, a wide variety of dienophiles performed

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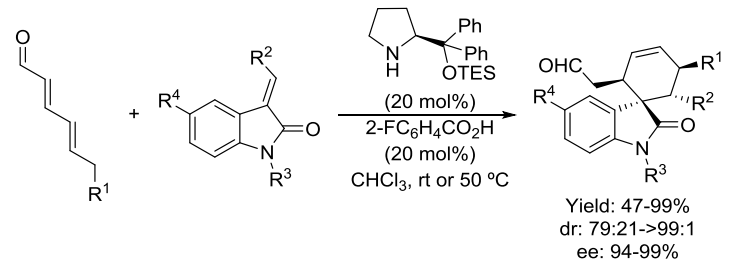
[1] For reviews on enantioselective Diels−Alder reactions, see: (a) Corey, E. J. *Angew. Chem. Int. Ed*. **2002**, *41*, 1650. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed*. **2002**, *41*, 1668. (c) Corey, E. J. *Angew. Chem., Int. Ed*. **2009**, *48*, 2100. (d) Juhl, M.; Tanner, D. *Chem. Soc. Rev*. **2009**, *38*, 2983. (e) Lelais, G.; MacMillan, D. W. C. *Aldrich Chim. Acta* **2006**, *39*, 79. (f) Merino, P.; Marques-Lopez, E.; Tejero, T.; Herrera, R. P. *Synthesis*, **2010**, *1*, 1. (g) Heravi, M. M.; Vavsari, V. F. *RSC Adv*. **2015**, *5*, 50890. (h) Reddy, K. M.; Bhimireddy, E.; Thirupathi, B.; Breitler, S.; Yu, S.; Corey, E. J. *J. Am. Chem. Soc*. **2016**, *138*, 2443.

[2] 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.

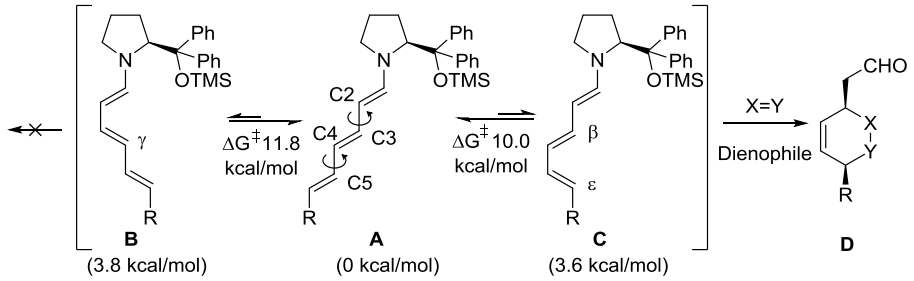
excellently in terms of yield, diastereo- and enantioselectivity, and the same applied to the use of 2,4-diunsaturated aldehydes with different substitution pattern.



Scheme 1.2

NMR and computational studies were carried out in order to give an explanation to the exceptional regioselectivity of the reaction. These studies revealed insightful data about the equilibrium between conformers of the trienamine intermediate (Scheme 1.3). As expected, the most stable conformer for trienamine intermediate is the all-*trans* isomer (see Scheme 1.3 **A**), in agreement with ^{1}H-NMR data analysis as it was the only observed diastereomer. This trienamine conformer can lead to the formation of the conformers **B** or **C** after single carbon-carbon bond rotation. Rotation of the C2-C3 bond renders the formation of the conformer **B**, which is sterically disfavored due to interactions between the chiral moiety of the catalyst and the unsaturated chain. On the other hand, rotation around C4-C5 bond, overcoming a lower activation barrier, gives the conformer **C** which is, additionally more reactive since its calculated HOMO is 2.17 eV higher in energy than the HOMO of **B**, making it a more active diene. In summary, the more energetically favored C4-C5 bond rotation and the increased reactivity of the HOMO in **C** justifies the prevailing β,ε-selectivity for trienamine reactivity.[2,3] The diastereo- and enantioselectivity of trienamine catalyzed reaction is governed by the preferential *endo*-approach of the dienophile through the chiral aminocatalyst discriminated less hindered side of the s-*cis* trienamine.

[3] Su, Z.; Kim, C. K. *Org. Biomol. Chem.* **2015**, *13*, 6313.



Scheme 1.3

Further advances on trienamine catalysis reported after the seminal work have been directed to the use of a wider number of electron-deficient olefins that could participate as dienophiles in Diels-Alder processes. In this sense, the robustness of the reaction has been tested with dienophiles such as: rhodanine derivatives,[4] benzofulvenes,[5] azlactones,[6] maleimides,[7] nitroalkenes,[8] olefinic cyanoacetates,[2] among others[9] (Scheme 1.4). All these examples include the use of different di- or trisubstituted olefins as dienophiles, which rendered densely substituted cyclohexenes. Alternatively, exocyclic electron-deficient alkenes (*e.g.* benzofulvenes and azlactones), can produce spirocyclic compounds in a stereoselective way; proving the usefulness of trienamine catalysis as a very powerful synthetic tool to achieve high molecular complexity from relatively simple starting materials, with excellent outcome in terms of yield, diastereo- and enantioselectivity, in a

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4 Zhu, K.; Huang, H.; Wu, W.; Wei, Y.; Ye, J. *Chem. Commun.* **2013**, *49*, 2157.

5 Donslund, B. S.; Nielsen, R. P.; Mønsted, S. M. N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 11124.

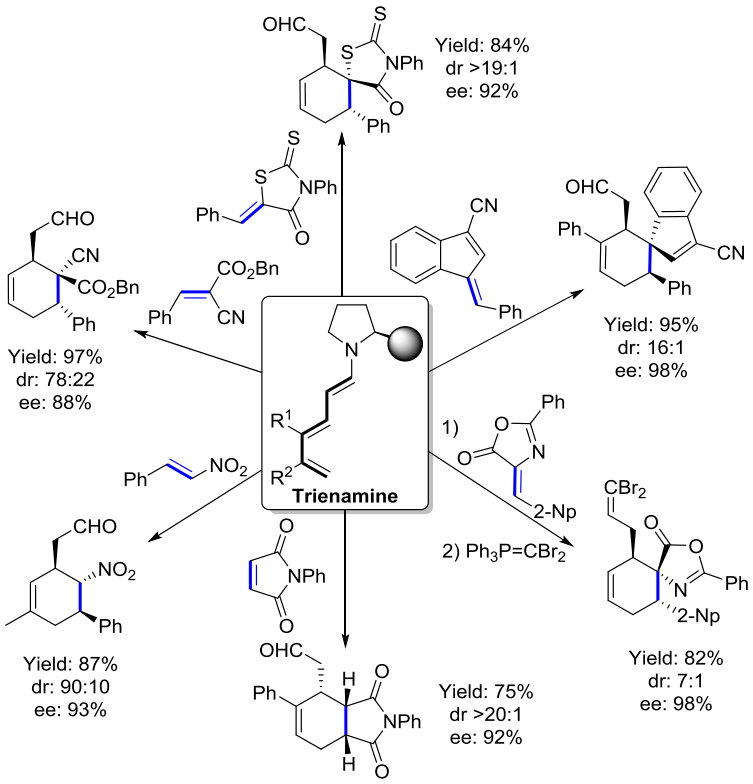
6 Jiang, H.; Gschwend, B.; Albercht, Ł.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032.

7 Sellstedt, M.; Schwalfenberg, M.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. *Org. Biomol.Chem.* **2016**, *14*, 50.

8 (a) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638. For other reaction of trienamines with nitroalkenes, see: (b) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (c) Xiao, Y.-C.; Yue, C.-Z.; Chen, P.-Q.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 3208.

9 For other dienophiles in trienamine catalysed Diels-Alder reactions, see: (a) 4-nitro-5-styrylisoxazoles: Li, Y.; López-Delgado, F. J.; Jørgensen, D. K. B.; Nielsen, R. P.; Jiang, H.; Jørgensen, K. A. *Chem. Commun.* **2014**, *50*, 15689. (b) Methiodide salts: Zhang, S.-J.; Zhang, J.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2013**, *15*, 968. (c) 3-Olefinic benzofuranones: Li, X.; Lin, M.-H.; Han, Y.; Wang, F.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 114. (d) Azadienes: Ma, C.; Gu, J.; Teng, B.; Zhou, Q.-Q.; Li, R.; Chen, Y.-C. *Org. Lett.* **2013**, *15*, 6206. (e) Olefinic butenolides: Hejmanowska, J.; Dziegielewski, M.; Kowalczyk, D.; Albrecht, Ł. *Synlett.* **2014**, *25*, 2957. (f) 3-(fosforylmethylene)-oxindoles: Zhou, Q.-Q.; Yuan, X.; Xiao, Y.-C.; Dong, L.; Chen, Y.-C. *Tetrahedron*, **2013**, *69*, 10369.

single synthetic step. Other examples in the literature include the use of hetero-dienophiles in trienamine catalysed transformations, such as thio-Diels-Alder[10] and aza-Diels-Alder[11] reactions.

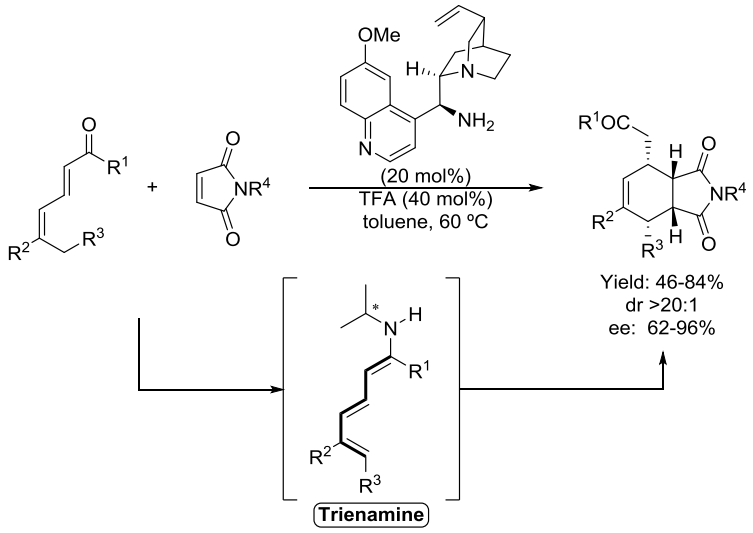


Scheme 1.4

Trienamine catalysis is not limited to the use of polyunsaturated aldehydes. α,β,γ,δ-Diunsaturated ketones are also adequate substrates to undergo trienamine formation, typically requiring the use of a chiral primary amine (*e.g.* 9-amino-9-deoxyepiquinine) and an acid additive in order to facilitate the more difficult activation by condensation of ketone

[10] Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H., Jørgensen, K. A. *J. Am. Chem. Soc*. **2013**, *135*, 5200.
[11] Liu, J.-X.; Zhou, Q.-Q.; Deng, J.-G.; Chen, Y.-C.*Org. Biomol. Chem.* **2013**, *11*, 8175.

substrates and promote the reactive intermediate formation. However, a specific design of the dienone was also found to be necessary to achieve satisfactory levels of regio- and stereoselectivity. On one hand, the use of α-enolizable ketones that may divert the reaction pathway to the cross-trienamine formation had to be avoided (R^1 = Ph).[12] On the other hand, introducing an additional substituent on the δ-position (R^3 = Me) to prevent side-reactivity and increase the HOMO energy of the trienamine intermediate (Scheme 1.5).[13]

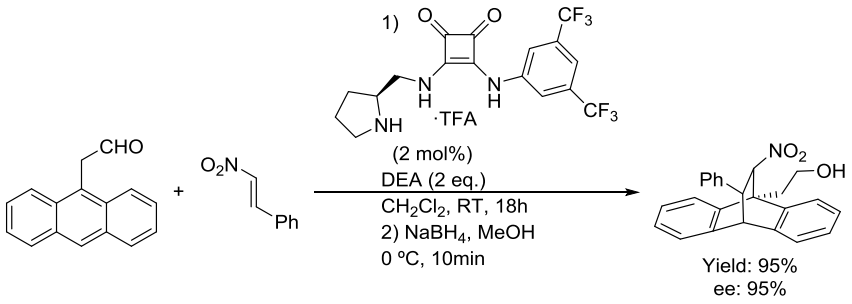


Scheme 1.5

When effective stereocontrol cannot be achieved by steric bias because the structure of the dienal or dienone substrate does not imply enough conformational rigidity to generate a single conformer, dual activation using bifunctional catalysts appears as a methodological alternative. This is the case for the trienamine activation of 2-(anthracen-9-yl)-acetaldehyde shown on Scheme 1.6, where a bifunctional pyrrolidine-squaramide catalyst, directs the approach of nitrostyrene as dienophile through H-bonding

[12] Cross-trienamine is discussed in following paragraphs.
[13] Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2012**, *51*, 4401.

interactions.[14] Furthermore, the same bifunctional catalyst was employed to perform dual trienamine/H-bonding activation with 3-cyanochromones,[15] 1,4-naphtoquinones[16] and 3-coumarincarboxylates.[17] Additionally, urea[18] and thiourea[19] based bifunctional catalysts also achieved dual activation of diunsaturated aldehydes and nitroolefins.



Scheme 1.6

In some particular cases, a change in regioselectivity was accomplished in reactions under trienamine activation involving cross-conjugated trienamines as reactive intermediates.[20] Cross-conjugated trienamines were traditionally considered as non-productive intermediates coexisting in equilibrium with the reactive linear trienamine that, as later demonstrated, presented selectivity for δ,γ'-carbon functionalization. However, an specific substitution pattern on the diunsaturated aldehyde is necessary to preferentially display the cross-conjugated trienamine reactivity, which gave access to the selective [4+2] reaction on the γ'- and δ-positions (Scheme 1.7). Mechanistic studies were carried out to explain this behavior, concluding that, although cross-trienamine formation was

14 Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 10271.

15 Albrecht, Ł.; Acosta, F. C.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 9088.

16 Albrecht, Ł.; Gómez, C. V.; Jacobsen, C. B.; Jørgensen, K. A. *Org. Lett.* **2013**, *15*, 3010.

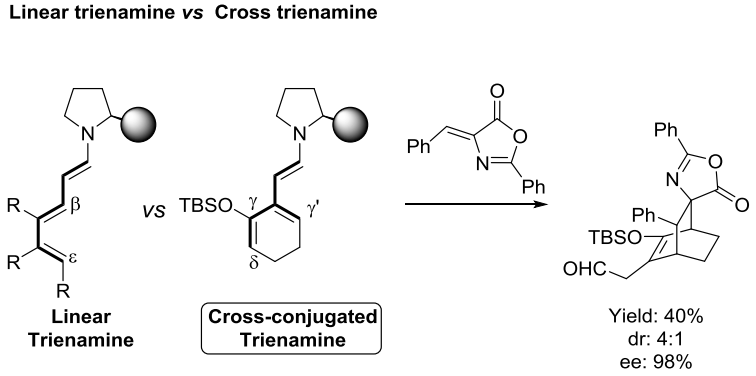
17 Albrecht, A.; Skrynska, A.; Pietrzak, A.; Bojanowski, J.; Albrecht, Ł. *Asian J. Org. Chem.*, **2016**, *5*, 1115.

18 Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 1020.

19 Monleón, A.; Glaus, F.; Vergura, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 2478.

20 (a) Halskov, K. S.; Hohansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943. For more examples of cross-trienamine reactivity, see: (b) Zhou, Z.; Wang, Z.-X.; Ouyang, Q.; Du, W.; Chen, Y.-C. *Chem. Eur. J.* 10.1002/chem.201605606.

energetically disfavored compared to the linear trienamine formation, the reaction yielded the most stable γ'-δ adducts under thermodynamic conditions.[21]



Scheme 1.7

In order to expand the molecular diversity of potential carbon and heteroatom scaffolds that can be accessed applying trienamine activation, several cascade or tandem processes comprising an initial [4+2] cycloaddition have also been developed. As depicted on Scheme 1.8, with a thorough design of the dienophile incorporating additional reactive sites within its structure, the formyl group could be intramolecularly trapped to render hemiaminal or hemiacetal-containing polycyclic compounds of growing structural complexity in a single synthetic step. Such is the case of the reaction between quinine imines and catalytically generated trienamines that, after the [4+2] reaction, underwent aromatization to generate an aniline intermediate, which followed in the *N*-nucleophilic ring-closing with the formyl group.[22] Other cascade processes initiated with the formal [4+2] cycloaddition and sequential nucleophilic ring-closing with either *N*-nucheophiles,[23]

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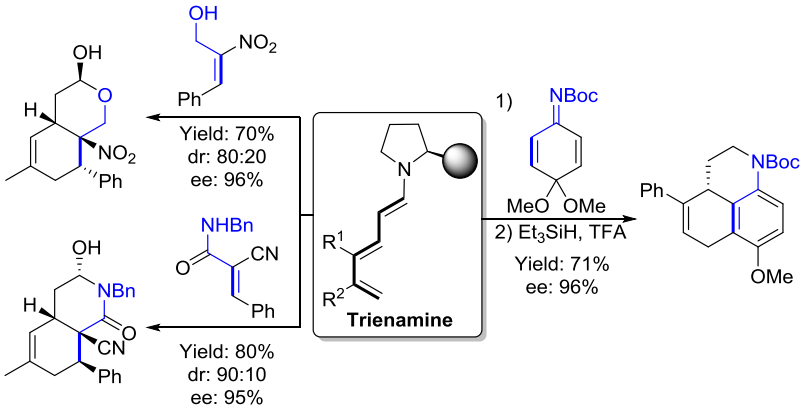
21 For a deep mechanistic study on cross-conjugated trienamine, see: Dieckmann, A.; Breugst, M.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 3237. Unique γ'-functionalization is also documented in this work.

22 Gu, J.; Xiao, B.-X.; Chen, Y.-R.; Du, W.; Chen, Y.-C. *Adv. Synth. Catal*. **2016**, *358*, 296.

23 Gómez, C. V.; Cruz, D. C.; Mose, R.; Jørgensen, K. A.; *Chem. Commun*. **2014**, *50*, 6035.

or alcohols[24] have been additionally developed. Additionally, other sequential catalytic and stoichiometric transformations were designed with a similar purpose.[25]



Scheme 1.8

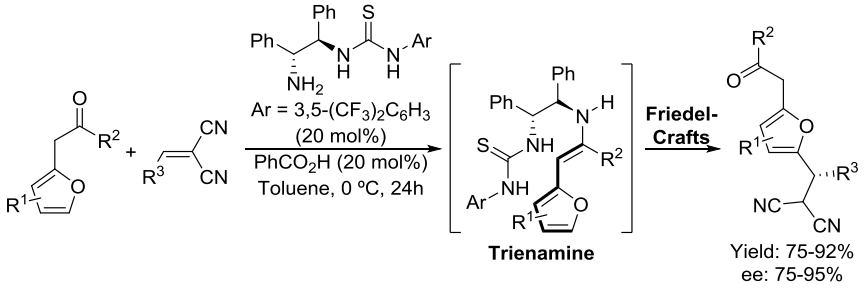
Although the main reactivity feature provided by trienamine intermediates is the [4+2] cycloaddition, other aminocatalytic reactions going through trienamine intermediate, have been reported. Such is the case of the Friedel-Crafts[26] reaction of 2-furfuryl ketones and alkylidenemalononitriles in which a chiral primary amine, upon condensation with the ketone, induces a HOMO-raising effect on the aromatic π-system, thus enabling C(sp^2)-C(sp^3) bond formation (Scheme 1.9). In this reaction, a single regioisomer was isolated in spite of the multiple nuclephilic positions of the trienamine, and high enantioselectivities

[24] Cruz, D. C.; Mose, R.; Gómez, C. V.; Torbensen, S. V.; Larsen, M. S.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 1131.

[25] (a) Ma, C.; Jia, Z.-J.; Liu, J.-X.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2013**, *52*, 948. (b) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310. (c) Yuan, X.; Zhang, S.-J.; Du, W.; Chen, Y.-C. *Chem. Eur. J.* **2016**, *22*, 11048. (d) Chintalapudi, V.; Galvin, E. A.; Greenaway, R. L.; Anderson, E. A. *Chem. Commun.* **2016**, *52*, 693. (e) Portalier. F.; Bourdreux, F.; Marrot, J.; Moreau, X.; Coeffard, V.; Greck, C. *Org. Lett.* **2013**, *15*, 564. (f) Pantaine, L.; Coeffard, V.; Moreau, X.; Greck, C. *Eur. J. Org. Chem.* **2015**, 2005.

[26] (a) Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *Compt. Rend.*, **1877**, *84*, 1450.

were observed, regardless of the remote position of the reacting ε-carbon from the catalysts binding point.[27]



Scheme 1.9

As outlined on the examples reviewed up to this point, trienamine catalysis is an expanding field that offers an increasing number of opportunities, especially in enantioselective [4+2] cycloaddition reactions, providing a single-step approach to the nantioselective synthesis of high complexity structures, although the synthetic possibilities and mechanistic understanding of these reactions in asymmetric catalysis are far from being completely explored.

In particular, the application of enamine activation to vinylogous systems entails several reactivity issues related to the covalent nature of the interaction between the catalyst and the substrate. Implementation of dienamine or trienamine-mediated reactions requires of the use of carbonyl compounds presenting higher level conjugation of the carbonyl group used as starting material. In this sense, the reagents to be activated by the catalyst through condensation move from simple enolizable aldehydes (enamine catalysis) to α,β-unsaturated aldehydes (dienamine catalysis) and α,β,γ,δ-diunsaturated aldehydes (trienamine catalysis). This implies that higher activation barriers need to be overcome in the condensation step with the aminocatalyst, which leads to a progressive depletion in reactivity and reduced TON/TOF numbers.

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[27] (a) Li, J.-L.; Yue, C.-Z.; Chen, P.-Q.; Xiao, Y.-C.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5449. For other examples of Friedel-Crafts alkylation by trienamine catalysis, see: (b) Skrzynska, A.; Przydacz, A.; Albrecht, Ł. *Org. Lett.* **2015**, *17*, 5682. (c) Yang, G.-J.; Du, W.; Chen, Y.-C. *J. Org. Chem.* **2016**, *81*, 10056.

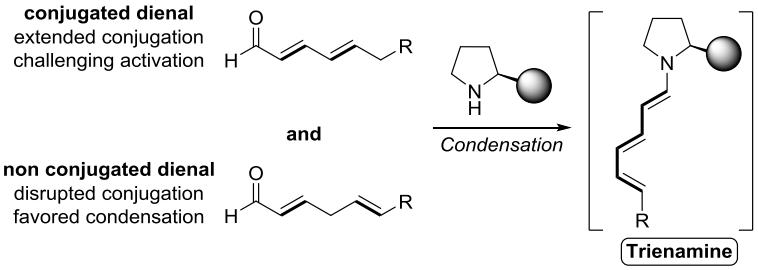
2. SPECIFIC OBJECTIVES AND WORK PLAN

From the literature examples presented before, it can be concluded that enantioselective Diels-Alder reactions using dienals under trienamine catalysis is a very powerful strategy for the synthesis of high optical purity complex molecules from easily accessible starting materials, which has been demonstrated in several successful examples. Nevertheless, little interest has been drawn to the investigation of alternative trienamine precursors different from the evident α,β,γ,δ-diunsaturated aldehydes and ketones.

In this context, it is worth to remark the already mentioned challenge that lies behind the activation of substrates with multiple conjugated carbon-carbon double bonds, such as α,β,γ,δ-diunsaturated carbonyl compounds. Considering the inherent reactivity of these substrates towards condensation with aminocatalyst, is handicapped in comparison with the related unconjugated aldehydes or ketones due to the additional energy barrier that has to be overcome associated with the extended conjugation. This issue was noticeable, as outlined along the previously presented examples, observing that reactions often required of increased reaction temperatures that resulted in narrower substrate scope or diminished stereocontrol.

Since the decreased rate for the condensation step of the aminocatalyst with (poly)unsaturated aldehydes is presumably due to the stability of the conjugated system, disruption of the conjugation would increase the electrophilic character of the carbonyl group, thus favoring the condensation step. Hence, it is hypothesized that the energy barrier required to activate polyunsaturated carbonyl compounds with aminocatalysts could be minimized **using non-conjugated diunsaturated aldehydes as more reactive starting materials in a chiral secondary amine promoted Diels-Alder reaction under trienamine catalysis**. The design of the polyunsaturated aldehyde to show an increased tendency to condense requires disruption in the conjugated system, by means of the introduction of a methylene spacer between carbon-carbon double bonds of the dienal. The aminocatalytic reaction on the non-conjugated substrate should be facilitated because the

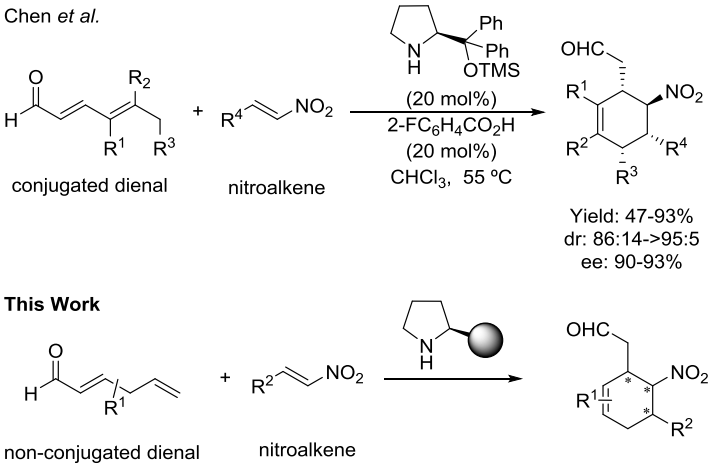
condensation step is expected to be favored for the non-conjugated substrate compared to the fully conjugated substrate. In fact, the activation energy for the condensation step of non-conjugated aldehydes, such as the presented in Scheme 2.1, with aminocatalysts should be similar to that of the formation of a α,β-unsaturated iminium ion. On the other hand, the aminocatalyst, once condensed with the carbonyl compound would trigger the conjugation of all the double bonds of the system, speeding up the trienamine intermediate formation. Employing either conjugated or non-conjugated dienals, the trienamine intermediate accessed would be indistinctive in terms of *E*/*Z* geometry control and chiral induction by the organocatalyst (Scheme 2.1).



Scheme 2.1

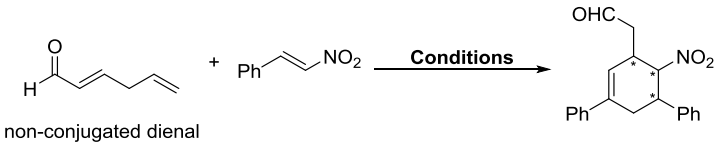
To achieve the aim of the project, the following work plan was established:

1. *Proof of concept:* In order to demonstrate the viability of the suggested strategy, suitable substrates needed to be synthesized, which involved the already mentioned non-conjugated diunsaturated aldehyde as well as its fully-conjugated analog to evaluate and compare the reactivity of each of the structural isomers in a test reaction. In particular, this model reaction would be the Diels-Alder reaction under trienamine activation with nitroalkenes as electron-deficient dienophiles, reported by Chen *et al*. (Scheme 2.2).[8a]



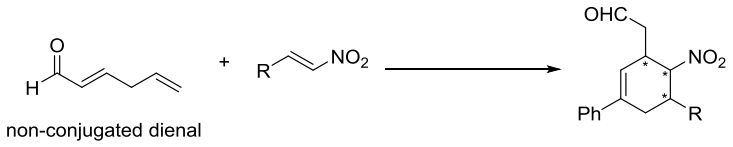
Scheme 2.2

2. *Optimization of the reaction conditions*: Using as model the reaction of Chen *et al.*, a variety of chiral secondary amines will be tested to identify the catalyst that provides best reaction outcome. This also implies the optimization of other reaction parameters, such as solvent, additives, temperature, in order to achieve optimal yield and stereocontrol for the reaction (Scheme 2.3).



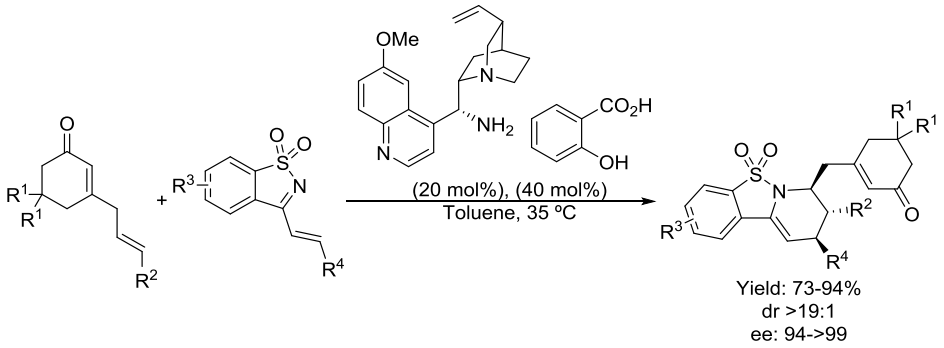
Scheme 2.3

3. *Scope of the reaction*: With the optimal conditions for the reaction in hand, the methodology will be extended to the use of different nitroalkenes, with the aim to build a library of polysubstituted cyclohexenes and to stablish the potential of the reaction toward application in synthesis (Scheme 2.4).



Scheme 2.4

It should be mentioned that, concomitant to the accomplishment of the present research work, Chen *et al.* reported the employment of cyclic 2,5-dienones that, in combination with chiral primary amines derived from cinchona, resulted in the activation of the terminal double bond for a formal [4+2] cycloaddition with aza-dienes (Scheme 2.5).[28] Later on, other contributions involving the use of 3,5-dienones have been also reported.[29]



Scheme 2.5

As a consequence of the application of the interrupted conjugation strategy, the potential substrate scope of reactions under trienamine activation could be increased, enabling the use of carbonyl compounds that have been proven inert due to their structural stability.

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[28] Feng, X.; Zhou, Z.; Ma, C.; Yin, X.; Li, R.; Dong, L.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2013**, *52*, 14173.

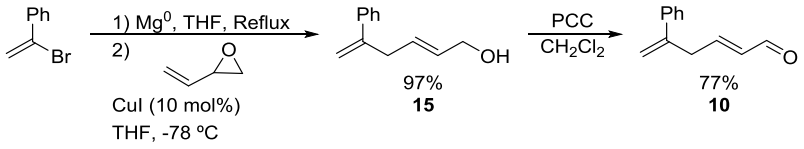
[29] For later works encompassing the employment of 2,5- and 3,5-dienones, see: (a) Zhou, Z.; Feng, X.; Yin, X.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 2370. (b) Chen, P.-Q.; Xiao, Y.-C.; Yue, C.-Z.; Chen, Y.-C. *Org. Chem. Front.* **2014**, *1*, 490. (c) Feng, X.; Zhou, Z.; Yin, X.; Li, R.; Chen, Y.-C. *Eur. J. Org. Chem.* **2014**, 5906.

3. RESULTS AND DISCUSSION

Once objectives for the project and a work plan have been discussed and established, the most relevant results obtained in this research are disclosed in the following paragraphs.

3.1 Proof of concept

First of all, due to the lack of bibliographic methods for the straightforward and scalable synthesis of dienlas with interrupted conjugation, a strategy was developed to access these substrates. Among different methods available in the literature, it was found that the Grignard reagent derived from α-bromostyrene reacted with racemic 2-vinyloxirane in a conjugate fashion under CuI catalysis, leading to the formation of (*E*)-5-phenylhexa-2,5-dien-1-ol (**15**).[30] The copper catalyzed reaction proceeded efficiently delivering selectively the conjugate addition product as *E* isomer, which was stable for months stored at -20 ºC. Finally, after the evaluation of various oxidation conditions on **15**, like using 2-iodoxybenzoic acid, Dess-Martin periodinane or Swern oxidation, among others, it was determined that commercially available pyridinium chlorocromate provided (*E*)-5-phenylhexa-2,5-dienal (**10**) in a satisfactory yield (Scheme 3.1). Aldehyde **10** had to be directly used after isolation to prevent decomposition.

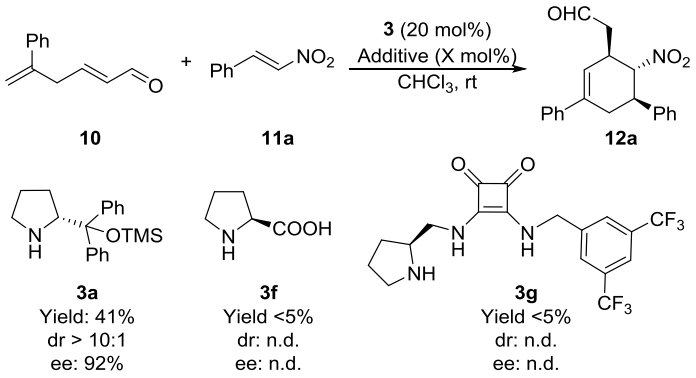


Scheme 3.1

With dienal **10** in hand, the evaluation of its ability to undergo fast activation in the presence of chiral secondary amine was tested in the Diels-Alder reaction with *trans*-β-

[30] Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Scheleif, W. A.; Huff, J. R.; Anderson, P. A. *J. Med. Chem.* **1993**,*36*, 2300.

nitrostyrene (**11a**). Different organocatalysts were tested at room temperature: proline derived catalysts (**3a** and **3f**) were evaluated in combination with 20 mol% of benzoic acid,[31] and the bifunctional catalyst (**3g**) together with one equivalent of *N*,*N*-diethylacetamide based on literature precedents.[32] In all cases a 20 mol% of catalyst was used and a 1:1 ratio of aldehyde (**10**) and trans-β-nitrostyrene (**11a**) (Scheme 3.2).



Scheme 3.2

Diphenylprolinol derivative **3a**, showed moderate activity promoting the Diels-Alder reaction achieving a 41% yield in 24 hours with an enantiomeric excess of 92%. The adduct **12a** needed to be derivatized the corresponding alcohol using $NaBH_4$ in methanol at 0 ºC to enable the chiral HPLC separation and the determination of the enantiomeric excess.[33] When the amino acid L-proline (**3f**) was tested, no product formation was observed, in a similar way to the bifunctional catalyst **3g**, which dinde provide perceptible amount of product. With these results, catalyst **3a** with benzoic acid as additive was selected for following optimization reactions.

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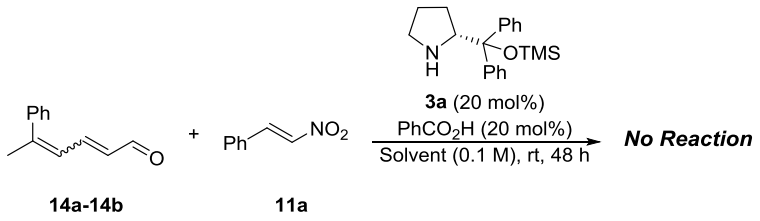
[31] The benzoic acid was the optimal additive for the trienamine catalysed reaction described on: Ref. 8a.

[32] Catalyst **3c** is often employed with one equivalent of *N*,*N*-diethylacetamide. For example, see: Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 10271.(Ref. 14).

[33] The *ee* was measured on compound **13a**, product of the reduccion of **12a** with $NaBH_4$. See Chapter 7.

To proof the initial hypothesis, the reaction was carried out using the conjugated analogs of aldehyde **10**, in both *Z* and *E* isomeric forms (**14a**, **14b**), under the same experimental conditions in which the product **12a** was obtained in 47% yield. After prolonged reaction times, only starting materials were recovered, not observing any evidence of product **12a** formation, confirming that conjugated isomers**14a** and **14b** resulted unreactive under the reaction conditions, thus demonstrating the increased reactivity of dienals with interrupted conjugation over conjugated dienals towards trienamine activation and Diels-Alder reaction (Scheme 3.3).

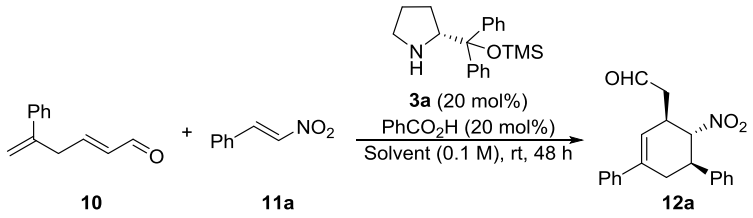


Scheme 3.3

3.2 Optimization of the reaction conditions

Once the ability of the dienal **10** with interrupted conjugation to undergo efficient Diels-Alder reaction under trienamine activation in the presence of catalyst **3a**, the optimization of other experimental variables was then devised assessing the influence of using excess of each of the reactants and the solvent on the reaction (Table 3.1).

Table 3.1: Evaluation of excess of reagents and solvent.[a]



Entry	10/11a ratio	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	1:1	$CHCl_3$	41	>10:1	92
2	1:1.3	$CHCl_3$	39	>10:1	92
3	1.3:1	$CHCl_3$	47	>10:1	92
4	1.3:1	CH_2Cl_2	20	>10:1	93
5	1.3:1	THF	8	>10:1	n.d.[e]
6	1.3:1	Toluene	66	>10:1	93
7	1.5:1	Toluene	54	10:1	66
8	1.7:1	Toluene	30	7:1	n.d.[e]

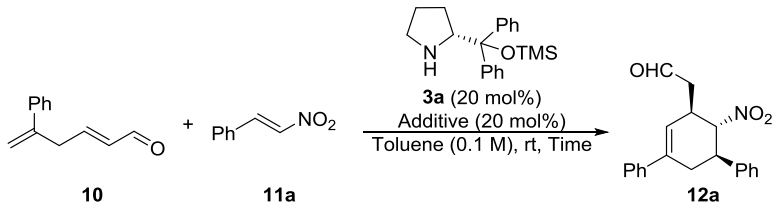
[a] Reactions performed in 0.2 mmol scale of limiting reagent in 2 mL of solvent. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis of the corresponding reduced adduct **13a**. [e] n.d.: Not determined.

As represented in Table 3.1, using aldehyde as limiting reagent in excess on nitrostyrene was not beneficial for the reaction in terms of yield (entry 2), whereas the employment of increased amounts of aldehyde **10** resulted in a slight increase in yield (entry 3), compared to results obtained using equimolar quantities of reagents (entry 1),

maintaining high level of diastereo- and enantioselectivity. Continuing with the evaluation of solvents, using nitrostyrene as limiting reagent, dichlormethane led to a substantial drop in yield (entry 4), in a similar way to more polar solvents, such as tetrahydrofuran, which almost completely suppressed the reaction (entry 5), in contrast to the non-polar solvent toluene, which afforded the product with higher yield and satisfactory stereoselectivity (entry 6). The diastereo- and enantioselectivity have no dependence on the solvent employed getting similar results with the all the solvents tested. Seeking an improvement on the yield, the effect of increasing loadings of aldehyde (**10**) was evaluated, observing that further increasing the aldehyde loading resulted in a detriment, not only to the yield, but also to the stereoselectivity of the reaction (entries 7-8). Therefore, the solvent choosen was toluene and the optimal reactants ratio was settled in 1.3 equivalents of aldehyde with respect to nitrostyrene.

The influence of the additives was then explored, substituting the benzoic acid for acids with different pKa and also surveying the possibility to use Brønsted bases as additive (Table 3.2).

Table 3.2: Acid and basic additive survey.[a]



Entry	Additive	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	$PhCO_2H$	48	66	>10:1	92
2	4-$MeOC_6H_4CO_2H$	48	41	>10:1	n.d.[e]
3	4-$FOC_6H_4CO_2H$	48	53	>10:1	n.d.[e]
4	4-$NO_2C_6H_4CO_2H$	48	27	>10:1	n.d.[e]

5	NaOAc	40	96	>10:1	90
6	NaCN	48	<5	-	-
7	DABCO	48	<5	-	-
8	DBU	48	<5	-	-
9	none	12	92	>10:1	94

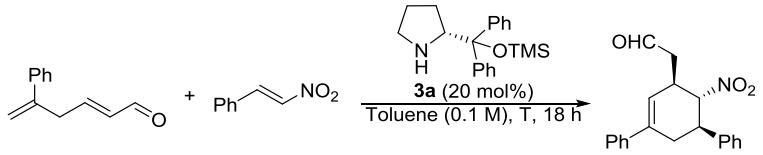
[a] Reactions performed in 0.2 mmol scale of **11a** and 0.26 mmol of **10** in 2 mL of toluene. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excess determined by HPLC analysis of the corresponding reduced adduct **13a**. [e] n.d.: Not determined.

The use of benzoic acid derivatives, for the fine tuning of the additives pKa, from the more acidic 4-nitrobenzoic acid to the less acidic 4-methoxynitrobenzoic acid, resulted in no improvement on the yield of the reaction (entries 1-4).[34] The incorporation of sodium acetate led to a remarkable increase in yield maintaining satisfactory levels of diastereo- and enantioselectivity (entry 5), while other bases like sodium cyanide, DABCO and DBU inhibited the reaction (entries 6-8). Surprisingly, the reaction in the absence of additive afforded the product with excellent yield and improved enantioselectivity (entry 9), reaching completion in a considerably reduced period of 12 hours. The shortened reaction time together with the operational simplicity and reduced cost performing the reaction in absence of additive was considered to be better.

Finally, the influence of the temperature on the reaction was evaluated. To check the sensitivity of the reaction with variation on the temperature, the following temperatures were evaluated: 4, 20 and 30ºC, in 18 hours reaction (Table 3.3).

[34] pKa values for $PhCO_2H$: 4.20; 4-$MeOC_6H_4CO_2H$: 4.47; 4-$FC_6H_4CO_2H$: 4.14; 4-$NO_2C_6H_4CO_2H$: 3.44.

Table 3.3: Evaluation of the effect of the temperature.[a]

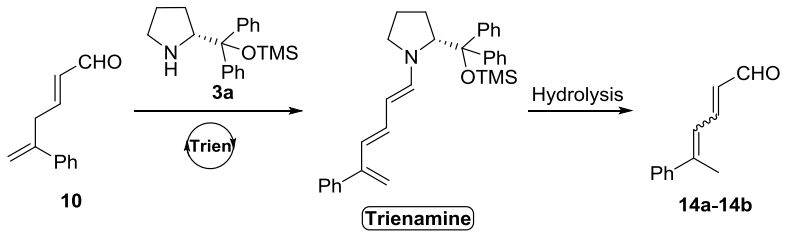


10 **11a** **12a**

Entry	Temp (ºC)	Yield (%)[b]	dr[c]	ee (%)[d]
1	4	67	>10:1	91
2	20	99	>10:1	94
3	30	61	>10:1	64

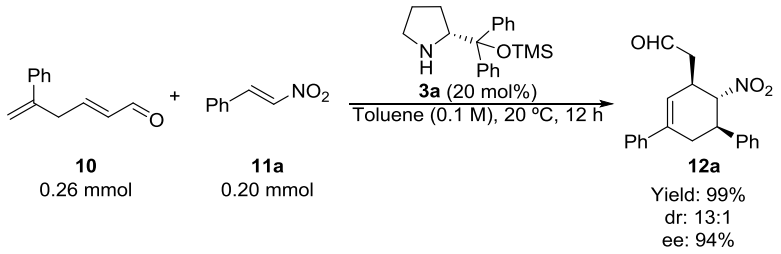
[a] Reactions performed in 0.2 mmol scale of **11a** and 0.26 mmol of **10** in 2 mL of toluene in a thermostatic bath.[b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture.[d] Enantiomeric excess determined by HPLC analysis of the corresponding reduced adduct **13a**.

It was observed that at 4 ºC the yield of the reaction decreased, resulting in a slower reaction rate due to the decrease in temperature, with no improvement in the enantioselectivity. For the reaction at 30 ºC, the enantioselectivity was considerably lower, which was interpreted to be associated with decomposition of the catalyst by cleavage of the trimethylsilyl group. The decrease in yield as a consequence of a raise in the reaction temperature was explained with the observation of the formation of several side products. For reaction temperatures over 20 ºC, ^{1}H-NMR analysis of crude reaction mixtures disclosed an increased formation of aldehydes (2*E*,4*E*)-5-phenylhexa-2,4-dienal (**14a**) and (2*E*,4*Z*)-5-phenylhexa-2,4-dienal (**14b**), conjugated isomers of (*E*)-5-Phenylhexa-2,5-dienal (**10**). **14a** and **14b** are presumably formed after the condensation of the catalyst **3a** with the aldehyde **10**, leading to the formation of trienamine/iminium ion intermediates in equilibrium, which allow the conjugation of the double bonds and formation of aldehydes **14a-b** after catalyst hydrolysis (Scheme 3.4). Since the formation of the non-productive isomers **14a-b** gained relevance at temperatures over 20 ºC, the best temperature for running the reaction was set to 20 ºC carefully controlled by thermostatic bath.



Scheme 3.4

Finally, given the presented results, the catalyst **3a** in toluene in the absence of additive with an excess of aldehyde at 20 ºC are the best conditions to carry out the reaction in terms of yield and stereoselectivity (Scheme 3.5). The aforementioned conditions were considered satisfactory to test the method employing substrates with structural variations.

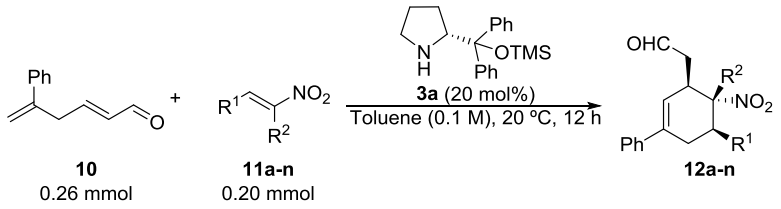


Scheme 3.5

3.3 Scope of the reaction

Once the optimal reaction conditions were established, the method was extended to the use of nitroalkenes with different substitution patterns and electronic properties.

Table 3.4: Scope of the reaction.[a]

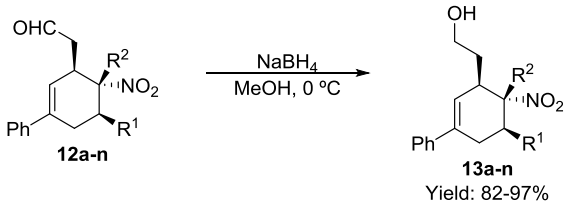


Entry	Product	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	**12a**	Ph	H	99	13:1	94
2	**12b**	4-$MeOC_6H_4$	H	93	>20:1	93
3	**12c**	3-$MeOC_6H_4$	H	91	16:1	90
4	**12d**	2-$MeOC_6H_4$	H	92	12:1	97
5	**12e**	4-MeC_6H_4	H	85	19:1	92
6	**12f**	4-$BnOC_6H_4$	H	98	16:1	96
7	**12g**	4-ClC_6H_4	H	99	14:1	90
8	**12h**	3-ClC_6H_4	H	94	12:1	93
9	**12i**	2-ClC_6H_4	H	88	14:1	96
10	**12j**	4-BrC_6H_4	H	92	13:1	96
11	**12k**	2-BrC_6H_4	H	81	13:1	92
12	**12l**	2-Thienyl	H	87	13:1	97
13	**12m**	2-Furyl	H	80	>20:1	89
14	**12n**	Ph	Me	64	16:1	96

[a] Reactions performed in 0.2 mmol scale of **11a-n** and 0.26 mmol of **10,** using 20 mol% of **3a** in 2 mL of toluene at 20 ºC in a thermostatic bath for 12 h.[b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture.[d] Enantiomeric excess determined by HPLC analysis of the corresponding reduced adduct **13a-n**.

As outlined in Table 3.4, the reaction proceeds satisfactorily with a wide range of nitroolefins, including substituted aromatics with electron-donating (entries 2-6), electron-withdrawing groups (entries 7-11) and heteroaromatics (entries 12-13). The use of *ortho*-substituted aromatic rings (entries 4, 9, 11) was well tolerated and α,β-disubstituted nitroalkene (entry 14) also proceeded satisfactorily in the reaction, forming cyclohexenes with a cuaternary stereocenter. The diastereoselectivity of the process is in all cases high (dr >10:1) in favor of the *exo* adduct.

In all cases, as trials for the chromatographic separation of aldehyde species on chiral stationary phase HPLC resulted in the decomposition of the product, in order to determine its enantiomeric excess, derivatization of the aldehydes **12a-n** to the corresponding alcohols **13a-n** was necessary, using for this purpose $NaBH_4$ in methanol at 0 ºC, enabling the chiral HPLC separation of the enantiomers and the determination of the enantiomeric excess. The reductions proceeded smoothly with almost quantitative yields (Scheme 3.6).



Scheme 3.6

The absolute configuration of the adduct **12e** was assigned by single-crystal X-ray analysis of the product (Figure 3.1), and the configuration of all other adducts were established by analogy. The absolute configuration was in agreement with previously reported [4+2] cycloadditions in trienamine catalysis, where fully conjugated dienals were employed.[8a-b]

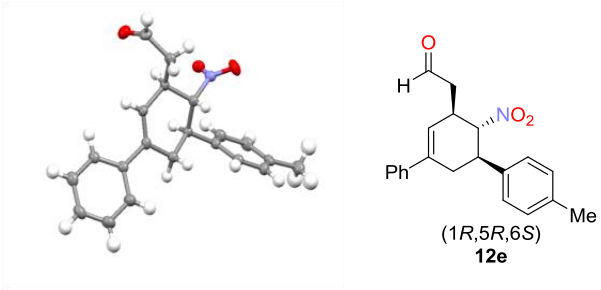
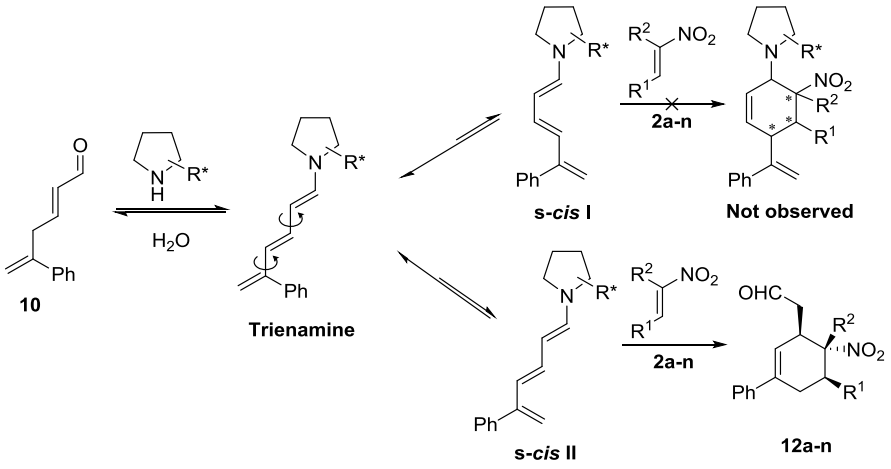


Figure 3.1

3.4 Mechanistic insights

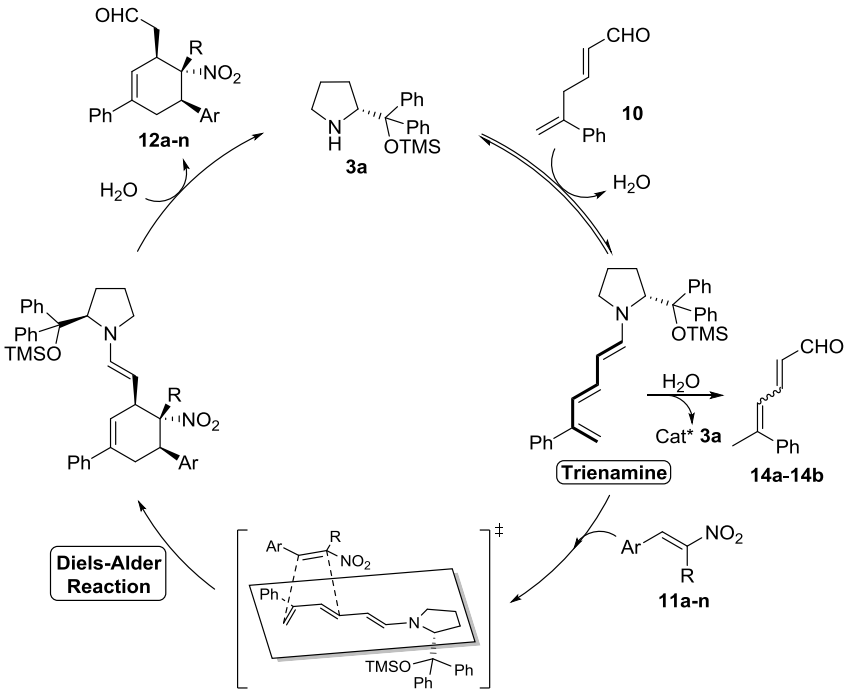
Considering the background knowledge on trienamine catalysis from the previously summarized research works and experimental observations acquired during the production of the current project, the following mechanistic proposal and reasoning for the regio- and stereochemical outcome are presented. As discussed on the introduction of this chapter, computational studies revealed that reactions under trienamine activation, proceed with complete β,ε-regioselectivity, leading to the unique formation of adducts **12a-n** through the **s-*cis* II** intermediate due to steric interactions between the chirality inducing moiety and the unsaturated chain together with the increased HOMO energy (Scheme 3.7). The **s-*cis* I** intermediate is not productive in the reaction since no α,γ-selective product formation was observed, although it could coexist in equilibrium with more thermodynamically stable isomers of the trienamine. Bound to this assumption, only the **s-*cis* II** trienamine isomer will be considered on the proposed catalytic cycle.



Scheme 3.7

The catalytic cycle begins with the condensation of the aminocatalyst **3a** with the aldehyde **10**, leading to the formation of the iminium ion, which follows deprotonation on

γ-position to give the trienamine intermediate. At this point, two different pathways emerge: on one hand the trienamine can undergo hydrolysis of the catalyst through vinylogous iminium ion intermediate resulting in the formation of conjugated aldehydes **14a**-**14b** as side products. On the other hand, the trienamine can react with nitroalkenes in a formal Diels-Alder reaction in either concerted or stepwise mechanism, which undergoes hydrolysis releasing the cyclohexene adducts **12a-n** and the catalyst **3a** (Scheme 3.8).



Scheme 3.8

The generation of stereogenic centers occurs during the formal Diels-Alder reaction, being the steric bulk of the substituent on the aminocatalyst responsible for asymmetric induction by steric bias. This bulky substituent induces an efficient differentiation between the two faces of the conjugated π-system, forcing the approach of the nitroalkene through its less hindered face, as depicted on Scheme 3.8. The *exo*-selective diastereoselectivity of

the reaction is in agreement with previously reported methods in the literature involving the use of trienamines,[8a-b,9b,10,25a-b] or other dienes.[35] Electrostatic repulsion between the negatively charged nitro group and the high electron density on the trienamine is proposed to drive the nitro group far from the electron-rich conjugated system, being this effect dominant over secondary orbital interactions or steric repulsion factors.

Regarding the concerted or stepwise nature of the [4+2] cycloaddition, literature background stands for the concerted Diels-Alder process, giving account for the absence of detected reaction intermediates and the high diastereo- and enantioselectivities of the processes. Indeed, a possible stepwise mechanism, would imply a cascade Michael/Michael process, where the most stable conformer of the trienamine, with *E*,s-*trans*,*E*-geometry, would very likely be the reactiving intermediate. The chiral information of the catalyst for *E*,s-*trans*,*E* trienamine lies far away from the reacting ε-carbon atom, thus a cascade Michael/Michael process would eventually lead to poor stereocontrol, supporting the hypothesis for a concerted mechanism.

[35] For *exo*-selective Diels-Alder reaction of nitroolefins with Danishefsky's diene, see: Node, M.; Nishide, K.; Imazato, H.; Kurosaki, R.; Inoue, T.; Ikariya, T. *Chem. Commun.* **1996**, 2559.

4. CONCLUSION

Considering the results obtained during the realization of this project, the following conclusions can be drawn:

- Non-conjugated diunsaturated aldehydes can be used as efficient substrates in reactions under trienamine activation, such as the Diels-Alder reaction with nitrostyrenes. This methodology has advantages over the use of conjugated dienals as substrates, since conjugated polyunsaturated carbonyl compounds are either unreactive or need of higher reaction temperatures to develop the same reactivity.

- (*E*)-5-phenylhexa-2,5-dienal (**10**) has proven to be reactive in combination with the commercially available catalyst **3a** with diverse nitroalkenes containing β-aryl substituents with different electronic properties and substitution patterns, also tolerating substitution on α position, with excellent yields and outstanding diastereo- and enantioselectivities in the formation of cyclohexenes **12a-n**.

- The described Diels-Alder reaction between (*E*)-5-phenylhexa-2,5-dienal (**10**) and nitroestyrenes through trienamine activation very likely proceeds in a concerted manner, due to the absence of detected intermediates and high stereoselectivties achieved.

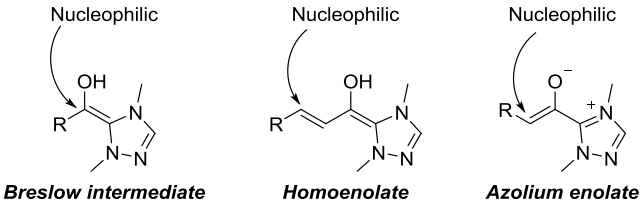
Chapter 4

4

N-Heterocyclic Carbene Catalyzed [4+2] Cycloaddition Reaction

1. [4+2] CYCLOADDITIONS UNDER NHC-CATALYSIS *VIA* AZOLIUM ENOLATES

N-Heterocyclic carbenes (NHC), as presented in Chapter 1, have demonstrated a remarkable proficiency catalyzing asymmetric transformations leading to complex structures not easily accessible by other procedures.[1] One of the most interesting features of NHCs is the ability to trigger a formal polarity inversion (*umpolung*) process on aromatic or α,β-unsaturated aldehydes, reversing the inherent reactivity of carbonyl compounds from originally electrophilic, prone to undergo 1,2- or 1,4-addition, to become nucleophilic, displaying acyl anion or homoenolate reactivity respectively. However, NHCs can also promote other transformations on aldehydes that do not strictly involve a polarity reversal process. Such is the case for reactions proceeding through azolium enolates (Scheme 1.1).



Scheme 1.1

Related to the topic disclosed in this chapter is the ability of azolium enolates to participate as electron-rich dienophiles in Diels-Alder type reactions under inverse electron-demand. This reactivity was firstly reportedby Bode et al. in 2006, in a aza-Diels-Alder reaction between α,β-unsaturated aldehydes and *N*-protected-α,β-unsaturated imines under NHC catalysis (Scheme 1.2).[2]. This strategy enabled the enantioselective formation of

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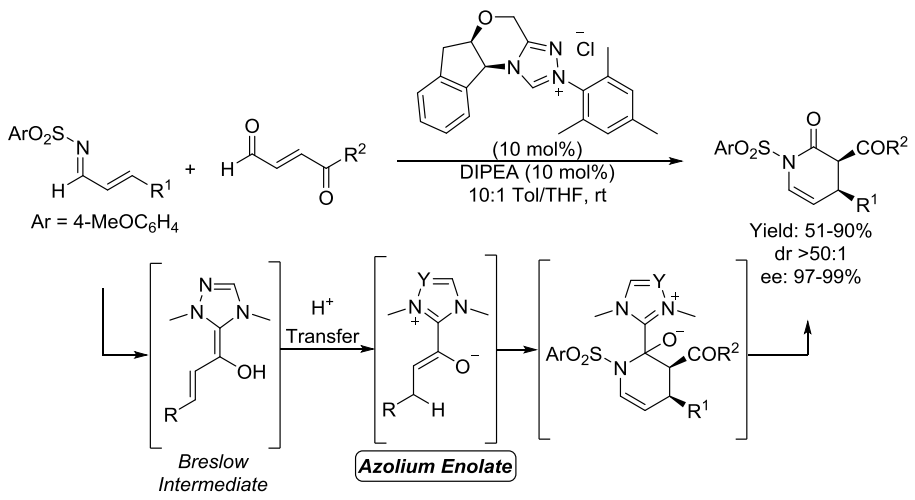
1 For selected reviews on the use of NHC as organocatalyst, see: (a) Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14912. (b) Walden, D. M.; Ogba, O. M.; Johnston, R. C.; Cheong, P. H. *Acc. Chem. Res.* **2016**, *49*, 1279. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.

2 He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

nitrogen containing heterocycles with high yields, excellent estereoselectivity and under mild conditions.[3]



Scheme 1.2

In this example, the catalyst induced the formation of the diene Breslow intermediate from α,β-unsaturated aldehydes, that next underwent proton transfer[4] rendering the azolium enolate species. Azolium enolates are very reactive dienophiles, as consequence of the high electron density on π–orbitals of the triazolium moiety conjugated with the enolate. This catalytically generated high-energy HOMO species, react with electron-deficient dienes, like α,β-unsaturated imines used in this example, in an inverse electron demand Diels-Alder process.[5] The alcoxide that results from the [4+2] cycloaddition process, induces the carbonyl double bond formation, while the NHC, in its

[3] Previuosly reported procedures required of high pressures of temperatures, see: (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (c) Sisti, N. J.; Motorina, I. A.; Tran Huu Dau, M. E.; Riche, C. Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715.

[4] Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11158.

[5] For selected reviews on IEDDA reactions, see: a) Jiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515; b) Knall, A.-C.; Slugovc, C. *Chem. Soc. Rev.* **2013**, *42*, 5131.

azolium form, acts as an extraordinary leaving group that results in the catalyst turnover (Scheme 1.2).

Considering the stereochemical outcome of the reaction, the extraordinary selectivity in the formation of the *cis* diastereomer is associated to the preferential *Z*-configuration of the enolate.[6] The diastereoselective formation of this *Z* enolate is explained by considering the exclusive participation of the most stable Breslow intermediate isomer in a preferred s-*trans* conformation that, after proton shift, renders the *Z*-azolium enolate, which takes part in the subsequent *endo*-selective IEDDA cycloaddition with the diene, to deliver [4+2] adducts (Scheme 1.2).

This seminal work inspired a number of strategies employing chiral carbene catalysts for the *in situ* generation of *azolium enolates* as chiral electron-rich alkenes to go through enantioselective Diels-Alder type cycloadditions with electron-defficient dienes. This is the case of α-hydroxy enones[7] or alkylidene diketones[8] that react in a similar fashion to α,β-unsaturated imines in IEDDA reactions giving highly stereoselective access to oxygen containing heterocycles (Scheme 1.3).[9]

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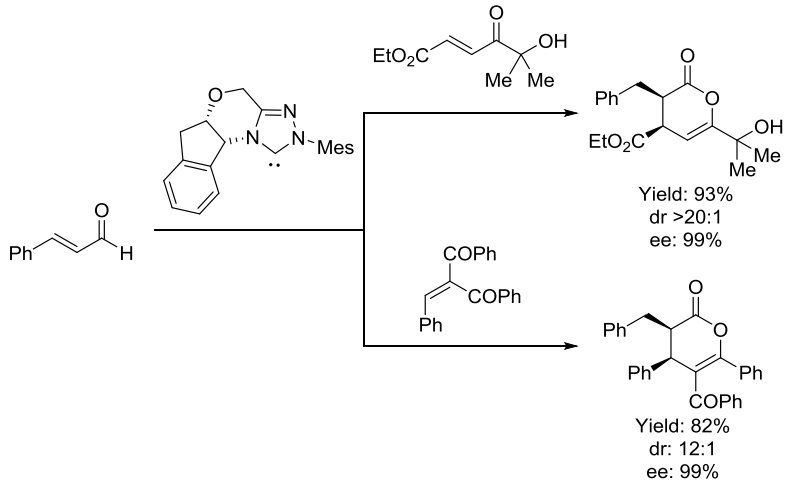
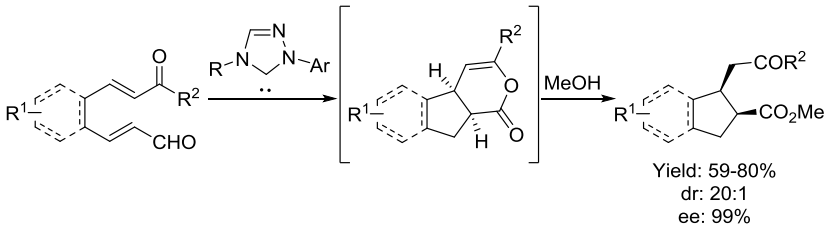
6 Allen, S. E.; Mahatthananchai, J.; Bode, J. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 12098.
7 Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *PNAS* **2010**, *107*, 20661.
8 Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708.
9 For an example of the use of α,β-unsaturated aldehydes as enolate precursors in a 1,4-addition to nitroalkenes, see: Wu, Z.; Wang, X.; Li, F.; Wu, J.; Wang, J. *Org. Lett.* **2015**, *17*, 3588.



Scheme 1.3

Intramolecular versions of this reaction have been reported using substrates bearing α,β-unsaturated aldehydes tethered to dienes, which under NHC catalysis gave access to heteroatom-containing polycyclic adducts (Scheme 1.4).[10] In this report, the final adducts needed to be subjected to methanolysis due to the instability of the product during isolation process, yielding the corresponding methyl esters in good yields and excellent stereoselectivities.[11]



Scheme 1.4

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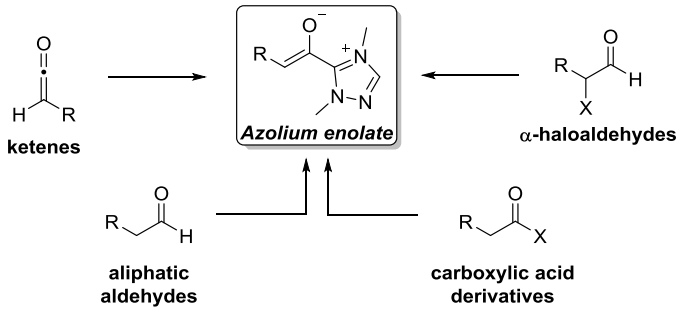
10 Philips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107.

11 For examples of the use of α,β-unsaturated aldehydes as enolate precursors in intramolecular Aldol reactions, see: (a) Wadamoto, M.; Philips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098. (b) Phillips, E. M.; Wadamoto, M.; Scheidt, K. A. *Synthesis* **2009**, *4*, 687.

The *in situ* generation of azolium enolates is not restricted to the use of α,β-unsaturated aldehydes as substrates. Alternative methodologies have been developed to produce *azolium enolate* intermediates from distinct precursors, such as ketenes, α-halo aldehydes, aliphatic aldehydes in oxidative conditions and carboxylic acid derivatives (Scheme 1.5) In the following paragraphs the most prominent features of each of these strategies is presented.



Scheme 1.5

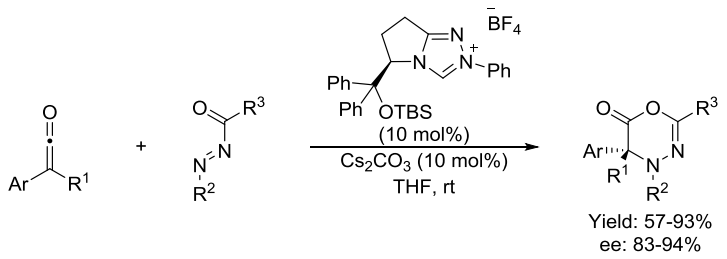
For example, ketenes have demonstrated suitability to experience, in analogy to α,β-unsaturated aldehydes, 1,2-addition with carbenes forming azolium enolate intermediate directly, avoiding the proton-transfer event characteristic of α,β-unsaturated aldehydes, providing a suitable activated diene to take part in IEDDA reactions.

The [4+2] cycloaddition reactivity of ketene derived azolium enolates has been tested with various heterodienes,[12] including: *N*-benzoyldiazenes,[13] which react in a [4+2] type cycloaddition with the *in situ* generated dienophiles with excellent yields for the enantioselective formation of 1,3,4-oxadiazines, as depicted on Scheme 1.6. This reaction exemplifies the advantage that resides on the use of ketenes as azolium enolate precursors,

[12] (a) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. Chem. *Eur. J.* **2008**, *14*, 8473. (b) Lv, H.; Chen, X.-Y.; Sun, L.-h.; Ye, S. *J. Org. Chem.* **2010**, *75*, 6973. (c) Jian, T.-Y.; Shao, P.-L.; Ye, S. *Chem. Commun.* **2011**, *47*, 2381.

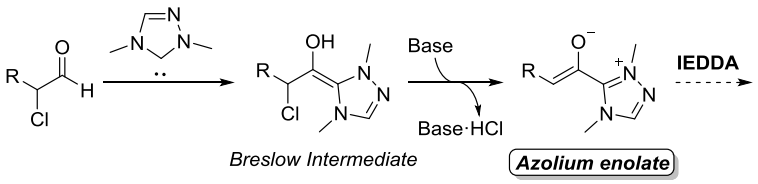
[13] Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 192.

since these substrates enable the access to heterocycles with quaternary stereocenters, a feature not reachable by other strategies.



Scheme 1.6

In a similar way, α-chloro aldehydes have shown similar properties as substrates, to form a chlorinated Breslow intermediates under NHC catalysis which has inclination to undergo chlorine elimination, yielding the azolium enolate, as activated diene, to take part in [4+2] reactions (Scheme 1.7).



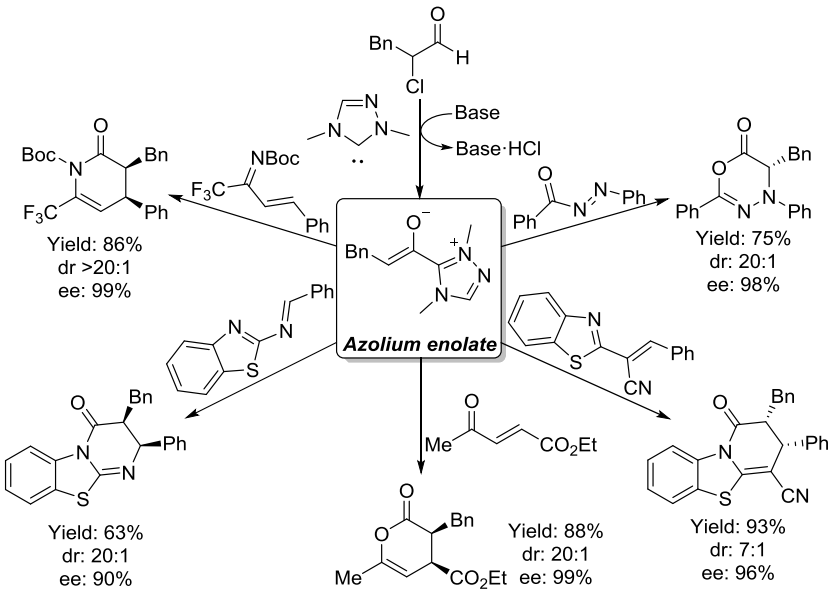
Scheme 1.7

The reactivity of azolium enolates derived from α-chloro aldehydes has been studied with a number of dienes, such as oxodiazenes,[14] styrylbenzothiazoles,[15] enones,[16] *N*-(benzothiazoyl)imines[17] and trifluoromethyl azadienes,[18] demonstrating that α-chloro aldehydes are a source of azolium enolates as effective as α,β-unsaturated aldehydes,

[14] Yang, L.; Wang, F.; Lee, R.; Lv, Y.; Huang, K.-W.; Zhong, G. *Org. Lett.* **2014**, *16*, 3872.
[15] Song, X.; Ni, Q.; Zhu, C.; Raabe, G.; Enders, D. *Synthesis*, **2015**, *47*, 421.
[16] He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088.
[17] Ni, Q.; Song, X.; Xiong, J.; Raabe, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 1263.
[18] Wang, D.-L.; Liang, Z.-Q.; Chen, K.-Q.; Sun, D.-Q.; Ye, S. *J. Org. Chem.* **2015**, *80*, 5900.

producing complex asymmetric nitrogen and/or oxygen containing heterocyclic compounds from easily accessible starting materials (Scheme 1.8).[19]

In this process stoichiometric amounts of hydrogen chloride are generated, thus the presence of stoichiometric base is necessary to shift the reaction equilibrium to the azolium enolate formation.



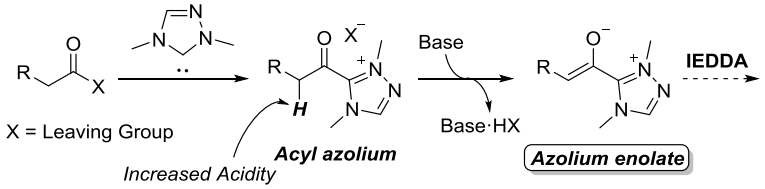
Scheme 1.8

The role of the chlorine in the azolium enolate formation is to act as a leaving group, therefore other functional groups are also appropriate to accomplish the same purpose. This

[19] For the use of α-chloroaldehyde bisulfate salts as azoliun enolate precursors, see: He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817.

is the case of other halogens (*e.g.* bromine), phenoxide[20] and aroyloxides,[21] that under NHC catalytic conditions deliver azolium enolate intermediates.

Esters and anhydrides offer an alternative possibility in the generation of azolium enolates under certain conditions in the presence of a carbene catalyst. Carbonyls with good leaving groups undergo 1,2-addition of NHC catalyst to the carbonyl, forming an acyl azolium intermediate with increased acidity of the α-proton. An appropriate base capable to abstract the acidic α-proton would render the azolium enolate that, as mentioned before, can take part in IEDDA processes (Scheme 1.9). Like in the case of α-chloro aldehydes, this strategy requires stoichiometric amounts of base.



Scheme 1.9

Other choice is to use simple aliphatic aldehydes under NHC catalysis in oxidative conditions. The carbene catalyst performs a 1,2-addition on the carbonyl group of aliphatic aldehydes that, after a proton-shift, yields the Breslow intermediate. This enamine is prone to be oxidized in the presence of certain oxidants, forming the acyl azolium intermediate. As explained in the case of carbonyl groups with good leaving groups, a base promotes the acyl azolium deprotonation generating the azolium enolate, enabling the formation of the activated dienophile and the IEDDA reaction with appropriate dienes (Scheme 1.10).

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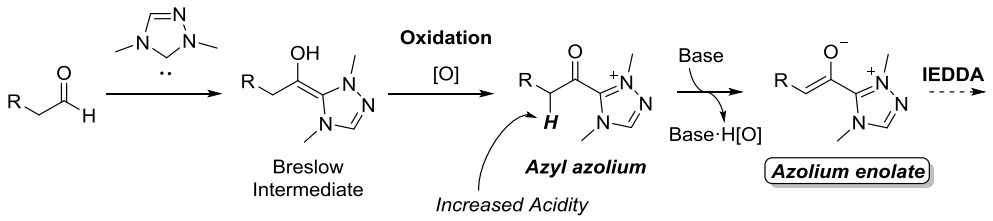
[20] Philips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105.

[21] (a) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373. (b) Davies, A. T.; Pickett, P. M.; Slawin, M. Z.; Smith, A. D. *ACS Catal.* **2014**, *4*, 2696.



Scheme 1.10

The last two strategies for the generation of azolium enolates are illustrated on Scheme 1.11. Aliphatic aldehydes, in the presence of a NHC, phenazine and base are transformed into azolium enolates that react with enones in a [4+2] fashion yielding asymmetric γ-lactones with excellent stereoselectivities (Scheme 1.11 right).[22] For the use of activated carboxylates, 4-nitrophenol was found to perform better than other *O*-aromatic and *O*-alkylic moieties as leaving group. 4-Nitrophenyl carboxylates, under basic and NHC catalytic conditions, produce azolium enolates that were captured with α,β-unsaturated imines in IEDDA process delivering enantioenriched γ-lactams (Scheme 1.11 left).[23]

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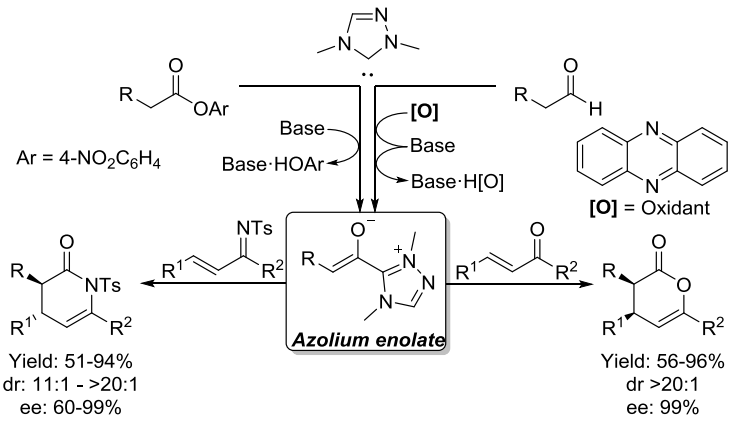
[22] Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem Int. Ed.* **2012**, *51*, 12330. α,β-Ketimines were also tested in this work.

[23] (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154. For the *in situ* generation of activated carbonyls from carboxylic acids, see: (b) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 10589.



Scheme 1.11

There is an additional approach for the generation of azolium enolates. The use of cyclopropanes, with a specific substitution pattern, enabled a different access to NHC catalyzed formation of azolium enolates. Formylcyclopropanes with electron-withdrawing groups,[24] undergo 1,2-addition of the carbene to the carbonyl, forming the Breslow intermediate. The cyclopropane is, at this point, substituted with adjacent electron-donating (the enaminol of the Breslow intermediate) and electron-withdrawing groups, thus it can be considered as the colloquially named Donor-Acceptor cyclopropane.[25] This type of cyclopropanes easily experience ring-opening event due to their ring strain and thermodynamical instability, giving rise to the azolium enolate, the activated dienophile for [4+2] cycloaddition reactions (Scheme 1.12).[26]

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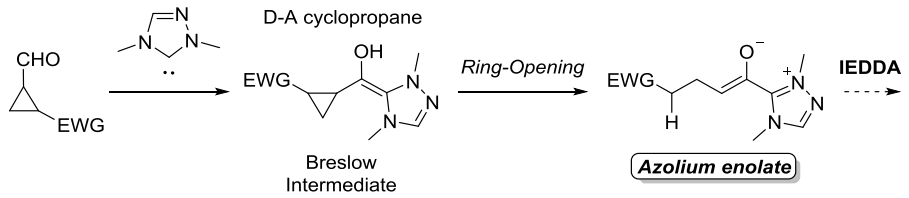
[24] For the first example on the use of formylc cyclopropanes under NHC catalysis in redox esterification, see: (a) Shon, S. S.; Bode, J. W. *Angew. Chem. Int. Ed.* **2006**, *45*, 6021. For redox amidation, see: (b) Bode, J. W.; Shon, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798.

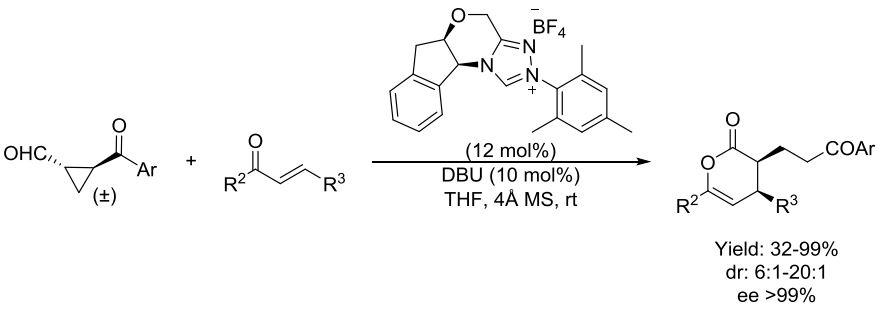
[25] For selected reviews on Donor-Acceptor cyclopropanes, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151; (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321; (c) YaMel'nikov, M.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun*. **2011**, *21*, 293; (d) Cavitt, M. A.; Phun, K. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804; (e) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed*. **2014**, *53*, 5504; (f) Novikov, R. A.; Tomilov, I. V. *Mendeleev Commun*. **2015**, *25* ,1; (g) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem*., **2015**, *13* , 655.

[26] For formylcyclopropane derived azolium enolates in: Ring-expansion reactions, see: (a) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett*. **2009**, *11*, 1623; Rearrangement reactions, see (b) Candich, L.; Lupton, D. W. *Chem. Sci.* **2012**, *3*, 380; (c) Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 58; Dormino reactions, see: (d)



Scheme 1.12

The unique example in the literature representing a successful application of asymmetric NHC catalyzed azolium enolate formation from formylcyclopropanes in formal [4+2] cycloaddition reaction is depicted on Scheme 1.13.[27] This methodology uses racemic mixtures of *trans*-disubstituted formylcyclopropanes with a chiral carbene catalyst to form the azolium intermediate, which takes part in a formal hetero-Diels-Alder reaction with chalcones as oxodienes. The products of the reaction, in a similar way to previously presented examples, are asymmetric δ-lactones, obtained in moderate to excellent yields and outstanding stereoselectivities. However, this method presented some limitations regarding the substrate scope, since it was restricted to the use of chalcones and phenone-substituted formylcyclopropanes.



Scheme 1.13

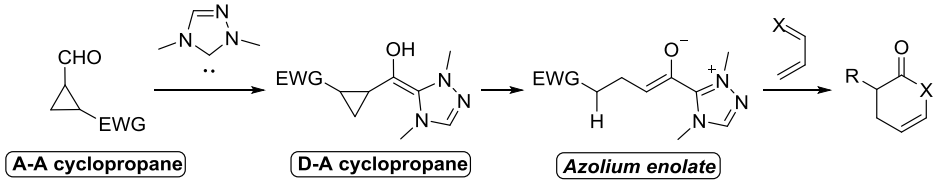
Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949; (e) Di, D.; Li, L.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 4379; (f) Li, L.; Du, D.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2011**, 614.

[27] Lv, H.; Mo, J.; Fang, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366.

In summary, NHCs have unarguably demonstrated outstanding capacity to catalytically generate azolium enolates from a quite diverse range of carbonyl compounds. These enolates often react as activated dienophiles with different heterodienes in highly stereoselective reactions leading to the formation of six member hetero-cycloadducts. This strategy represents a very powerful synthetic tool to efficiently access enantioenriched δ-lactams and δ-lactones under mild conditions.

2. SPECIFIC OBJECTIVES AND WORK PLAN

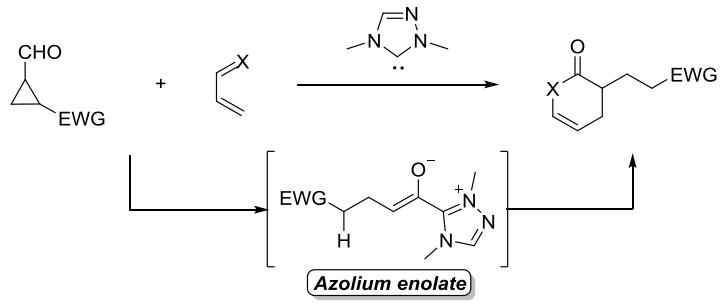
Taking into account the presented bibliographic revision, there are still abundant opportunities for the innovation on the field of asymmetric NHC catalyzed azolium enolate chemistry including the use of novel precursors of the azolium enolate or different heterodienes. In this context, the objective of the present project is to develop an **NHC-catalyzed activation of formylcyclopropanes for the catalytic generation of donor-acceptor cyclopropanes and their reaction with heterodienes** (Scheme 2.1).



Scheme 2.1

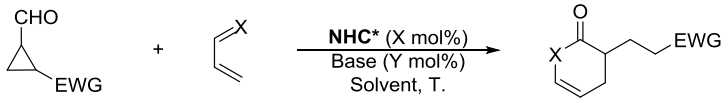
To accomplish the aforementioned objective, the subsequent work plan was followed:

1. *Proof of concept:* In order to verify the capacity of formylcyclopropanes to experience ring-opening under NHC catalysis, the viability of the reaction will be tested using formylcyclopropanes substituted with an electron-withdrawing group in a carbene catalytic system together with a suitable diene able to react with azolium enolate intermediates to get evidence of the formation of envisaged cycloadduct (Scheme 2.2).



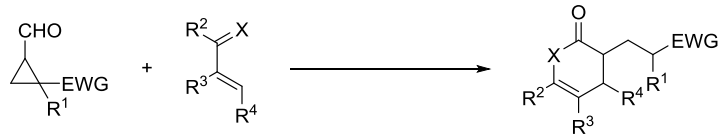
Scheme 2.2

2. *Optimization of the reaction conditions*: Using the aforementioned formylcyclopropane and the adequate diene as model substrates for the reaction, diverse combinations and ratios of NHCs and base sources will be tested, as well as the influence of the solvent to obtain satisfying results of yield and stereoselectivity (Scheme 2.3).



Scheme 2.3

3. *Scope of the reaction*: When the exploration of reaction conditions conclude with satisfactory results, the applicability of the method will be extended to the use of formylcyclopropanes with a range of substituents and diversely substituted dienes, studying the effect of structural modification of the substrates on the yield, diastereo- and enantioselectivity of the process (Scheme 2.4).



Scheme 2.4

3. RESULTS AND DISCUSSION

Now that the objectives of the work have been defined and the work plan has been established, the most significant results gathered in the accomplishment of the present project are presented in the following paragraphs.

3.1 Proof of concept

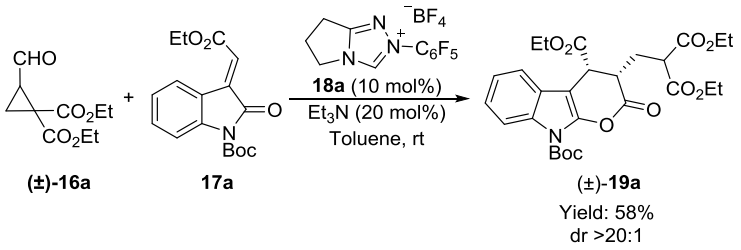
As suggested on the work plan, advantage was taken of the thermodynamic instability of cyclopropane motif[28] and the ability of NHCs to trigger *umpolung* processes on carbonyl compounds, formylcyclopropanes are chosen as candidate substrates. An additional requirement for the cyclopropane is to bear electron-withdrawing groups on an adjacent position to the formyl group in order to overcome the kinetic stability of the smallest carbocycles, enabling NHC catalyzed generation of donor-acceptor cyclopropanes and their ring-opening,[25] which would lead to the formation of a very reactive azolium enolate intermediate. Therefore, formylcyclopropanes substituted with two ester groups were selected. These substrates ensured the accepting capacity provided by the double ester substitution and, at the same time, precluded the existence of *cis*/*trans* isomers, although the molecule remained asymmetric.

With respect to the structure of the diene, since the aim was to find reactivity with alkene species with high HOMO energies (*i.e.* azolium enolates), electron deficient dienes were elected, among which heterodienes stand out for their proven aptitude to take part in IEDDA reactions as outlined on the literature survey of this chapter. Due to the high efficiency shown in bibliographic precedents, the underutilized alkylideneoxindoles were chosen as adequate dienes for this purpose.

---

[28] For selected reviews on cyclopropane reactivity, see: (a) Danishefsky, S. *Acc. Chem. Res*. **1979**, *12*, 66. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev*. **2007**, *107*, 3117. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (f) Wang, Z. *Synlett* **2012**, 2311. (g) Green, J. R.; Snieckus, V. *Synlett* **2014**, *25*, 2258.

In light of all the aforementioned considerations, the reaction between diethyl 2-formylcyclopropane-1,1-dicarboxylate (**16a**) and *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**17a**) under NHC catalysis was tested. Firstly, the reaction was evaluated under common NHC catalytic conditions, which were the achiral triazolium salt (**18a**) using triethylamine as base in toluene at room temperature (Scheme 3.1).



Scheme 3.1

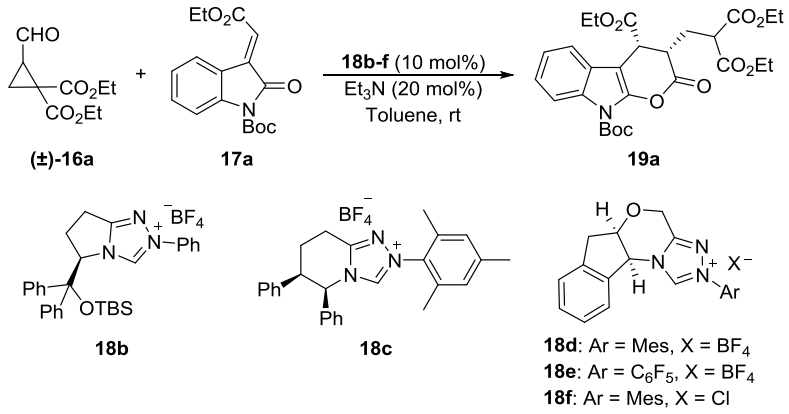
The reaction proceeded rendering the desired cycloadduct **19a** displaying the relative configuration shown on Scheme 3.1[29] in a promising 58% yield and as a unique diastereomer, proving the ability of NHC to trigger the ring-opening of formylcyclopropane and possibility to develop a catalytic and asymmetric synthetic method. This procedure was employed to synthesize racemic standards for HPLC separation of enantiomers and determination of the enantiomeric excess of adducts.

[29] Determined by X-ray analysis of monocrystal of (±)-**19a**.

3.2 Optimization of the reaction conditions

With evidences of the viability of the reaction, the efforts were directed to develop an asymmetric transformation by means of the use of chiral NHC precursors (**18b-f**) under analogous conditions, which consist of equimolar amounts of diethyl 2-formylcyclopropane-1,1-dicarboxylate (**16a**) and *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**17a**), together with triethylamine in toluene as solvent (Table 3.1).

Table 3.1: Survey of chiral NHC catalysts.[a]



Entry	Catalyst	Yield (%)[b]	dr[c]	ee (%)[d]
1	**18b**	<5	n.d.[e]	n.d.[e]
2	**18c**	25	>20:1	46
3	**18d**	60	>20:1	99
4	**18e**	<5	n.d.[e]	n.d.[e]
5	**18f**	52	>20:1	99

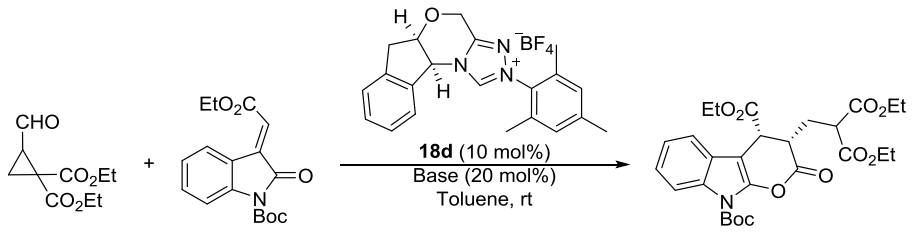
[a] Reactions performed in 0.2 mmol scale of **16a** and **17a**, using 10 mol% of triazolium salt **18b-f**, and 20 mol% of Et_3N in 2.0 mL of toluene at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis. [e] n.d.: Not determined.

Among the chiral scaffolds of the triazolium salt precatalysts tested, the aminoindanol-based catalyst **18d** prevailed over other chiral motifs (entries 1-3) achieving excellent levels of enantiocontrol on the reaction and an encouraging 60 % yield. The aromatic substituent on the triazole ring plays an important role on the activity of the catalyst, observing the total depletion of reactivity when the electron-withdrawing perfluorophenyl replaces the mesityl group (entry 4).[30] Modification of the counteranion of the cabene precursors did not show significant effect on the reaction outcome (entry 5). Therefore, triazolium salt **18d** was chosen to carry on with the optimization experiments.

The absolute configuration was determined by X-Ray diffraction of a single crystal, being the major enantiomer the (3*S*,4*R*) as represented on Table 3.1.[31]

Continuing with the screening of reaction conditions, a number of diverse basic sources, whose main role is the deprotonation of the catalyst precursor and the generation of the catalytically active carbene species, were evaluated (Table 3.2).

Table 3.2: Influence of the base source on the reaction.[a]



(±)-16a **17a** **19a**

Entry	Base	Yield (%)[b]	dr[c]	ee (%)[d]
1	Et_3N	60	>20:1	99
2	DIPEA	66	>20:1	99
3	K_2CO_3	22	>20:1	92

[30] For insights on the influence of *N*-mesityl group on NHC-catalyzed reactions, see: Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192.

[31] For further insights on the acquisition of the X-ray structure for the elucidation of the absolute structures of the major enantiomer, see Section 3.3 Scope of the reaction, later in this chapter.

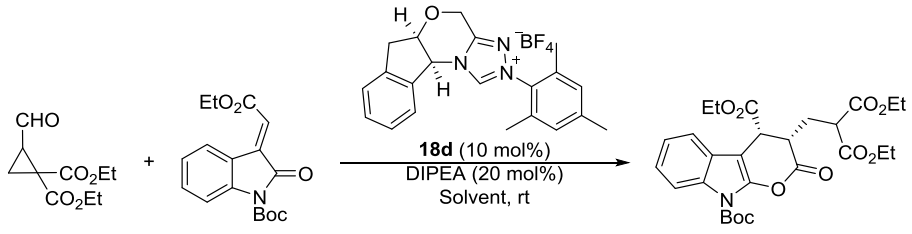
4	Cs_2CO_3	28	>20:1	94
5	DMAP	39	>20:1	98
6	DBU	57	>20:1	98

[a] Reactions performed in 0.2 mmol scale of **16a** and **17a**, using 10 mol% of triazolium salt **18d**, and 20 mol% of base in 2.0 mL of toluene at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d]Enantiomeric excesses determined by HPLC analysis.

As represented on Table 3.2, compared to triethylamine (entry 1) the yield increased slightly when using a more hindered base *N*,*N*-diisopropylethylamine maintaining excellent stereocontrol (entry 2). Inorganic bases as carbonates (entries 3-4) led to notably decrease in yield, presumably for the inferior solubility in toluene and stronger organic bases (entries 5-6) failed to provide improved results.

Although the diastereo- and enantioselectivity of the reaction were controlled, the yield remained below expectations, thus the reaction was then carried out in solvents of different nature seeking an improvement on yield (Table 3.3).

Table 3.3: Evaluation of different solvents.[a]

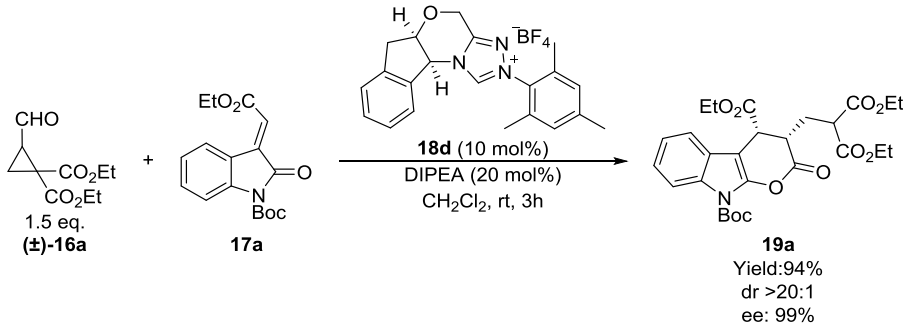


Entry	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	Toluene	66	>20:1	99
2	THF	18	>20:1	n.d.[e]
3	Hexane	<5	n.d.[e]	n.d.[e]
4	CH_2Cl_2	71	>20:1	99
5[f]	CH_2Cl_2	94	>20:1	99

[a] Reactions performed in 0.2 mmol scale of **16a** and **17a**, using 10 mol% of triazolium salt **18d**, and 20 mol% of DIPEA in 2.0 mL of solvent at room temperature. [b] Isolated product yield after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d] Enantiomeric excesses determined by HPLC analysis. [e] n.d.: Not determined. [f] 1.5 equivalents of **16a** were used.

The reaction was negatively affected when polar solvents as tetrahydrofuran were used (entry 2), observing low yields. In the same line, non-polar solvents, like hexane, inhibited the product formation after long reaction times (entry 3). Performing the reaction in dichloromethane improved the yield to some extent (entry 4) and modification of the reactant's ratio to 1.5 equivalents of aldehyde **16a**, afforded the product with almost quantitative yield as a single diastereomer with remarkable enantioselectivity (entry 5).

Once the most important reaction parameters were evaluated, it was concluded that the optimal conditions for the studied reaction implicated the employment of 1.5 equivalents of diethyl 2-formylcyclopropane-1,1-dicarboxylate (**16a**) with respect to *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**17a**), in combination with triazolium salt **18d** and *N,N*-diisopropylethylamine in dichloromethane at room temperature (Scheme 3.2).



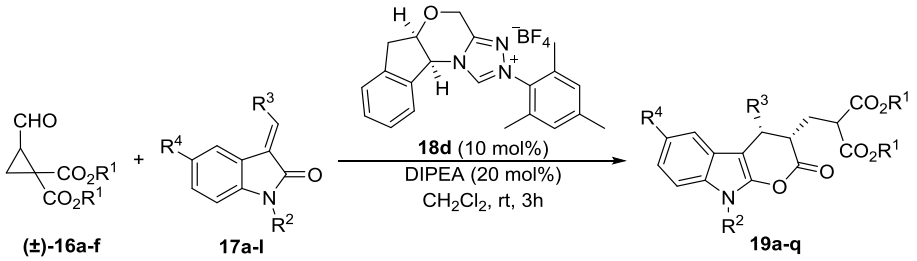
Scheme 3.2

The aforementioned conditions were considered satisfactory to test the method employing substrates with structural variations.

3.3 Scope of the reaction

Since experimental conditions that provide satisfactory results were found, it was decided to evaluate the optimal reaction conditions with formylcyclopropanes with different substituents on the ester moieties, modification on the indole's *N*-protecting groups, other electron-withdrawing groups on the β-position on the alkylideneoxindole and substitution on the aromatic ring (Table 3.4).

Table 3.4: Scope of the reaction.[a]



Entry	Product	R^1	R^2	R^3	R^4	Yield (%)[b]	ee (%)[c]
1	**19a**	Et	Boc	CO_2Et	H	94	99
2	**19b**	Et	Cbz	CO_2Et	H	79	99
3	**19c**	Et	Fmoc	CO_2Et	H	99	>99
4	**19d**	Et	Me	CO_2Et	H	49	96
5	**19e**	Et	Bn	CO_2Et	H	36	88
6	**19f**	Et	Ac	CO_2Et	H	49	91
7	**19g**	Me	Boc	CO_2Et	H	85	99
8	**19h**	Allyl	Boc	CO_2Et	H	86	98
9	**19i**	*i*-Pr	Boc	CO_2Et	H	6	99
10	**19j**	CH_2-*c*C_3H_5	Boc	CO_2Et	H	88	99
11	**19k**	$(CH_2)_4OBn$	Boc	CO_2Et	H	89	>99
12	**19l**	Et	Boc	CO_2Bn	H	82	99
13	**19m**	Et	Boc	CO_2*t*-Bu	H	97	99

14	**19n**	Et	Fmoc	CO_2t-Bu	H	82	>99
15	**19o**	Et	Boc	COPh	H	60	92
16	**19p**	Et	Boc	CO_2Et	Me	85	99
17	**19q**	Et	Boc	CO_2Et	OMe	89	98

[a] Reactions performed in 0.2 mmol scale of **17a-l** and 0.3 mmol of **16a-f**, using 10 mol% of triazolium salt **18d**, and 20 mol% of DIPEA in 2.0 mL of dichloromethane at room temperature for 3 h. dr >20:1 in all cases by ^{1}H-NMR. [b] Isolated product yield after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis.

The reaction tolerates diverse protecting groups on the indole moiety providing, in general, excellent results; however *N*-carbamate substituted alkylidedeneoxindoles delivered the product in considerably better yields than *N*-alkyl substituted alkylidedeneoxindoles (entries 1-6). Excellent performance was observed for a number of substituents on the ester groups on the formylcyclopropanes (entries 7-11), although increase of bulkiness on these substituents strongly decreases the reactions yield (entry 9, R^1 = *i*-Pr). The variability was also extended to the electron-withdrawing substituent on the β-position of the alkylideneoxindoles from assorted ester groups (entries 12-14) to benzoyl group (entery 15) with satisfactory outcome. Finally, the alkyldeneoxindoles bearing substituents on 5-position also delivered the products successfully (entries 16-17). The reaction yielded in all cases cycloadducts**19a-q** as single diastereomer in moderate to excellent yields and high enantioselectivities.

Nevertheless the method presents some limitations regarding the structure of the reactants. In the case of formylcyclopropanes, the influence of two ester groups is inevitable since a single ester group is not sufficient to develop the expected reactivity. The same occurs with formylcyclopropanes bearing one or two ketones instead of carbonyls, as the reaction does not proceed to the product formation. A substituent like methyl group on C-2 position of 2-Formylcyclopropane-1,1-dicarboxylates prevents the 1,2-addition of the NHC to the formyl group, therefore depleting the reactivity, just like the aforementioned effect of bulky alkyl groups on the esters (*e.g. t*-Bu), showing complete inhibition of reaction.

Continuing with substrate restrictions, alkylideneoxindoles required strong electron-withdrawing groups on the alkene, since 3-alkylidene and 3-arylidene oxindoles failed to react under the specified conditions. Substitution on the aromatic ring with electron-withdrawing groups (*i.e*. NO_2, F, Cl, Br and I) was likewise unproductive regardless of their position on the aromatic moiety.

X-ray analysis of a single-crystal of compound **19l** was carried out to determined the absolute configuration of the adduct (Figure 3.1). The stereoconfiguration of all other adducts was then assigned by mechanistic analogy.

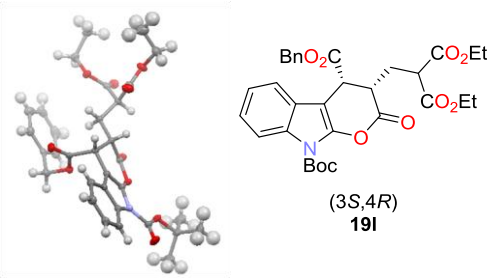
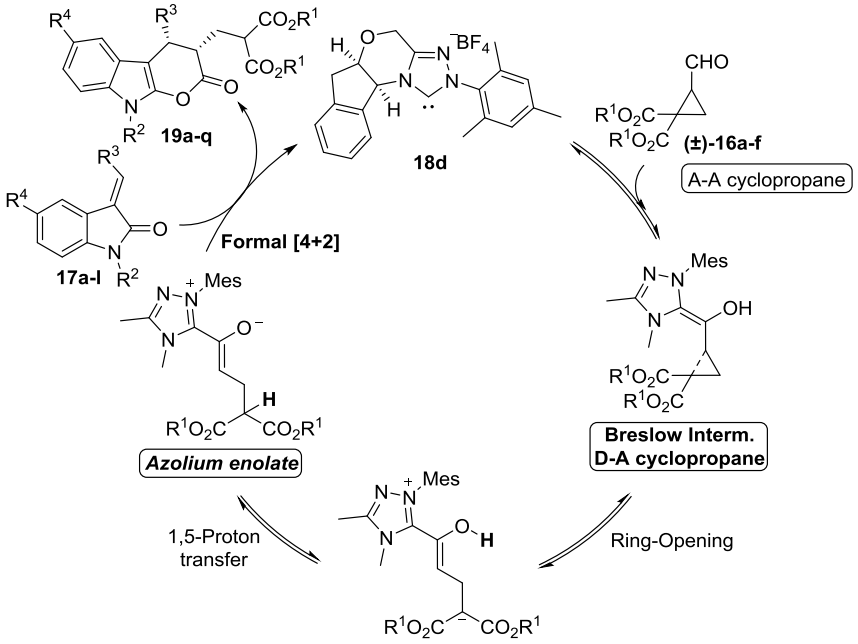


Figure 3.1

The observed absolute configuration was in agreement with reported bibliographic examples of azolium enolate [4+2] cycloadditions with heterodienes using aminoindanol based chiral catalyst **18d**.[2,7-8,27]

3.4 Mechanistic insights

Taking into account the results and observations compiled during the completion of the present research project and the support provided by the bibliographic background on NHC catalysis involving azolium enolate [4+2] reactions, the following mechanism was proposed (Scheme 3.3).



Scheme 3.3[32]

The reaction starts with the generation of the catalytically active carbene species through deprotonation of the triazolium salt **18d**, which performs a 1,2-addition to the aldehyde group present on the formylcyclopropane to form the Breslow intermediate. At this point, the *umpolung* process triggered by action of the NHC on the carbonyl group has converted the originally kinetically stable Acceptor-Acceptor formylcyclopropane

[32] Chiral backbone of the catalyst omitted for simplicity.

dicarboxylate **16a-f**, into the reactive Donor-Acceptor 1,2-enaminol-substituted cyclopropane dicarboxylate derivative which, due to the thermodynamic instability of the strained three-membered carbocycle, experiences a ring-opening event. The ring-opening intermediate presents a negative charge situated on the malonate moiety. To enable the azolium enolate formation, a 1,5-proton transfer has to occur, delivering the proton from the enol to the malonate rendering the reactive azolium enolate. The azolium enolate, as a high-energy HOMO species, reacts with the electron deficient heterodiene alkylideneoxindole **17a-l** in a formal [4+2] cycloaddition process furnishing product **19a-q** and catalyst recovery.

Based on literature precedents and the stereochemical outcome of the reaction, a transition state was suggested for the formal [4+2] reaction step between the azolium enolate and the akylideneoxindole to explain the diastereo- and enantioselectivity of the process (Figure 3.2)

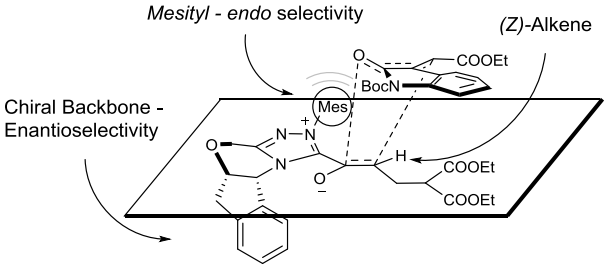


Figure 3.2

The high diastereoselectivity is a consequence of two factors. On one hand the spatial disposition of the bulky mesityl ring that stands perpendicular to the plane of the enolate efficiently preventing the diene to take an *exo* approach to the enolate. Therefore the *endo*-selectivity prevails, minimizing steric repulsive interactions between the mesityl and the diene. On the other hand, the enolate, since it comes from the most stable isomer of the Breslow intermediate,[6] acquires preferentially *Z*-conformation, arranging the relative

configuration of the two stereogenic centers to be *cis*. Finally, the chiral backbone of the catalyst performs the differentiation between the diastereotopic faces of the enolate, directing the incoming dienes from the top side of the plane and determining the enantioselectivity of the reaction.

4. CONCLUSION

With the results gathered during the accomplishment of the research work, the following conclusions are presented:

The work demonstrates that synthetically useful and versatile Donor-Acceptor cyclopropanes can be catalytically generated from stable and inert Acceptor-Acceptor cyclopropanes using NHC catalysis.

It has been proven that formylcyclopropanes act as azolium enolate precursors formed after Donor-Acceptor cyclopropane generation and ring-opening , which have been successfully trapped in a formal [4+2] reaction with alkylideneoxindoles.

The *in situ* generated azolium enolates and alkylideneoxindoles react to furnish heteroaromatic polycyclic asymmetric adducts as a single diastereomer, with moderate to excellent yields and high enantioselectivities.

Chapter 5

5

Strain-Release Amination

1. BICYCLO[1.1.1]PENTAN-1-AMINE: HISTORICAL REVIEW

The modern medicinal chemistry research relies on the discovery of new synthetic methods and applications to access bioisosteres[1] (molecular entities with different functional groups, but similar biological properties) as a vital strategy to deal with characteristics related to design and development of drug candidates.[2] The bioisosteric approach gives quick access to libraries of compounds providing solution to reiterative issues like metabolic instability, pharmacokinetic properties, optimization of molecules potency, selectivity profile and the limited intellectual property space.[3] Bioisosteric groups, although very useful for drug development, are unconventional as they are rarely present in natural products, like fluoroalkyl groups[4] and strained ring systems.[5]

Concerning strained ring systems, bicyclo[1.1.1]pentane is considered bioisostere of phenyl and *tert*-butyl groups.[5] In a study carried out by Pfizer to find novel chemotypes, bioisosteric relation of para-substituted phenyl ring with other chemical entities (*e.g.* alkyl, cycloalkyl, aryl) was established, concluding that the strained ring system bicyclo[1.1.1]pentane is ideally suited to increase the three-dimensionality and disruption of planarity of the molecule, preventing intermolecular π-stacking, compared to the parent molecule, with favorable results in terms of physiochemical and biopharmaceutical properties (Scheme 1.1).[6]

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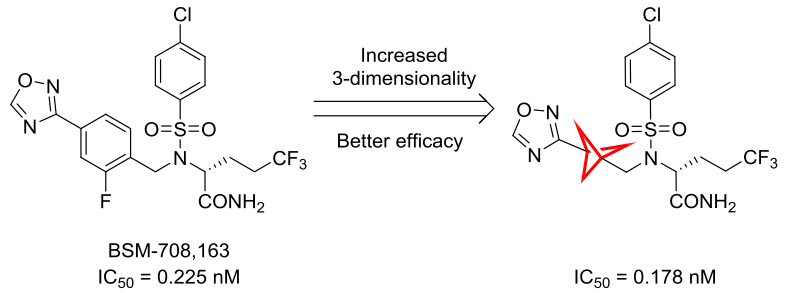
1 Erlenmeyer, H.; Berger, E. *Biochem. Z.* **1932**, *252*, 22.
2 Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.
3 Brown, N. *Bioisosteres in medicinal chemistry*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2012; 54: 237.
4 (a) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Isihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.
5 Westphal, M. V.; Wolfstädter, B. T; Plancher, J. M.; Gatfield, J.; Carreira, E. M. *ChemMedChem* **2015**, 10, 461.
6 Stepan, A. F. *et al. J. Med. Chem.* **2012**, *55*, 3414.



Scheme 1.1

The increasing number of patents containing the bicyclo[1.1.1]pentan-1-amine scaffold outline the importance of this strained carbocycle for pharmaceutical industry. The bicyclo[1.1.1]pentan-1-amine is present in important bioactive molecules, for example fluoroquinolone antibacterial agents,[7] Hsp90 inhibitors,[8] tropomyosin-related kinase inhibitors[9] and JNK pathway inhibitors[10] (Figure 1.1).

---

7 (a) Barbachyn, M. R.; Hutchinson, D. K.; Toops, D. S.; Reid, R. J.; Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W. Bioorg. Med. Chem. Lett. 1993, 3, 671. (b) Gammill, R. B.; Bisaha, S. N.; Timko, J. M.; Judge, T. M.; Barbachyn, M. R.; Kim, K. S. Preparation of Antibacterial Quinolone and Naphthyridone Compounds. (Upjohn Co., USA) WO 90/06307, June 14, 1990.

8 Kung, P.-P.; Meng, J. J. Preparation of Pyrazolylethoxyphenyl-pyrroloyrimidinamines as Heat Shock Protein-90 (HSP-90) Inhibitors (Pfizer Inc., USA); WO 2010/018481, Feb 18, 2010.

9 Andrews, M. D.; Bagal, S. K.; Gibson, K. R.; Omoto, K.; Ryckmans, T.; Skerratt, S. E.; Stupple, P. A. Pyrrolo[2,3-d]pyrimidine derivatives as inhibitors of tropomyosinrelated kinases and their preparation and use in the treatment of pain. WO 2012137089 (Pfizer Limited, UK) Mar 22, 2012.

10 Bennett, B. L.; Elsner, J.; Erdman, P.; Hilgraf, R.; Lebrun, L. A.; McCarrick, M.; Moghaddam, M. F.; Nagy, M. A.; Norris, S.; Paisner, D. A.; Sloss, M.; Romanow, W. J.; Satoh, Y.; Tikhe, J.; Yoon, W. H.; Delgrado, M. Preparation of substituted diaminocarboxamide and diaminocarbonitrile pyrimidines as JNK pathway inhibitors. (Signal Pharmaceuticals LLC, USA) WO 2012145569, April 20, 2012.

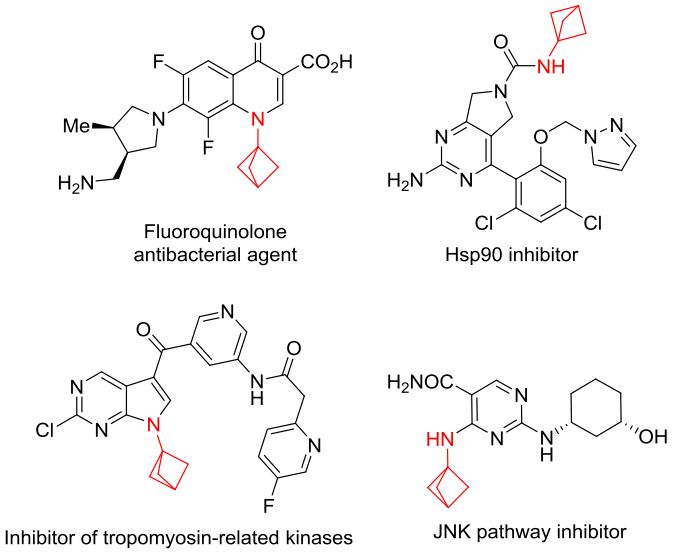
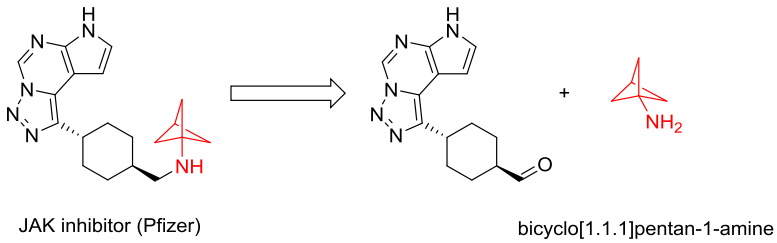


Figure 1.1

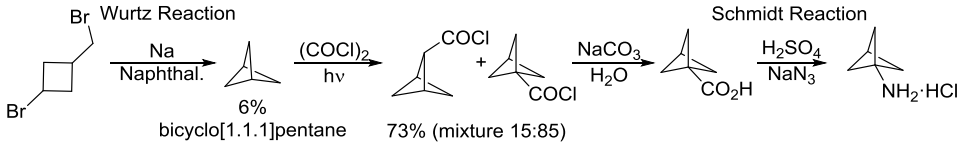
Although the documented importance of strained and bicyclic systems for drug development, hard access to these elusive motifs has driven to abandonment ongoing programs in drug research. Such is the case of the JAK (Janus kinase) inhibitor depicted on (Scheme 1.2) developed by Pfizer Laboratories,[11] a promising oncology clinical candidate that could not follow on to the next development steps due to problems to procure scalable quantities of bicyclo[1.1.1]pentan-1-amine.

[11] Hayashi, K.; Watanabe, T.; Toyama, K.; Kamon, J.; Minami, M.; Uni, M.; Nasu, M. Preparation of tricyclic heterocyclic compounds as JAK inhibitors. (Nissan Chemical Industries, Ltd., Japan) WO 2013024895, Aug 10, 2012.



Scheme 1.2

The first synthesis of bicyclo[1.1.1]pentan-1-amine was reported in 1970, a four step sequence beginning with a Wurtz reaction using sodium/naphthalene, followed by photochemical reaction with oxalyl chloride delivering a mixture of 1- and 2-bicyclo[1.1.1]pentanecarbonyl chlorides, subsequent basic hydrolysis and final Schmidt reaction which involves the use of sulfuric acid and azides (Scheme 1.3). The process gives access to the bicyclo[1.1.1]pentan-1-amine as an hydrochloride salt in low overall yield, and as a mixture of regioisomers. Additionally, some steps require the use of toxic and explosive chemicals and waste (hydrazoic acid).[12]

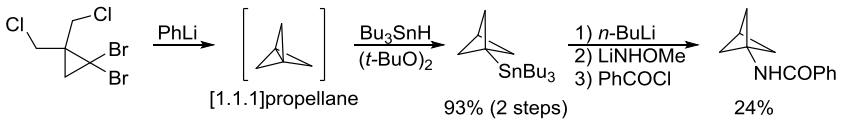


Scheme 1.3

The discovery of a more efficient methodology to synthesize [1.1.1]propellane,[13] from 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane in preparative scale, motivated the development of more attractive approaches to bicyclo[1.1.1]pentan-1-amine. The use of phenyllithium on the dibromocyclopropane produces the doble lithiation-alkylation yielding the [1.1.1]propellane, which was isolated from the salts by codistilation as an ethereal solution. The tricyclic compound had to be treated with tributyltin hydride and *tert*-

[12] Wiberg, K. B.; Williams, V. Z. *J. Org. Chem.* **1970**, *35*, 369.
[13] Semmler, K.; Szeimies, G.; Belzner, J. *J. Am. Chem. Soc.* **1985**, *107*, 6410.

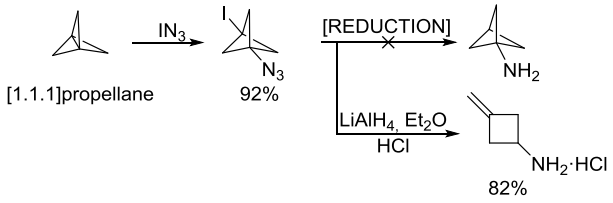
butyl peroxide to get the stable and chromatographically isolable 1-(tri-*n*-butylstannyl)bicycle[1.1.1]pentane selectively in almost quantitative yield using excess of [1.1.1]propellane. The organostannane compound was converted to the amine by treating with *n*-butyllithium and lithium methoxylamide in 24% yield (Scheme 1.4).[14] This three-step process significantly improves the obtention of the bibyclic scaffold: the dibromocyclopropane is a readily available material, in moderate overall yield and complete regioselectivity. Nevertheless drawbacks arise from the need to use considerable excess of [1.1.1]propellane (5 eq.), the toxicity of the organostannanes and the final product had to be isolated as a benzamide.



Scheme 1.4

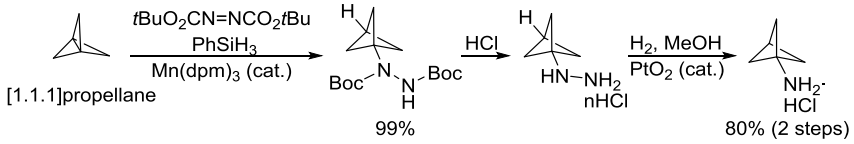
In this direction, the α,β-addition of pseudohalogen to olefins[15] motivated the use of this strategy for the funtionalization of the central bond of [1.1.1]propellane. This approach would refine bicyclo[1.1.1]pentan-1-amine since it avoids intermediates like 1-bicyclo[1.1.1]pentyl carboxylic acid and oganostannane. Iodine azide was used in addition reaction with [1.1.1]propellane rendering 3-iodobicyclo[1.1.1]pentyl azide, that after reduction would have provided the desired bicyclo[1.1.1]pentan-1-amine but, after a number of attempts employing different reducing conditions, 3-methylenecyclobutan-1-amine was obtained instead (Scheme 1.5).[16]

[14] Toops, D. S.; Barbachyn, M. R. *J. Org. Chem.* **1993**, *58*, 6505.
[15] Fowler, F. W.; Hassner, Al; Levy, L. A.*J. Am. Chem. Soc.* **1967**, *89*, 2077.
[16] Hossain, M. T.; Timberlake, J. W.; *J. Org. Chem.* **2001**, *66*, 4409.



Scheme 1.5

Additional efforts were carried out to transform 3-iodobicyclo[1.1.1]pentyl azide into bicyclo[1.1.1]pentan-1-amine testing different reducing conditions. The use of a catalytic hydrogenation to achieve the target molecule was suggested, obtaining, in the best case, a 16% yield for the reduction step using hydrogen and palladium hydroxide in methanol (Scheme 1.7A). Given the unsuccessful results, a parallel synthetic route was designed, using a hydrohydrazination strategy on [1.1.1]propellane followed by hydrolysis and hydrogenation rendering bicyclo[1.1.1]pentan-1-amine hydrochloride in 62% overall yield from dibromo-2,2-bis(chloromethyl)cyclopropane (Scheme 1.6).[17]

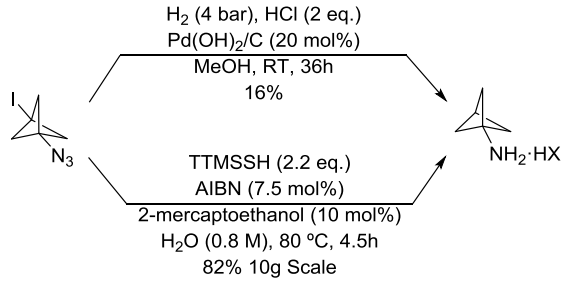


Scheme 1.6

Recently, another attempt to reduce 3-iodobicyclo[1.1.1]pentyl azide using radicalary reducing agents was reported. The reducing agent of choice was the bulky tris(trimethylsilyl)silane (TTMSS), which showed ability to reduce alkyl halides on top of alkyl azides and, in the presence of catalytic amounts of the radical initiator azobisisobutyronitrile (AIBN), that together with certain additives, solvent and temperature conditions, bicyclo[1.1.1]pentan-1-amine was obtained in overall yield 42% from the

[17] Bunker, K. D.; Sach, N. W.; Huang, Q.; Richardson, P. F. *Org. Lett.* **2011**, *13*, 4746.

dibromocyclopropane as a hydroiodide salt. This strategy allows the synthesis of the target ammonium iodide salt in 10 g scale (Scheme 1.7B).[18]



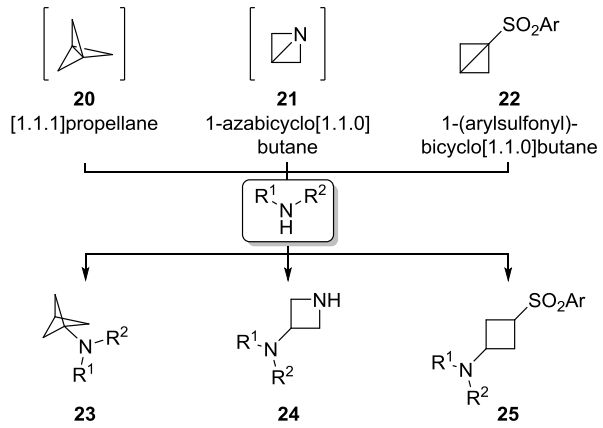
Scheme 1.7

Although considerable advances have been made in the synthesis of the pharmaceutically interesting however elusive bicyclo[1.1.1]pentan-1-amine, a scalable and applicable synthesis is already needed avoiding, if possible, the use of intermediates, to address a challenge synthetic community has been facing for the last five decades.

[18] Goh, Y. L.; Tam, R. K. W.; Bernardo, P. H.; Cheong, C. B.; Johannes, C. W.; William, A. D.; Adsool, V. A. *Org. Lett*. **2014**, *16*, 1884.

2. SPECIFIC OBJECTIVES AND WORK PLAN

In view of the ardent need of pharmaceutical industry to discover easily applicable and scalable methods to develop new strategies to access undiscovered drug candidates, and in particular the interest on the development on efficient synthetic routes to bicyclo[1.1.1]pentan-1-amine scaffold, the goal of this project is to **use the ring-strain content in bicyclic small rings as the driving force to achieve unprecedented synthetic transformations**. In this context, [1.1.1]propellane (**20**), 1-azabicyclo[1.1.0]butane (**21**) and 1-(arylsulfonyl)bicyclo[1.1.0]butane (**22**), substrates with noteworthy propensity to experience central bond cleavage, will be exposed to nucleophiles, such as amines, to access unconventional functionalized amines: [1.1.1]pentan-1-amines (**23**), azetidin-3-amines (**24**) and cyclobutanamines (**25**) (Scheme 2.1).

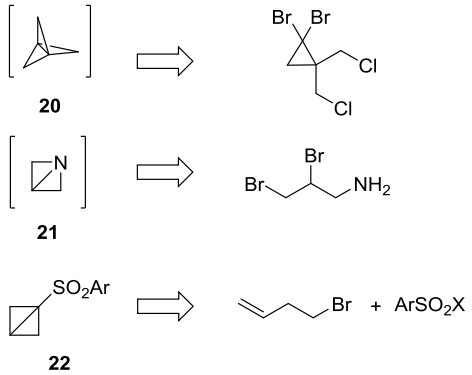


Scheme 2.1

To accomplish the aim of the project, the subsequent work plan was followed:

1. *Synthesis of the precursors*: Practical protocols required to be designed to synthesize the bicyclic precursors. The strategies followed to access the required bicyclic precursors

20, **21** and **22** will be described suing, when possible, commercially available reagents and conventional protocols (Scheme 2.2).



Scheme 2.2

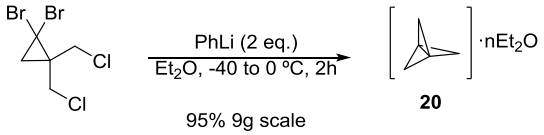
2. *Optimization and Scope of the reaction*: A concise evaluation of the most influential reaction conditions will be addressed, like the nature of the nucleophile, solvent or temperature, to achieve satisfactory levels of yield on the transformations under study. Finally, the applicability of the ring-strain release approach will be extended to the use of diversely substituted amine nucleophiles including derivatization of biologically active compounds, in order to prove the applicability and usefulness of the method.

3. RESULTS AND DISCUSSION

The most *ad rem* results in order to accomplish the aforementioned aim are displayed on the following paragraphs.

3.1 Synthesis of the precursors

As outlined on the work plan, the first issue to address was to develop suitable methodologies for the synthesis of the bicyclic precursors **20**, **21** and **22**. First, synthesis of [1.1.1]propellane (**20**) was performed adapting literature procedures for the purpose.[17,19] Commercially available 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane was dissolved in diethyl ether at -40 ºC and two equivalents of phenyl lithium where added preventing temperature rise. The reaction was left to reach 0 ºC and stirred for 2 h. Then, the [1.1.1]propellane (**20**) product was distilled and obtained as solution in diethyl ether,[20] whose concentration and reaction yield was determined by quantitative NMR experiment (Scheme 3.1).



Scheme 3.1

1-Azabicyclo[1.1.0]butane (**21**) was also synthesized following modified literature procedures in a two step sequence starting from allylamine which undergoes bromination of the alkene upon addition of bromine. The product is isolated by filtration as hydrobromide

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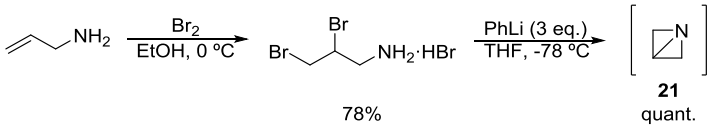
19 (a) Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. *J. Am. Chem. Soc.* **2001**, *123*, 3484. For the first reported synthesis , see: (b) Wiberg, J. B.; Walker, F. H. *J. Am. Chem. Soc.* **1982**, *104*, 5239.

20 [1.1.1]propellane **20** in ether solution was stable for weeks at -20 ºC.

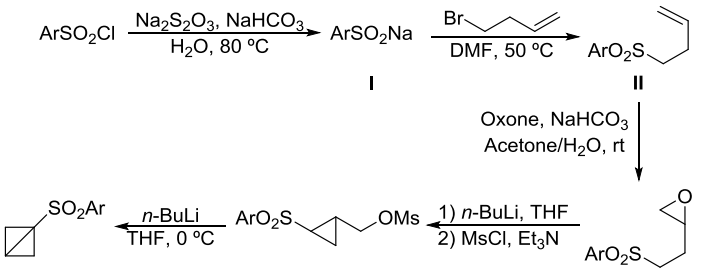
salt. The bicyclic azabutane is generated *in situ* by addition of phenyllithium (3 eq.) in tetrahydrofuran at -78 ºC (Scheme 3.2).[21]



Scheme 3.2

1-(Arylsulfonyl)bicyclo[1.1.0]butane's (**22**) synthesis was developed based on bibliographic precedents adapted to the purpose.[22] Arylsulfonyl chloride was reduced to the sodium sulfinate salt using sodium thiosulfate and sodium bicarbonate. The sulfinate salt acted as nucleophile in S_N2 type reaction with 4-bromobut-1-ene. The alkene on the product was treated with *in situ* generated dimethyldioxirane to render the epoxide, which was intramolecularly opened using basic conditions. The alcohol was converted to methylsulfonate and final intramolecular S_N2, triggered by *n*-BuLi, yielded the desired 1-(arylsulfonyl)bicyclo[1.1.0]butanes **22a-f** in the yields outlined on Table 3.1.

Table 3.1: Synthesis of 1-(arylsulfonyl)bicyclo[1.1.0]butanes **22a-f**.



Product (Ar)	I[a]	II[a]	III[a]	IV[a]	22[a]	Overall (g)[b]
22a (4-$MeOC_6H_4$)	99	60	99	81	37	17 (2.63)
22b (4-MeC_6H_4)	99	70	99	88	41	25 (3.10)

[21] Hayashi, K.; Kumagai, T.; Nagao, Y. *Heterocycles*, **2000**, *53*, 447.
[22] Gaoni, Y. *J. Org. Chem.* **1982**, *47*, 2564,

22c (C_6H_5)	c.a.[c]	82	92	94	40	28 (10.0)
22d (4-ClC_6H_4)	68	67	90	61	47	12 (1.23)
22e (4-$CF_3C_6H_4$)	73	96	90	95	41	25 (0.81)
22f (3,5-$(F)_2C_6H_4$)	99	73	90	74	31	15 (1.50)
22g (4-$NO_2C_6H_4$)	93	71	89	-[d]	-	-

[a] Isolated product yield after flash column chromatography purification. [b] Overall yield and isolated product mass (grams) in brackets. [c] c.a.: Commercially available. [d] Decomposition of the starting material.

A crystal structure was established for 1-(phenylsulfonyl)bicyclo[1.1.0]butane (**22c**) by X-ray analysis (Figure 3.1)

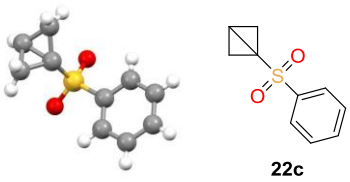
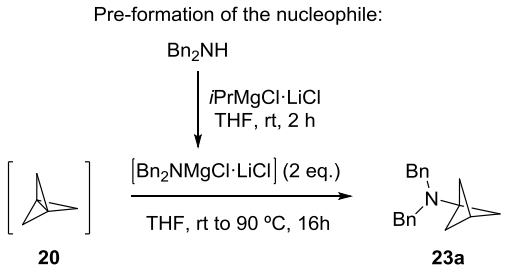


Figure 3.1

The electronically diverse 1-(arylsulfonyl)bicyclo[1.1.0]butanes **22a-f** were synthesized in order to provide starting materials for the amination reaction optimization, as described on following paragraphs.

3.2 Optimization of the reaction conditions

Inspired by the bibliographic evidences of the tendency of [1.1.1]propellane (**20**) to react with strong nucleophiles like *t*-BuLi,[23] the reactivity of **20** with metal amides was explored and, after extensive reaction condition exploration, it was concluded that amidemagnesium chloride·lithium chloride, directed the clean formation of product **23** in satisfactory yield using two equivalents of nucleophile in THF at 90 ºC in a sealed tube for 16 h (Scheme 3.3). The magnesium amide was prepared upon treatment of dibenzylamine with *i*PrMgCl·LiCl in THF.



Scheme 3.3

The reaction between the dibenzylaminemagnesium chloride and [1.1.1]propellane (**20**) was performed in >100g scale obtaining product **23a** in 54% yield, demonstrating the scalability of the process. Afterwards, the deprotection of the benzyl groups under standard hydrogenation conditions was successfully accomplished rendering bicyclo[1.1.1]pentan-1-amine in 30g scale as hydrochloride salt (Scheme 3.4). Consequently, this method represents an easy and efficient way for the multi-gram scale synthesis of bicyclo[1.1.1]pentan-1-amine.[24]

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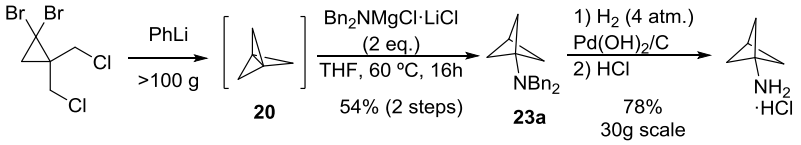
[23] (a) Della, E. W.; Taylor, D. K.; Tsanaktsidis, J. *Tetrahdron Lett*. **1990**, *31*, 5219. (b) Messner, M.; Kozhuskov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 1137.

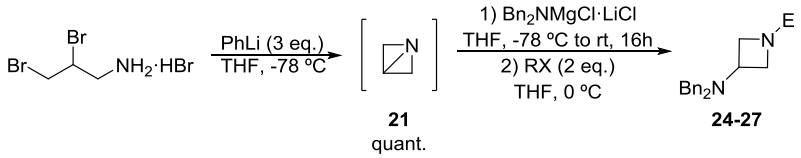
[24] Reactions performed in Pfizer industrial facilities by H. Zhu and J. Zhu.



Scheme 3.4

Taking advantage of the success of the method for the generation of an adequate amine nucleophiles for the ring-opening of [1.1.1]propellane (**20**), a similar strategy was adopted for the reaction with 1-azabicyclo[1.1.0]butane (**21**). The main challenge of this transformation lied on the stability and issues on the isolation of the products, especially due to the high polarity of *N*-H azetidines (**24**). These problems were circumvented by adding an external electrophile (RX) after completion of the reaction to render *N*-protected azetidines (**25**-**27**) which were easily isolated in acceptable yields as stable compounds (Table 3.2). Due to the excellent result provided, di-*tert*-butyl dicarbonate was chosen as the best electrophile to perform this transformation.

Table 3.2: Optimization for isolation of azetidine.[a]



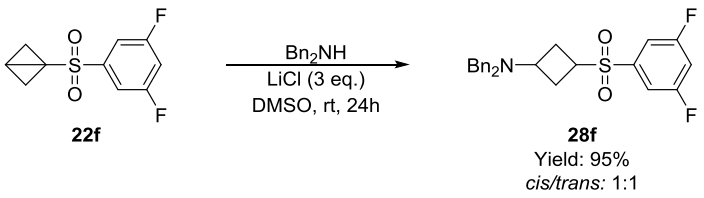
Entry	Product	RX	Yield (%)[b]
1	**24**	NH_4Cl	53
2	**25**	EtO_2CCl	82
3	**26**	Boc_2O	93
4	**27**	TsCl	78

[a] Reactions performed in 1.0 mmol scale of the hydrobromide salt. [b] Isolated product yield after flash column chromatography purification.

A different approach was necessary to achieve the reaction on 1-(arylsulfonyl)bicyclo[1.1.0]butanes (**22**), since the reaction using magnesium amide as

nucleophile led to the formation of polymeric products. The exploration of softer nucleophiles concluded finding that secondary amines were sufficient to perform the Michael-type reaction on the activated bicyclo[1.1.0]butanes under certain conditions, which included the use of polar solvents and high temperatures. The challenge of this transformation lied on finding a suitable activating group to enable the product formation in satisfactory yield and avoiding the use of elevated temperatures, problems that were solved surveying 1-(arylsulfonyl)bicyclo[1.1.0]butanes (**22a-f**) with different electronic properties.

It was found that a relation could be established between the yield of the reaction and the electronic effect of the aryl substituent on the sulfone. Electron-rich and neutral aromatic substituents showed poor conversions, while electron-deficient aryl groups are superior, observing the following trend: the stronger the electron-withdrawing groups present on the aromatic, the better the yield of the reaction is. Alternatively, addition of lithium chloride to the reaction mixture renders the product in almost quantitative yield. Therefore, the best sulfone for this transformation was **22f** in combination with lithium chloride as an additive (Scheme 3.5).[25]



Scheme 3.5

Due to the lack of stereocontrol on the reaction, the 1,3-disubstituted butane products (**28**) were formed as 1:1 isomeric mixtures, which was not an inconvenience since the aim was to introduce the cyclobutane scaffold and the sulfone needed to be removed for that purpose. The sulfone was efficiently detached after treatment with magnesium in

[25] Screening of reaction conditions was carried out by J. Wang.

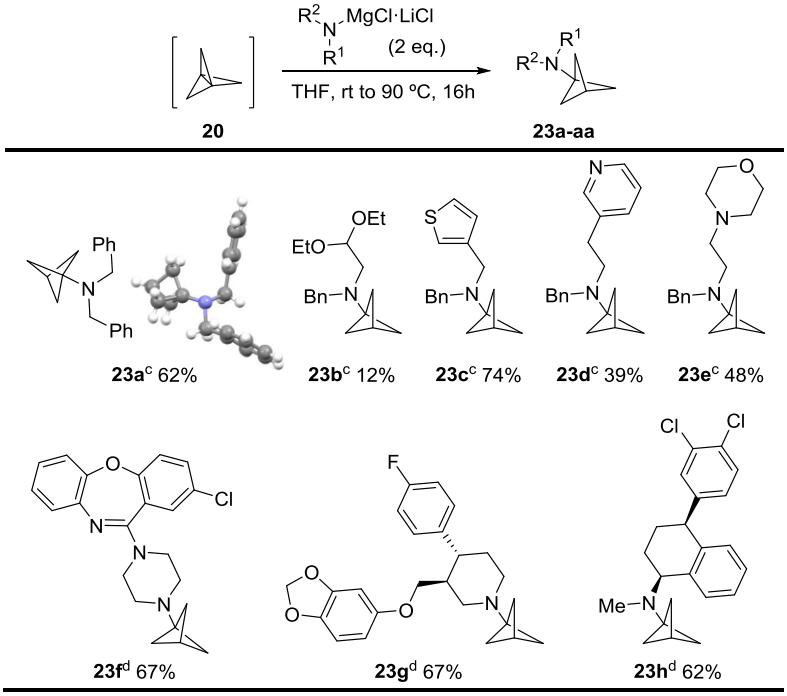
methanol in quantitative yield. This reaction was compatible with the previous Michael step in a one-pot procedure.

3.3 Scope of the reaction

Since satisfactory results were achieved for the transformations under study, it was decided to evaluate the scope of the presented reactions with a range of secondary amines to access libraries of synthetically elusive structures with strained rings attached to amine functional groups.

The amination procedure of [1.1.1]propellane (**20**) using a wide variety of *in-situ* generated amidemagnesium chloride·lithium chloride was tested trying to proof the applicability of the reaction with as diverse as possible secondary amines (Table 3.3).

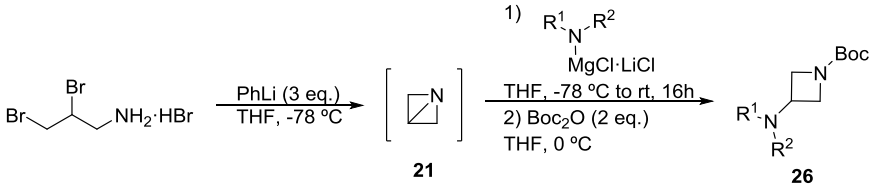
Table 3.3: Scope for the amination of [1.1.1]propellane **20**.[a]



[a] Reactions performed in 0.5 mmol scale of [1.1.1]propellane (**20**) and 2 eq. of the corresponding amidemagnesium chloride in THF. [b] Isolated product yield after flash column chromatography purification. [c] Compounds synthesized by the PhD candidate. [d] Compounds synthesised by J. M. Lopchuck.

The reaction performs satisfactorily with secondary amine substrates bearing miscellaneous functional groups, like acetals (**23b**), benzyl ethers, ketals (**23g**) and heteroaromatics (**23c-d**). Commercial drugs with a secondary amine present on their structure were also tested (**23f-h**) on the reaction confirming the potential of the method for the late-stage functionalization of complex bioactive compounds in order to access otherwise unattainable bioisosteres.[26] Crystal structure of compound **23a** could be measured after crystallization and X-ray diffraction analysis.

In analogous way, a range of secondary amines were subjected to reaction with 1-azabicyclo[1.1.0]butane (**21**) to render *N*-Boc protected azetidine products (**26**) (Scheme 3.6).[27]



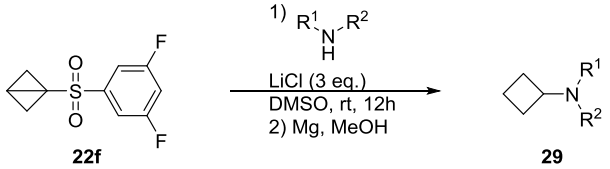
Scheme 3.6

Azetidine products were successfully formed using various secondary amines as precursors among which pharmaceutical agents were present. The yields were moderate although satisfactory since this strategy enabled the formation of *N*-protected or free azetidine substituted amines in a single synthetic step.[26]

[26] For the complete scope of the reaction see: Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science*, **2016**, *351*, 241.

[27] Compounds synthesized by J. M. Lopchuck and C.-M. Pan.

Finally the scope of the cyclobutylation was explored in a similar way using a range of free secondary amines as nucleophiles with the best performing 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (**22g**) under optimal reaction conditions. As previously mentioned, as the desulfonylation reaction was compatible with the Michael step, both processes were carried out in one-pot avoiding isolation steps (Scheme 3.7).[28]



Scheme 3.7

The reactions proceeded with moderate to excellent yield for the two step sequence rendering cyclobutane substituted amines. Some examples for the introduction of cyclobutyl functionality on biologically active compounds containing secondary amines were also successfully tested.[26]

In view of the findings collected in the accomplishment of the presented research work, it can be expected that the strain-release amination concept will be surely applied to a wider scope of nuchleophiles, strained rings, and will find application on other research areas.[29]

[28] Compounds synthesized by J. Wang.

[29] The strain-release procedure for 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (**22g**) has already found application on peptide labelling, see: Ref: 26

4. CONCLUSION

The results and observations attained during the realization of the presented research project led to the following conclusions:

An alternative route, characterized by its simplicity and efficiency, for the synthesis of bicyclo[1.1.1]pentan-1-amine from commercially available materials was described, which provides the pharmaceutically interesting product in 30g scale.

Effective and innovative methods have been presented for the synthesis of strained carbo-and heterocycles. The reactivity of the strained rings has been optimized in different approaches for each case: finding suitable nucleophiles for reaction with [1.1.1]propellane (**20**), achieving appropriate isolation procedures for the azetidines and designing the correct 1-(arylsulfonyl)bicyclo[1.1.0]butane (**22**) to render products satisfactorily.

Operative protocols have been established for any-stage introduction of small rings, such as bicycle[1.1.1]pentane, azetidine and cyclobutane, in secondary amines, giving access to traditionally elusive structural motives, including examples of functionalized drugs and other bioactive compounds.

Chapter 6

6

Final conclusions

1. CONCLUSIONS

The present work gathers a number of asymmetric cycloaddition reactions in which the common feature is the catalytic generation of the reactive intermediates employing for that purpose organocatalysis through different strategies. Experimental results collected during the accomplishment of this work lead to the following conclusions.

Nitrone ylides as 1,3-dipoles in [3+2] cycloaddition reaction through cooperative H-bonding/iminium ion activation. It has been demonstrated that regioselectivity change could be achieved for [3+2] cycloaddition of nitrones requiring, for this purpose, a careful design of the nitrone and a complex catalytic system, involving the use of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea and triethylamine, that enabled the efficient formation of nitrone ylides, which took part in the organocatalyzed asymmetric [3+2] cycloaddition with α,β-unsaturated aldehydes under iminium ion activation promoted by a chiral diphenylprolinol derivative to deliver densely substituted *N*-hydroxypyrrolidines containing a quaternary stereocenter in high yields, good diastereoselectivity and excellent enantioselectivity. Adducts were subjected to various successful transformations to illustrate the diversity in reactivity that the *N*-hydroxypyrrolidine adducts provide.

Favoring trienamine activation through unconjugated dienals in [4+2] cycloaddition with nitroalkenes. The work verified that non-conjugated diunsaturated aldehydes could efficiently take part in trienamine catalyzed Diels-Alder reactions. It was observed that fully conjugated aldehydes did not react with nitroalkenes under the same reaction conditions in which the non-conjugated aldehyde did, confirming the hypothesis of the increased reactivity of dienals with disrupted conjugation over conjugated dienals in trienamine catalysis. Non-conjugated aldehyde (*E*)-5-phenylhexa-2,5-dienal has proven to be reactive in combination with a chiral diphenylprolinol derivative with electronically and structurally diverse nitroalkenes, in excellent yields and outstanding diastereo- and enantioselectivities in the formation of highly substituted cyclohexenes.

***N*-Heterocyclic carbene catalyzed generation of Donor-Acceptor cyclopropanes in [4+2] cycloaddition with Michael acceptors.** The work confirmed that the *umpolung* effect triggered by NHC catalysis on carbonyl compounds turned stable and inert Acceptor-Acceptor formylcyclopropanes into synthetically useful and versatile Donor-Acceptor cyclopropanes. D-A species underwent cyclopropane ring-opening, producing azolium enolate intermediates which were trapped in [4+2] cycloaddition reaction with alkylideneoxindoles, furnishing heteroaromatic polycyclic adducts as single diastereomer, with moderate to excellent yields and high enantioselectivities.

Strain-release amination, a project developed during a short stay in the research group of Prof. Phil S. Baran in The Scripps Research Institute. Scalable, efficient and straightforward route to bicyclo[1.1.1]pentan-1-amine was described. Innovative methods were presented for the synthesis of strained carbo-and heterocycles, such as, [1.1.1]propellane, 1-azabicyclo[1.1.0]butane and various 1-(arylsulfonyl)bicyclo[1.1.0]butanes. Operative protocols have been established for any-stage introduction of small rings, such as bicycle[1.1.1]pentane, azetidine and cyclobutane, in secondary amines, giving access to traditionally elusive structural motives, including examples of functionalized drugs and other bioactive compounds.

Chapter 7

7

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 25ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282 MHz for ^{19}F) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and and 125.7 MHz ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals[2] ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR; MeOH, 3.31 ppm for ^{1}H NMR, MeOD, 49.0 ppm for ^{13}C NMR); 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; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for nucleus assignement. Selective NOE, NOESY, COSY, HSQC experiments were adquired to confirm precise molecular conformation and to assist in convoluting complex multiplet signals.[3]

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100, a Perkin-Elmer 1600 and a Perkin-Elmer Spectrum BX apparatus, 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) on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI+ or ESI-) or on a Micromass GCT spectrometer using chemical ionization (CI).

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 was performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak *AD-H, AS-H, IA, IC, ID-3, IE-3* and *OD-H* columns (0.46 cm x 25 cm) were used; specific conditions are indicated for each case.

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

X-ray data collections were performed in an Agilent Supernova diffractometer equipped with Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250μm FWHM beam size). The sample was kept at 120 K with 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 140ºC, 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, *p*-anisaldehyde, phosphomolybdic acid, potasium permanganate or iodine dips.[6] For flash chromatography Silicycle 40-63, 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. *Purification of Laboratory Chemicals*, 7th ed., Elsevier: Oxford, 2012.

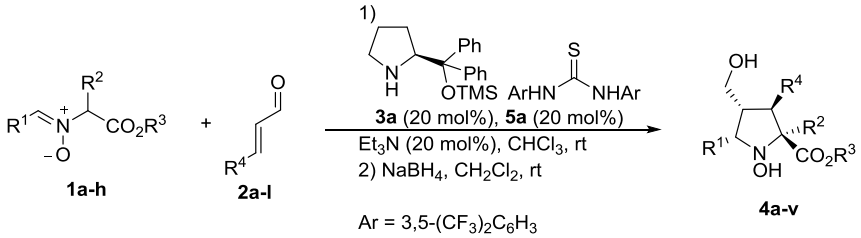
5 Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, 1975.

6 Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlin, 1969.

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

2. ORGANOCATALYTIC ENANTIOSELECTIVE [3+2] CYCLOADDITION OF NITRONE YLIDES

2.1 Synthesis of 1-hydroxypyrrolidine adducts 4a-v



General Procedure A for the Preparation of 1-Hydroxypyrrolidine Adducts **4a-r**, **4u**:

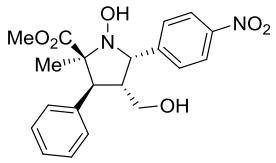
The corresponding nitrone **1a-d, 1g,** (0.20 mmol), 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea **5a** (0.04 mmol) and triethylamine (0.04 mmol) were added to a solution of (2*S*)-2-[diphenyl[(trimethilsilyl)oxy]methyl]pyrrolidine **3a** (0.04 mmol) and the corresponding α,β-unsaturated aldehyde **2a-l** (0.24 mmol) in dry chloroform (0.4 mL) in an screw capped vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature, until achievement of full conversion. The crude reaction mixture was concentrated and redissolved in dry dichloromethane (2 ml) and $NaBH_4$ (0.80 mmol) was added. The reaction was stirred at room temperature for 4 hours, and then 4 mL of water were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 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 (*n*-pentane/Et_2O 1:1 to 3:7) to afford pure alcohols **4a-r**, **4u.**

General Procedure B for the Preparation of 1-Hydroxypyrrolidine Adducts **4s**, **4t**, **4t'**, **4v**:

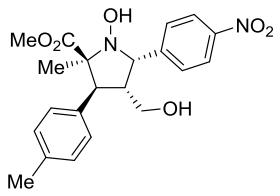
The corresponding nitrone **1e-f**, **1h** (0.40 mmol), 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea **5a** (0.20 mmol) and triethylamine (0.20 mmol) were added to a solution of (2*S*)-2-[diphenyl[(trimethilsilyl)oxy]methyl]pyrrolidine **3a** (0.04 mmol) and the corresponding α,β-unsaturated aldehyde **2a**, **2c** (0.20 mmol) in dry chloroform (0.4 mL) in an screw capped vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature, until achievement of full conversion. The crude reaction mixture was concentrated and redissolved in dry dichloromethane (2 ml) and

$NaBH_4$ (0.80 mmol) was added. The reaction was stirred at room temperature for 4 hours, and then 4 mL of water were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 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 (*n*-pentane/Et_2O 1:1 to 3:7) to afford pure alcohols **4s**, **4t**, **4t'**, **4v**.

The racemic standards, prepared in order to find HPLC separation conditions were synthesized according to aforementioned procedures using racemic mixture of enantiomers of catalyst **3a** (*R* and *S*).

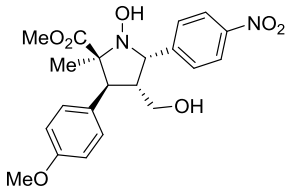


Methyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (4a). Following the general procedure **A**, **4a** (71 mg, 0.18 mmol) was isolated as a pale yellow oil, starting from aldehyde **2a** (32 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 92%. d.r. 5:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.29* (s, 3H, CH_3C), 1.57 (s, 3H, CH_3C), 3.06 (d, *J* = 10.9 Hz, 1H, C_3-H), 3.10-3.26 (m, 2H, CH_2), 3.40 (tdd, *J* = 11.0, 6.8, 4.5 Hz, 1H, C_4-H), 3.53 (s, 3H, CH_3O), 3.74* (s, 3H, CH_3O), 4.63* (d, *J* = 10.5 Hz, 1H, C_5-H), 4.95 (s, 1H, NOH), 5.01* (s, 1H, NOH), 5.36 (d, *J* = 10.9 Hz, 1H, C_5-H), 7.19-7.37 (m, 5H, C_{arom}-H), 7.72 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.77* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.24 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, MeOD) (* denotes minor diastereomer resonances) δ 10.6* (CH_3C), 22.4 (CH_3C), 45.3* (C_4), 46.5 (C_4), 51.7 (C_3), 52.7* (C_3), 52.8 (CH_3O), 55.5 (CH_3O), 62.6 (CH_2OH), 62.8* (CH_2OH), 68.8* (C_5), 71.0 (C_5), 74.9*(C_2), 76.5 (C_2), 123.7 (C_{arom}-H), 128.4* (C_{arom}-H), 128.6 (C_{arom}-H), 129.3* (C_{arom}-H), 129.4 (C_{arom}-H), 129.7 (C_{arom}-H), 130.0* (C_{arom}-H), 131.1* (C_{arom}-H), 131.1 (C_{arom}-H), 138.2 (**C**$_{arom}$-C_3), 138.6* (**C**$_{arom}$-C_3), 148.3 (C_{arom}-NO_2), 148.4* (C_{arom}-NO_2), 149.1* (**C**$_{arom}$-C_5), 150.3 (**C**$_{arom}$-C_5), 173.8 (CO), 176.1* (CO). IR ($CHCl_3$): 3476 (O-H st), 2951 (C-H st), 1725 (C=O st), 1597 (C=C st), 1518 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{22}N_2NaO_6]^+$: 409.1370 (M^++Na); found: 409.1369. The ee (98%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=38.76 min, τ_2=108.00 min.



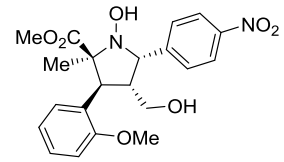
Methyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (4b). Following the general procedure **A**, **4b** (67 mg, 0.17 mmol) was isolated as a pale yellow oil, starting from aldehyde **2b** (39 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 84%. d.r. 6:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.28* (s, 3H, CH_3C). 1.55 (s, 3H, CH_3C), 2.33 (s, 3H, C_{arom}-CH_3), 2.34* (s, *J* = 1.8 Hz, 3H, C_{arom}-CH_3), 3.01 (d, *J* = 11.0 Hz, 1H, C_3-H), 3.04-3.24 (m, 2H, CH_2), 3.29-3.44 (m, 1H, C_4-H), 3.55 (s, 3H, CH_3O), 3.73* (s, 3H, CH_3O), 4.60* (d, *J* = 10.4 Hz, 1H,

C_5-H), 5.01 (s, 1H, NOH), 5.07* (s, 1H, NOH), 5.33 (d, *J* = 11.0 Hz, 1H, C_5-H), 7.10-7.16 (m, 4H, C_{arom}-H), 7.70 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.75* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.22 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* denotes minor diastereomer resonances) δ 11.0* (CH_3C), 21.2 (CH_3C), 21.8 (C_{arom}-CH_3), 45.2* (C_4), 45.8 (C_4), 50.5* (C_3), 51.7 (C_3), 52.4* (CH_3O), 53.8 (CH_3O), 62.2 (CH_2), 62.4* (CH_2), 67.9* (C_5), 70.1 (C_5), 73.3* (C_2), 75.3 (C_2), 123.5 (C_{arom}-H), 123.5* (C_{arom}-H), 128.4 (C_{arom}-H), 129.1* (C_{arom}-H), 129.3* (C_{arom}-H), 129.4 (C_{arom}-H), 129.5 (C_{arom}-H), 133.0 (**C**$_{arom}$-CH_3), 133.7* (**C**$_{arom}$-CH_3), 137.6* (**C**$_{arom}$-C_3), 137.9 (**C**$_{arom}$-C_3), 147.0* (C_{arom}-NO_2), 147.4 (C_{arom}-NO_2), 148.3 (**C**$_{arom}$-C_5), 172.3 (CO), 174.5* (CO). IR ($CHCl_3$): 3468 (O-H st), 2951 (C-H st), 1724 (C=O st), 1597 (C=C st), 1517 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{24}N_2NaO_6]^+$: 423.1527 (M^++Na); found: 423.1533. The ee (99%) was determined by HPLC using a *Chiralpak OD-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=20.88 min, τ_2=57.05 min.

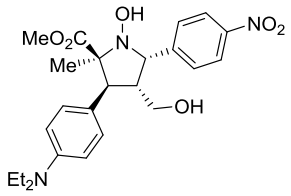


Methyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4c). Following the general procedure **A**, **4c** (71 mg, 0.17 mmol) was isolated as a yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 85%. d.r. 6:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.28* (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C), 2.99 (d, *J* = 11.0 Hz, 1H, C_3-H), 3.06-3.25 (m, 2H, CH_2), 3.34 (tdd, *J* = 11.1, 6.9, 4.5 Hz, 1H, C_4-H), 3.55 (s, 3H, CH_3O_2C), 3.73* (s, 3H, CH_3O_2C), 3.79 (s, 3H, C_{arom}-OCH_3), 3.80* (s, 3H, C_{arom}-OCH_3), 4.60* (d, *J* = 10.5 Hz, 1H, C_5-H), 4.97 (s, 1H, NOH), 5.03* (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C_5-H), 6.85 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.16 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.70 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.75* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.22 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* denotes minor diastereomer resonances) δ 10.9* (CH_3C), 21.8 (CH_3C), 45.3* (C_4), 45.9 (C_4), 50.1* (C_3), 51.7 (C_3), 52.4* (**C**H_3O_2C), 53.4 (**C**H_3O_2C), 55.4 (C_{arom}-O**C**H_3), 62.2 (CH_2), 62.4* (CH_2), 67.8* (C_5), 70.0 (C_5), 73.2* (C_2), 75.3 (C_2), 113.9* (C_{arom}-H), 114.7 (C_{arom}-H), 123.5 (C_{arom}-H), 123.6* (C_{arom}-H), 128.0 (**C**$_{arom}$-C_3), 129.4 (C_{arom}-H), 129.5* (C_{arom}-H), 129.6* (C_{arom}-H), 130.3 (C_{arom}-H), 131.1* (C_{arom}-H), 131.1 (C_{arom}-H), 138.2 (C_{arom}), 138.6* (C_{arom}), 147.0* (**C**$_{arom}$-NO_2), 147.4 (**C**$_{arom}$-NO_2), 147.5* (**C**$_{arom}$-C_5), 148.3 (**C**$_{arom}$-C_5), 159.2* (**C**$_{arom}$-OCH_3), 159.4 (**C**$_{arom}$-OCH_3), 172.3 (CO), 174.5* (CO). IR ($CHCl_3$): 3462 (O-H st), 2951 (C-H st), 1724

(C=O st), 1612 (C=C st), 1514 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{24}N_2NaO_7]^+$: 439.1476 (M^++Na); found: 439.1476. The ee (>99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=53.17 min, τ_2=112.73 min.

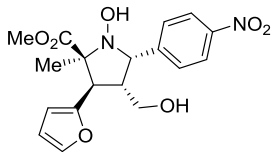


Methyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(2-methoxyphenyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4d). Following the general procedure **A**, **4d** (60 mg, 0.14 mmol) was isolated as a yellow oil, starting from aldehyde **2d** (40 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 72%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.55 (s, 3H, CH_3C), 1.57* (s, 3H, CH_3C), 3.09-3.18 (m, 2H, CH_2), 3.24-3.37 (m, 1H, C_4-H), 3.52 (s, 3H, CH_3O_2C), 3.76* (s, 3H, CH_3O_2C), 3.79* (s, 3H, C_{arom}-OCH_3), 3.84 (s, 3H, C_{arom}-OCH_3), 4.96* (s, 1H, NOH), 5.02 (s, 1H, NOH), 5.35 (d, *J* = 10.7 Hz, 1H, C_5-H), 6.86-6.98 (m, 2H, C_{arom}-H), 7.19-7.31 (m, 2H, C_{arom}-H), 7.73 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.24 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (CH_3C), 44.9 (C_4), 45.9 (C_3), 51.6 (**C**H_3O_2C), 55.6 (C_{arom}-O**C**H_3), 62.5 (CH_2), 70.2 (C_5), 75.5 (C_2), 110.9, 120.7, 123.5 (C_{arom}-H), 124.8 (**C**$_{arom}$-C_3), 127.9 (C_{arom}-H), 128.8 (C_{arom}-H), 129.5 (C_{arom}-H), 147.4 (C_{arom}-NO_2), 148.3 (**C**$_{arom}$-C_5), 158.1 (**C**$_{arom}$-OCH_3), 172.8 (CO). IR ($CHCl_3$): 3476 (O-H st), 2948 (C-H st), 1725 (C=O st), 1598 (C=C st), 1518 (NO_2 st), 1345 (NO_2 st), 1246 (C-O st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{24}N_2NaO_7]^+$: 439.1476 (M^++Na); found: 439.1467. The ee (94%) was determined by HPLC using a *Chiralpak OD-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=21.49 min, τ_2=82.02 min. $[\alpha]_D^{20}$: +22.9 (*c*=1.0, $CHCl_3$).



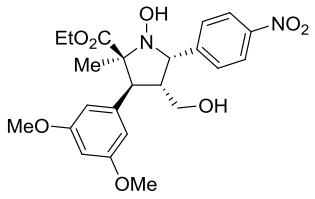
Methyl (2S,3S,4R,5S)-3-(4-(diethylamino)phenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4e). Following the general procedure **A**, **4e** (68 mg, 0.15 mmol) was isolated as a yellow oil, starting from aldehyde **2e** (49 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 74%. d.r. 2:1. ^{1}H NMR

(300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.07-1.22 (m, 6H, C**H**$_3$CH$_2$), 1.29* (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C), 2.89 (d, *J* = 11.0 Hz, 1H, C_3-H), 2.93-3.26 (m, 2H, C**H**$_2$OH), 3.26-3.40 (m, 5H, C_4-H, CH_3C**H**$_2$), 3.58 (s, 3H, CH_3O), 3.73* (s, 3H, CH_3O), 4.58* (d, *J* = 10.5 Hz, 1H, C_5-H), 4.97 (s, 1H, NOH), 5.04* (s, 1H, NOH), 5.30 (d, *J* = 11.0 Hz, 1H, C_5-H), 6.55-6.64 (m, 2H, C_{arom}-H), 6.99-7.09 (m, 2H, C_{arom}-H), 7.70 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.75* (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.22 (d, *J* = 8.7 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* denotes minor diastereomer resonances) δ 10.9* (CH_3C), 12.7 (**C**H$_3$CH$_2$), 21.8 (CH_3C), 44.4 (CH_3**C**H$_2$), 45.3* (C_4), 45.9 (C_4), 50.2* (CH_3O), 51.7 (C_3), 52.3* (C_3), 53.6 (CH_3O), 62.5 (CH_2OH), 62.6* (CH_2OH), 67.9* (C_5), 70.1 (C_5), 73.5*(C_2), 75.3 (C_2), 111.5* (C_{arom}-H), 111.8 (C_{arom}-H), 121.9 (**C**$_{arom}$-C_3), 122.5* (**C**$_{arom}$-C_3), 123.4 (C_{arom}-H), 123.5* (C_{arom}-H), 129.4 (C_{arom}-H), 129.4 (C_{arom}-H), 129.5* (C_{arom}-H), 130.1* (C_{arom}-H), 147.3* (C_{arom}-NO_2), 147.4 (C_{arom}-NO_2), 147.4* (**C**$_{arom}$-C_5), 147.7 (**C**$_{arom}$-C_5), 148.5 (C_{arom}-NCH_2), 172.5 (CO), 174.8* (CO). IR ($CHCl_3$): 3541 (N^+-H st), 3314 (O-H st), 2978 (C-H st), 1715 (C=O st), 1613 (C=C st), 1518 (NO_2 st), 1342 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{24}H_{32}N_3O_6]^+$: 458.2286 (M^++H); found: 458.2296. The ee (>99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=36.56 min, τ_2=100.12 min.

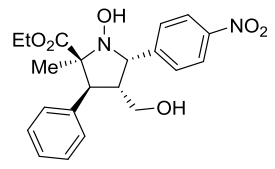


Methyl (2S,3R,4R,5S)-3-(furan-2-yl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4f). Following the general procedure **A**, **4f** (70 mg, 0.19 mmol) was isolated as a colorless oil, starting from aldehyde **2f** (29 mg, 0.24 mmol) and nitrone **1a** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 93%. d.r. 9:1. ^{1}H NMR (300 MHz, MeOD) (* indicates minor diastereomer resonances) δ 1.26* (s, 3H, CH_3C), 1.64 (s, 3H, CH_3C), 3.07-3.23 (m, 3H, C_3-H, C**H**$_2$OH), 3.27-3.39 (m, 1H, C_4-H), 3.65 (s, 3H, CH_3O), 3.84* (s, 3H, CH_3O), 4.57* (d, *J* = 10.2 Hz, 1H, C_5-H), 5.23 (d, *J* = 10.6 Hz, 1H, C_5-H), 6.18-6.31 (m, 1H, $C_{Heteroarom}$-H), 6.38 (dd, *J* = 3.3, 1.9 Hz, 1H, $C_{Heteroarom}$-H), 7.44 (dd, *J* = 1.9, 0.9 Hz, 1H, $C_{Heteroarom}$-H), 7.77 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.23 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, MeOD) (* denotes minor diastereomer resonances) δ 22.8 (CH_3C), 44.3* (CH_3**C**H$_2$), 45.6 (C_4), 46.7* (C_3), 48.9 (C_3), 51.9 (CH_3O), 52.9* (CH_3O), 62.5 (CH_2OH), 62.8* (CH_2OH), 69.5* (C_5), 70.8 (C_5), 74.1* (C_2), 75.1 (C_2), 108.2 ($C_{Heteroarom}$-H), 108.6* ($C_{Heteroarom}$-H), 111.2* ($C_{Heteroarom}$-H), 111.3 ($C_{Heteroarom}$-H), 123.7 (C_{arom}-H), 123.8* (C_{arom}-H), 131.0 (C_{arom}-H), 143.2* ($C_{Heteroarom}$-H), 143.3 ($C_{Heteroarom}$-H), 148.4 (C_{arom}-NO_2), 148.5* (C_{arom}-NO_2), 148.7

(**C**$_{arom}$-C$_5$), 149.9 (**C**$_{arom}$-C$_5$), 153.4 (**C**$_{arom}$-C$_3$), 153.8* (**C**$_{arom}$-C$_3$), 173.8 (CO), 175.8* (CO). IR ($CHCl_3$): 3347 (O-H st), 2951 (C-H st), 1725 (C=O st), 1598 (C=C st), 1517 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{18}H_{20}N_2NaO7]^+$: 399.1163 (M^++Na); found: 399.1164. The ee (>99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=39.64 min, τ_2=90.27 min. $[\alpha]_D^{20}$: +10.1 (*c*=1.0, MeOH).

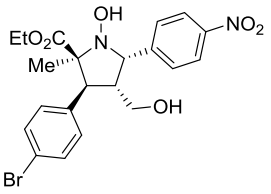


Ethyl (2S,3S,4R,5S)-3-(3,5-dimethoxyphenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4g). Following the general procedure **A**, **4g** (77 mg, 0.17 mmol) was isolated as a yellow oil, starting from aldehyde **2g** (46 mg, 0.24 mmol) and nitrone **1b** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 83%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.09 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.20* (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.58 (s, 3H, CH$_3$C), 2.98 (d, *J* = 10.9 Hz, 1H, C$_3$-H), 3.07-3.26 (m, 2H, C**H**$_2$OH), 3.35 (tdd, *J* = 11.0, 6.8, 4.5 Hz, 1H, C$_4$-H), 3.78 (s, 6H, CH$_3$O), 3.95-4.14 (m, 2H, CH$_3$C**H**$_2$), 4.93 (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C$_5$-H), 6.34-6.54 (m, 3H, C$_{arom}$-H), 7.70 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 8.23 (d, *J* = 8.8 Hz, 2H, C$_{arom}$-H). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 22.1 (**C**H$_3$C), 45.7 (C$_4$), 54.2 (C$_3$), 55.5 (CH$_3$O), 61.0 (CH$_3$**C**H$_2$), 62.2 (CH$_2$OH), 70.1 (C$_5$), 75.0 (C$_2$), 99.5 (C$_{arom}$-H), 107.0 (C$_{arom}$-H), 108.4* (C$_{arom}$-H), 123.5 (C$_{arom}$-H), 123.9* (C$_{arom}$-H), 128.7* (C$_{arom}$-H), 129.4 (C$_{arom}$-H), 138.6 (**C**$_{arom}$-C$_3$), 147.4 (C$_{arom}$-NO$_2$), 148.2 (**C**$_{arom}$-C$_5$), 171.8 (CO). IR ($CHCl_3$): 3458 (O-H st), 2984 (C-H st), 1720 (C=O st), 1597 (C=C st), 1518 (NO_2 st), 1346 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{23}H_{28}N_2NaO_8]^+$: 483.1738 (M^++Na); found: 483.1719. The ee (>99%) was determined by HPLC using a *Chiralpak OD-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=42.39 min, τ_2=62.72 min. $[\alpha]_D^{20}$: +13.4 (*c*=1.0, $CHCl_3$).

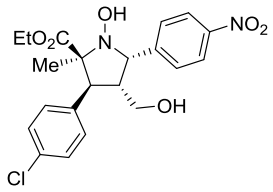


Ethyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (4h). Following the general procedure **A**, **4h** (67 mg, 0.17 mmol) was isolated as a pale yellow oil, starting from aldehyde **2a** (32 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%),

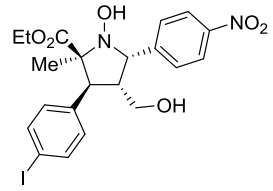
thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 84%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH$_2$), 1.57 (s, 3H, CH_3C), 3.06 (d, *J* = 10.8 Hz, 1H, C_3-H), 3.10-3.25 (m, 2H, C**H**$_2$OH), 3.39 (tdd *J* = 10.9, 6.8, 4.5 Hz, 1H, C_4-H), 3.87-4.09 (m, 2H, CH_3C**H**$_2$), 5.00 (s, 1H, NOH), 5.36 (d, *J* = 10.9 Hz, 1H, C_5-H), 7.19-7.39 (m, 5H, C_{arom}-H), 7.71 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.23 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (**C**H$_3$CH$_2$), 22.0 (CH_3C), 45.6 (C_4), 54.0 (C_3), 60.9 (CH_3**C**H$_2$), 62.2 (CH_2OH), 70.1 (C_5), 75.1 (C_2), 123.5 (C_{arom}-H), 128.0 (C_{arom}-H), 128.6 (C_{arom}-H), 128.7 (C_{arom}-H), 129.4 (C_{arom}-H), 136.2 (**C**$_{arom}$-C_3), 147.4 (C_{arom}-NO_2), 148.2 (**C**$_{arom}$-C_5), 171.8 (CO). IR ($CHCl_3$): 3468 (O-H st), 2980 (C-H st), 1716 (C=O st), 1602 (C=C st), 1518 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{24}N_2NaO_6]^+$: 423.1527 (M^++Na); found: 423.1530.The ee (99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=35.88 min, τ_2=144.72 min. $[\alpha]_D^{20}$: +17.9 (*c*=1.0, $CHCl_3$).



Ethyl (2S,3S,4R,5S)-3-(4-bromophenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4i). Following the general procedure **A**, **4i** (78 mg, 0.16 mmol) was isolated as a colorless oil, starting from aldehyde **2h** (52 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 81%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.07 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.43* (s, 3H, CH_3C), 1.55 (s, 3H, CH_3C), 3.04 (d, *J* = 10.8 Hz, 1H, C_3-H), 3.06-3.23 (m, 2H, C**H**$_2$OH), 3.33 (tdd, *J* = 11.0, 6.6, 4.5 Hz, 1H, C_4-H), 3.87-4.15 (m, 2H, CH_3C**H**$_2$), 5.01 (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C_5-H), 5.43* (s, 1H, NOH), 7.04* (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.15 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.45 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.69 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.10* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.22 (d, *J* = 9.0 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 21.9 (CH_3C), 45.5 (C_4), 53.4 (C_3), 61.1 (CH_3**C**H$_2$), 62.0 (CH_2OH), 69.9 (C_5), 74.9 (C_2), 122.0 (C_{arom}-Br), 123.5, 129.4, 130.4, 131.8 (C_{arom}-H), 135.5 (**C**$_{arom}$-C_3), 147.4 (C_{arom}-NO_2), 148.0 (**C**$_{arom}$-C_5), 171.6 (CO). IR ($CHCl_3$): 3465 (O-H st), 2984 (C-H st), 1717 (C=O st), 1598 (C=C st), 1518 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}BrN_2NaO_6]^+$: 501.0534 ($M^+$+Na); found: 501.0632. The ee (99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=45.59 min, τ_2=105.29 min. $[\alpha]_D^{20}$: +24.7 (*c*=1.0, $CHCl_3$).

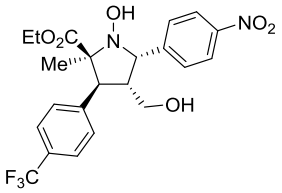


Ethyl (2S,3S,4R,5S)-3-(4-chlorophenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4j). Following the general procedure **A**, **4j** (82 mg, 0.19 mmol) was isolated as a colorless oil, starting from aldehyde **2i** (42 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 94%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.07 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.56 (s, 3H, CH_3C), 3.06 (d, *J* = 10.8 Hz, 1H, C_3-H), 3.09-3.24 (m, 2H, C**H**$_2$OH), 3.34 (tdd, *J* = 10.8, 6.7, 4.6 Hz, 1H, C_4-H), 3.88-4.13 (m, 2H, CH$_3$C**H**$_2$), 4.94 (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C_5-H), 7.21 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.30 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.70 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.23 (d, *J* = 8.7 Hz, 2H, C_{arom}-H).^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 21.9 (CH$_3$C), 45.6 (C_4), 53.3 (C_3), 61.1 (CH$_3$**C**H$_2$), 62.0 (CH$_2$OH), 69.9 (C_5), 75.0 (C_2), 123.6 (C_{arom}-H), 128.9 (C_{arom}-H), 129.4 (C_{arom}-H), 130.0 (C_{arom}-H), 133.9 (C_{arom}-Cl), 134.9 (**C**$_{arom}$-C_3), 147.5 (C_{arom}-NO_2), 148.0 (**C**$_{arom}$-C_5), 171.6 (CO). IR ($CHCl_3$): 3447 (O-H st), 2980 (C-H st), 1715 (C=O st), 1598 (C=C st), 1518 (NO_2 st), 1346 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{21}H_{23}ClN_2NaO_6$]$^+$: 457.1142 (M^++Na); found: 457.1111. The ee (98%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=42.62 min, τ_2=107.87 min. $[\alpha]_D^{20}$: +28.1 (*c*=1.0, $CHCl_3$).

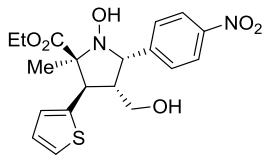


Ethyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-iodophenyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4k). Following the general procedure **A**, **4k** (91 mg, 0.17 mmol) was isolated as a pale yellow oil, starting from aldehyde **2j** (62 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 86%. d.r. 5:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.59 (s, 3H, CH_3C), 3.03 (d, *J* = 10.7 Hz, 1H, C_3-H), 3.07-3.24 (m, 2H, C**H**$_2$OH), 3.33 (tdd, *J* = 10.9, 6.6, 4.6 Hz, 1H, C_4-H), 3.89-4.14 (m, 2H, CH$_3$C**H**$_2$), 4.96 (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C_5-H), 7.02 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.65 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 7.70 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.23 (d, *J* = 8.8 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 21.9 (**C**H$_3$C), 45.4 (C_4), 53.5 (C_3), 60.9 (CH$_3$**C**H$_2$),

62.2 (CH_2OH), 69.9 (C_5), 75.0 (C_2), 93.5 (C_{arom}-I), 123.6 (C_{arom}-H), 129.4 (C_{arom}-H), 130.6 (C_{arom}-H), 136.2 (**C_{arom}**-C_3), 137.9 (C_{arom}-H), 147.5 (C_{arom}-NO_2), 148.0 (**C_{arom}**-C_5), 171.6 (CO). IR ($CHCl_3$): 3465 (O-H st), 2984 (C-H st), 1716 (C=O st), 1598 (C=C st), 1517 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}IN_2NaO_6]^+$: 549.0493 ($M^+$+Na); found: 549.0503. The ee (99%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=50.81 min, τ_2=109.43 min. $[\alpha]_D^{20}$: +52.6 (*c*=1.0, $CHCl_3$).

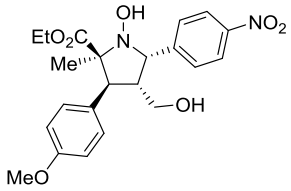


Ethyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (4l). Following the general procedure **A**, **4l** (80 mg, 0.17 mmol) was isolated as a pale yellow oil, starting from aldehyde **2k** (80 mg, 0.40 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 85%. d.r. 4:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.59 (s, 3H, CH_3C), 3.09-3.26 (m, 3H, C_3-H, CH_2OH), 3.34-3.47 (m, 1H, C_4-H), 3.88-4.12 (m, 2H, CH_3C**H**$_2$), 4.95 (s, 1H, NOH), 5.37 (d, *J* = 10.8 Hz, 1H, C_5-H), 7.41 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.59 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 7.71 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.25 (d, *J* = 8.9 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9 (**C**H$_3$CH$_2$), 21.9 (**C**H$_3$C), 45.4 (C_4), 53.7 (C_3), 61.1 (CH_3**C**H$_2$), 62.0 (CH_2OH), 69.9 (C_5), 75.0 (C_2), 123.6 (C_{arom}-H), 124.0* (C_{arom}-H), 125.6 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, **C_{arom}**H-F), 128.8 (q, $^1J_{C\text{-}F}$ = 272.4 Hz, C-F), 128.8* (C_{arom}-H), 129.1 (C_{arom}-H), 129.4 (C_{arom}-H), 130.3 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, F-**C_{arom}**), 140.8 (**C_{arom}**-C_3), 147.5 (C_{arom}-NO_2), 147.8 (**C_{arom}**-C_5), 171.5 (CO). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.5. IR ($CHCl_3$): 3476 (O-H st), 2987 (C-H st), 1716 (C=O st), 1601 (C=C st), 1518 (NO_2 st), 1346 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{22}H_{23}F_3N_2NaO_6]^+$: 491.1400 ($M^+$+Na); found: 491.1387. The ee (99%) was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=40.57 min, τ_2=91.21 min. $[\alpha]_D^{20}$: +23.6 (*c*=1.0, $CHCl_3$).



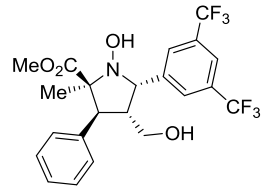
Ethyl (2S,3R,4R,5S)-1-hydroxy-4-(hydroxymethyl)-2-methyl-5-(4-nitrophenyl)-3-(thiophen-2-yl)pyrrolidine-2-carboxylate (4m). Following the general procedure **A**, **4m** (63 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from

aldehyde **2l** (33 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 78%. d.r. 7:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.64 (s, 3H, CH$_3$C), 3.13-3.44 (m, 4H, C_3-H, C_4-H, C**H**$_2$OH), 4.02-4.16 (m, 2H, CH$_3$C**H**$_2$), 4.89 (s, 1H, NOH), 5.29 (d, *J* = 7.2 Hz, 1H, C_5-H), 6.94-7.02 (m, 2H, $C_{Hetarom}$-H), 7.18-7.24 (m, 1H, $C_{Hetarom}$-H), 7.70 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.24 (d, *J* = 8.7 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 22.0 (**C**H$_3$C), 47.9 (C_4), 48.8 (C_3), 61.2 (CH$_3$**C**H$_2$), 61.7 (CH$_2$OH), 70.0 (C_5), 75.0 (C_2), 123.6 (C_{arom}-H), 124.9 ($C_{Heteroarom}$-H), 126.3 ($C_{Heteroarom}$-H), 127.1 ($C_{Heteroarom}$-H), 129.4 (C_{arom}-H), 129.4 (C_{arom}-H), 139.6 ($C_{Heteroarom}$-C_3), 147.5 (C_{arom}-NO_2), 148.0 (**C**$_{arom}$-C_5), 171.5 (CO). IR ($CHCl_3$): 3458 (O-H st), 2984 (C-H st), 1718 (C=O st), 1598 (C=C st), 1518 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{19}H_{22}N_2NaO_6S]^+$: 429.1019 ($M^+$+Na); found: 429.1091. The ee (>99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=43.05 min, τ_2=94.58 min. $[\alpha]_D^{20}$: +61.8 (*c*=0.7, $CHCl_3$).

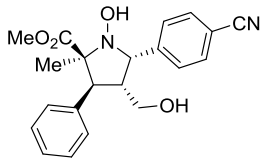


Ethyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methyl-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4n). Following the general procedure **A**, **4n** (71 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1b** (53 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 48h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 82%. d.r. 5:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.07 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.17* (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.53* (s, 3H, CH$_3$C), 1.55 (s, 3H, CH$_3$C), 3.00 (d, *J* = 10.9 Hz, 1H, C_3-H), 3.06-3.24 (m, 2H, C**H**$_2$OH), 3.34 (tdd, *J* = 11.0, 6.8, 4.5 Hz, 1H, C_4-H), 3.48* (d, *J* = 10.8 Hz, 1H, C_3-H), 3.79 (s, 3H, CH$_3$O), 3.91-4.14 (m, 2H, CH$_3$C**H**$_2$), 4.95 (s, 1H, NOH), 5.33 (d, *J* = 10.9 Hz, 1H, C_5-H), 6.85 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.18 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.53* (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.71 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 8.23 (d, *J* = 8.7 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 14.1 (**C**H$_3$CH$_2$), 21.9 (**C**H$_3$C), 45.8 (C_4), 53.4 (C_3), 55.4 (CH$_3$O), 60.9 (CH$_3$**C**H$_2$), 62.2 (CH$_2$OH), 70.1 (C_5), 75.1 (C_2), 114.1 (C_{arom}-H), 123.5 (C_{arom}-H), 128.1 (**C**$_{arom}$-C_3), 129.4 (C_{arom}-H), 129.7 (C_{arom}-H), 147.4 (C_{arom}-NO_2), 148.3 (**C**$_{arom}$-C_5), 159.4 (C_{arom}-O), 171.9 (CO). IR ($CHCl_3$): 3458 (O-H st), 2987 (C-H st), 1718 (C=O st),

1598 (C=C st), 1514 (NO_2 st), 1345 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{22}H_{26}N_2NaO_7]^+$: 453.1632 (M^++Na); found: 453.1613. The ee (98%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=54.85 min, τ_2=149.61 min. $[\alpha]_D^{20}$: +19.25 (*c*=1.0, $CHCl_3$).

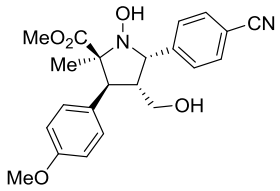


Methyl (2S,3S,4R,5S)-5-(3,5-bis(trifluoromethyl)phenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-3-phenylpyrrolidine-2-carboxylate (4o). Following the general procedure **A**, **4o** (76 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2a** (32 mg, 0.24 mmol) and nitrone **1c** (69 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 120h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 80%. d.r. 9:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.58 (s, 3H, CH_3C), 3.04-3.14 (m, 2H, C_3-H, C**H**$_a$H$_b$), 3.18 (dd, 1H, *J* = 11.1, 4.6 Hz, CH$_a$**H**$_b$), 3.30-3.43 (m, 1H, C_4-H), 3.54 (s, 3H, CH_3O), 3.75* (s, 3H, CH_3O), 4.94 (s, 1H, NOH), 5.40 (d, 1H, *J* = 10.9 Hz, C_5-H), 7.27-7.38 (m, 5H, C_{arom}-H), 7.81 (s, 1H, C_{arom}-H), 7.95-8.03 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7 (CH_3C), 45.3 (C_4), 51.7 (CH_3O), 54.0 (C_3), 62.0 (CH_2OH), 70.1 (C_5), 75.5 (C_2), 121.5 (C_{arom}-H), 125.4 (C-F), 128.2 (C_{arom}-H), 128.6 (C_{arom}-H), 128.8 (C_{arom}-H), 129.0 (C_{arom}-H), 131.2 (C_{arom}-CF_3), 131.6 (C_{arom}-CF_3), 136.3 (**C**$_{arom}$-C_3), 142.9 (**C**$_{arom}$-C_5), 172.0 (CO). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.6. HRMS: Calculated for $[C_{22}H_{21}F_6NNaO_4]^+$: 500.1267 ($M^+$+Na); found: 500.1263. The ee (98%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 0.9 mL/min; τ_1=26.69 min, τ_2=43.80 min. $[\alpha]_D^{20}$: +15.6 (*c*=0.7, $CHCl_3$).

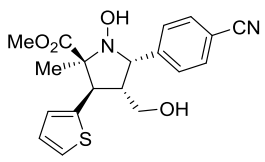


Methyl (2S,3S,4R,5S)-5-(4-cyanophenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-3-phenylpyrrolidine-2-carboxylate (4p). Following the general procedure **A**, **4p** (60 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2a** (32 mg, 0.24 mmol) and nitrone **1d** (46 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 96h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 82%. d.r. 9:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 1.54 (s, 3H, CH_3C), 3.03 (d, 1H, *J* = 10.9 Hz, C_3-H), 3.12 (dd, 1H, *J* = 11.4, 6.8 Hz, C**H**$_a$H$_b$), 3.17 (dd, 1H, *J* = 11.5, 4.7 Hz, CH$_a$**H**$_b$), 3.35 (tdd, *J* = 11.0, 6.8, 4.5 Hz, 1H, C_4-H), 3.50 (s, 3H,

CH_3O), 3.72* (s, 3H, CH_3O), 4.56*(d, 1H, J = 10.5 Hz, C_5-H), 4.86 (s, 1H, NOH), 4.98* (s, 1H, NOH), 5.28 (d, 1H, J = 11.0 Hz, C_5-H), 7.19-7.33 (m, 5H, C_6H_5), 7.62-7.71 (m, 4H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (CH_3C), 45.7 (C_4), 51.7 (CH_3O), 54.1 (C_3), 62.2 (CH_2OH), 70.3 (C_5), 75.4 (C_2), 111.4 (**C**$_{arom}$-CN), 119.0 (CN), 128.2 (C_{arom}-H), 128.6 (C_{arom}-H), 128.8 (C_{arom}-H), 129.4 (C_{arom}-H), 132.2 (C_{arom}-H), 136.3 (**C**$_{arom}$-C_3), 145.9 (**C**$_{arom}$-C_5), 172.2 (CO). HRMS: Calculated for $[C_{21}H_{22}N_2NaO_4]^+$: 389.1472 (M^++Na); found: 389.1464. The ee (96%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=27.10 min, τ_2=61.60 min. $[\alpha]_D^{20}$: +25.6 (*c*=0.2, $CHCl_3$).

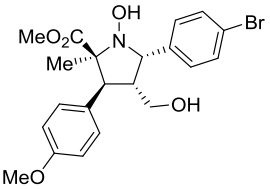


Methyl (2S,3S,4R,5S)-5-(4-cyanophenyl)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (4q). Following the general procedure **A**, **4q** (67 mg, 0.17 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1d** (46 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 96h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 84%. d.r. 9:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H, CH_3C), 2.16 (s, 1H, CH_2O**H**), 2.98 (d, 1H, J = 11.0 Hz, C_3-H), 3.06-3.21 (m, 2H, CH_2), 3.32 (tdd, J = 11.1, 6.8, 4.5 Hz, 1H, C_4-H), 3.55 (s, 3H, CH_3O_2C), 3.79 (s, 3H, C_{arom}-OCH_3), 4.94 (s, 1H, NOH), 5.27 (d, 1H, J = 10.9 Hz, C_5-H), 6.75-6.92 (m, 2H, C_{arom}-H), 7.05-7.21 (m, 2H, C_{arom}-H), 7.61-7.75 (m, 4H, C_{arom}-H). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 21.8 (CH_3C), 45.9 (C_4), 51.7 (**C**H_3O_2C), 53.5 (C_3), 55.4 (C_{arom}-O**C**H_3), 62.3 (CH_2OH), 70.2 (C_5), 75.3 (C_2), 111.3 (**C**$_{arom}$-CN), 114.2 (C_{arom}-H), 119.0 (CN), 128.1 (**C**$_{arom}$-C_3), 129.4 (C_{arom}-H), 129.6 (C_{arom}-H), 132.2 (C_{arom}-H), 146.2 (**C**$_{arom}$-C_5), 159.4 (**C**$_{arom}$-OCH_3), 172.3 (CO). HRMS: Calculated for $[C_{22}H_{22}N_2NaO_5]^+$: 4191567 (M^++Na); found: 419.1571. The ee (96%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=36.78 min, τ_2=56.78 min. $[\alpha]_D^{20}$: +33.3 (*c*=0.2, $CHCl_3$).

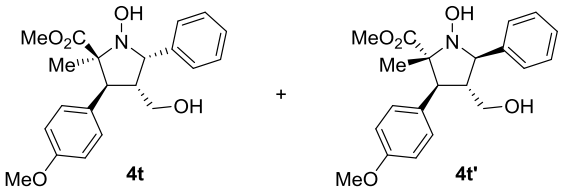


Methyl (2S,3R,4R,5S)-5-(4-cyanophenyl)-1-hydroxy-4-(hydroxymethyl)-2-methyl-3-(thiophen-2-yl)pyrrolidine-2-carboxylate (4r). Following the general procedure **A**, **4r** (61 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2l** (33 mg, 0.24 mmol) and nitrone **1d** (46 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg,

0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 96h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 82%. d.r. 10:1. ^{1}H NMR (300 MHz, MeOD) δ 1.57 (s, 3H, CH_3C), 3.05-3.13 (m, 1H, C**H**$_a$H$_b$OH), 3.14-3.21 (m, 1H, CH$_a$**H**$_b$OH), 3.29-3.36 (m, 2H, C_3-H, C_4-H), 3.65 (s, 3H, CH_3O), 5.11-5.23 (m, 1H, C_5-H), 6.94-7.06 (m, 2H, $C_{Hetarom}$-H), 7.30 (dd, *J* = 4.8, 1.6 Hz, 1H, $C_{Hetarom}$-H), 7.66-7.77 (m, 4H, C_{arom}-H). ^{13}C NMR (75.5 MHz, MeOD) δ 22.4 (CH_3), 49.2 (C_4), 50.5 (C_3), 51.9 (CH_3O), 62.1 (CH_2OH), 71.3 (C_5), 76.2 (C_2), 111.4 (**C**$_{arom}$-CN), 120.1 (C≡N), 125.5 ($C_{Heteroarom}$-H), 127.3 ($C_{Heteroarom}$-H), 127.8 ($C_{Heteroarom}$-H), 131.2 (C_{arom}-H), 132.5 (C_{arom}-H), 141.6 ($C_{Heteroarom}$), 148.1(C_{arom}), 173.7 (CO). IR ($CHCl_3$): 3389 (O-H st), 3218 (O-H st), 3009 (C-H st), 2237 (C≡N st), 1716 (C=O st), 1609 (C=C st) cm^{-1}. HRMS: Calculated for $[C_{19}H_{20}N_2NaO_4S]^+$: 395.1036 ($M^+$+Na); found: 395.1037. The ee (99%) was determined by HPLC using a *Chiralpak OD-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=29.15 min, τ_2=43.29 min. $[\alpha]_D^{20}$: +14.2 (*c*=1.0, MeOH).

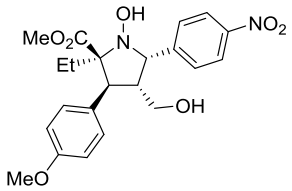


Methyl (2S,3S,4R,5S)-5-(4-bromophenyl)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (4s). Following the general procedure **B**, **4s** (46 mg, 0.10 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (34 mg, 0.20 mmol) and nitrone **1e** (114 mg, 0.40 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (100 mg, 0.20 mmol, 100 mol%) and Et_3N (28 μL, 0.20 mmol, 100 mol%) using $CHCl_3$ (0.4 mL) as solvent for 120h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 51%. d.r. 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH$_2$), 2.97 (d, *J* = 10.7 Hz, 1H, C_3-H, 3.10-3.36 (m, 3H, C_4-H, C**H**$_2$OH), 3.55 (s, 3H, CH_3O_2C), 3.79 (s, 3H, C_{arom}-OCH_3), 4.85 (s, 1H, NOH), 5.18 (d, 1H, *J* = 10.6 Hz, C_5-H), 6.81-6.88 (m, 2H, C_{arom}-H), 7.13-7.20 (m, 2H, C_{arom}-H), 7.39-7.44 (m, 2H, C_{arom}-H), 7.50-7.54 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (**C**H$_3$CH$_2$), 45.7 (C_4), 51.6 (**C**H$_3$O$_2$C), 53.3 (C_3), 55.4 (C_{arom}-O**C**H$_3$), 62.5 (CH_2OH), 69.8 (C_5), 75.2 (C_2), 114.1 (C_{arom}-H), 121.5 (C_{arom}-Br), 128.4 (**C**$_{arom}$-C_3), 129.6 (C_{arom}-H), 130.1 (**C**$_{arom}$-H), 131.8 (**C**$_{arom}$-H), 139.4 (**C**$_{arom}$-C_5), 159.4 (**C**$_{arom}$-OCH_3), 172.4 (CO). HRMS: Calculated for $[C_{21}H_{24}BrNNaO_5]^+$: 472.0736 (M^++Na); found: 472.0700. The ee (90%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=24.37 min, τ_2=35.53 min. $[\alpha]_D^{20}$: +27.0 (*c*=0.2, $CHCl_3$).

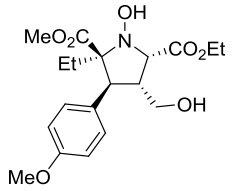


Methyl (2S,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methyl-5-phenylpyrrolidine-2-carboxylate (4t) and Methyl (2R,3S,4R,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-2-methyl-5-phenylpyrrolidine-2-carboxylate (4t'). Following the general procedure **B**, **4t** and **4t'** (34 mg, 0.09 mmol) were isolated as yellow oil, starting from aldehyde **2c** (33 mg, 0.20 mmol) and nitrone **1f** (83 mg, 0.40 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (100 mg, 0.20 mmol, 100 mol%) and Et_3N (28 μL, 0.20 mmol, 100 mol%) using $CHCl_3$ (0.4 mL) as solvent for 96h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 46%. d.r. 1:1. Data for **4t**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 3H, CH_3C), 2.99 (d, *J* = 10.7 Hz, 1H, C_3-H), 3.13-3.32 (m, 3H, CH_2, C_4-H), 3.55 (s, 3H, CH_3O_2C), 3.79 (s, 3H, C_{arom}-OCH_3), 4.89 (s, 1H, NOH), 5.22 (d, *J* = 10.5 Hz, 1H, C_5-H), 6.82-6.86 (m, 2H, C_{arom}-H), 7.14-7.21 (m, 2H, C_{arom}-H), 7.27-7.35 (m, 1H, C_{arom}-H), 7.37-7.43 (m, 2H, C_{arom}-H), 7.50-7.58 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, CDCl3) δ 22.0 (CH_3C), 45.9 (C_4), 51.6 (C_3), 53.1 (**C**H_3O_2C), 55.4 (C_{arom}-O**C**H_3), 62.5 (CH_2), 70.2 (C_5), 75.2 (C_2), 114.0 (C_{arom}-H), 127.8 (C_{arom}-H), 128.2 (C_{arom}-H), 128.5 (**C**$_{arom}$-C_3), 128.9 (C_{arom}-H), 129.7 (C_{arom}-H), 140.2 (C_{arom}-C_5), 159.3 (**C**$_{arom}$-OCH_3), 172.5 (CO). IR ($CHCl_3$): 3440 (O-H st), 2951 (C-H st), 1726 (C=O st), 1612 (C=C st), 1514 (NO_2 st), 1251 cm^{-1}. HRMS: Calculated for $[C_{21}H_{26}NO_5]^+$: 372.1811 (M^++H); found: 372.1816. The ee (94%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{1r}=14.46 min, τ_2=19.50 min. $[\alpha]_D^{20}$: +12.3 (*c*=1.0, $CHCl_3$). Data for **4t'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H, CH_3C), 2.34 (ddd, *J* = 9.5, 7.3, 4.5 Hz, 1H, C_3-H), 3.57-3.68 (m, 3H, CH_2, C_4-H), 3.80 (s, 3H, CH_3O_2C), 3.83 (s, 3H, C_{arom}-OCH_3), 4.45 (d, *J* = 9.6 Hz, 1H, C_5-H), 5.46 (s, 1H, NOH), 6.84-6.90 (m, 2H, C_{arom}-H), 7.21 (d, *J* = 2.0 Hz, 2H, C_{arom}-H), 7.31-7.35 (m, 1H, C_{arom}-H), 7.37-7.44 (m, 2H, C_{arom}-H), 7.52-7.58 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, CDCl3) δ 20.9 (CH_3C), 50.4 (C_4), 52.3 (C_3), 53.1 (**C**H_3O_2C), 55.4 (C_{arom}-O**C**H_3), 61.9 (CH_2), 70.0 (C_5), 72.6 (C_2), 113.9 (C_{arom}-H), 127.7 (C_{arom}-H), 127.9 (C_{arom}-H), 128.9 (C_{arom}-H), 130.8 (C_{arom}-H), 132.8 (**C**$_{arom}$-C_3), 141.2 (C_{arom}-C_5), 158.8 (**C**$_{arom}$-OCH_3), 176.3 (CO). IR ($CHCl_3$): 3440 (O-H st), 2951 (C-H st), 1726 (C=O st), 1612 (C=C st), 1514 (NO_2 st), 1251 cm^{-1}. HRMS: $[C_{21}H_{26}NO_5]^+$: 372.1811 (M^++H); found: 372.1816. The ee (92%)

was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_1=17.23 min, τ_2=24.04 min. $[\alpha]_D^{20}$: +34.5 (*c*=1.0, $CHCl_3$).



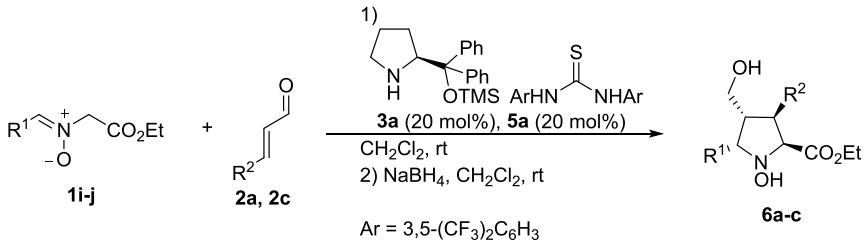
Methyl (2S,3S,4R,5S)-2-ethyl-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (4u). Following the general procedure **A**, **4u** (83 mg, 0.19 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1g** (43 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) and Et_3N (5.5 μL, 0.04 mmol, 20 mol%) using $CHCl_3$ (0.4 mL) as solvent for 72h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 96%. d.r. >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH$_2$), 1.85 (dq, *J* = 14.6, 7.3 Hz, 1H, CH$_3$C**H**$_a$H$_b$), 2.06 (dq, *J* = 14.6, 7.3 Hz, 1H, CH$_3$CH$_a$**H**$_b$), 2.06-3.37 (m, 4H, C_3-H, C_4-H, C**H**$_2$OH), 3.54 (s, 3H, CH$_3$O$_2$C), 3.80 (s, 3H, C_{arom}-OCH$_3$), 4.89 (s, 1H, NOH), 5.31 (d, *J* = 10.5 Hz, 1H, C_5-H), 6.81-6.90 (m, 2H, C_{arom}-H), 7.06-7.19 (m, 2H, C_{arom}-H), 7.68-7.73 (m, 2H, C_{arom}-H), 8.20-8.30 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.2 (**C**H$_3$CH$_2$), 25.1 (**C**H$_2$), 45.7 (C_4), 48.2 (C_3), 51.6 (**C**H$_3$O$_2$C), 55.4 (C_{arom}-O**C**H$_3$), 62.3 (CH$_2$OH), 70.2 (C_5), 77.7 (C_2), 114.2, 123.6 (C_{arom}-H), 128.4 (**C**$_{arom}$-C_3), 129.4, 129.5 (**C**$_{arom}$-H), 147.5 (**C**$_{arom}$-NO$_2$), 148.5 (**C**$_{arom}$-C_5), 159.3 (**C**$_{arom}$-OCH$_3$), 172.8 (CO). HRMS: Calculated for $[C_{22}H_{26}N_2NaO_7]^+$: 453.1632 (M^++Na); found: 453.1625. The ee (>99%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=33.43 min, τ_2=76.24 min. $[\alpha]_D^{20}$: +48.7 (*c*=0.6, $CHCl_3$).



5-Ethyl 2-methyl (2S,3S,4R,5S)-2-ethyl-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)pyrrolidine-2,5-dicarboxylate (4v). Following the general procedure **B**, **4v** (19 mg, 0.05 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (34 mg, 0.20 mmol) and nitrone **1h** (87 mg, 0.40 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%), thiourea **5a** (100 mg, 0.20 mmol, 100 mol%) and Et_3N (28 μL, 0.20 mmol, 100 mol%) using $CHCl_3$ (0.4 mL) as solvent for 144h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 25%. d.r. >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH$_2$C$_2$), 1.16 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$OOC), 1.85-2.07 (m, 2H, CH$_2$C$_2$), 2.91 (ddd, *J* = 8.6, 6.5, 4.6 Hz, 1H, C_4-H), 3.31 (t, *J* = 8.8 Hz, C**H**$_a$H$_b$OH), 3.69-3.93 (m, 8H, CH$_3$OC$_{arom}$, CH$_3$OOC,

C_2-H, $CH_a\mathbf{H_b}OH$), 4.08-4.27 (m, 3H, C_5-H CH_2CO), 6.10 (s, 1H, NOH), 6.77-6.89 (m, 2H, C_{arom}-H), 7.12-7.24 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.6 (**C**$H_3CH_2C_2$), 14.3 (**C**H_3CH_2CO), 25.4 (CH_3**C**H_2C_2), 47.3 (C_4), 53.4 (C_3), 53.8 (**C**H_3OOC), 55.4 (**C**H_3OC_{arom}), 61.3 (CH_2OH), 61.4 (CH_3**C**H_2CO), 67.0 (C_2), 75.0 (C_2), 114.3 (C_{arom}-H), 129.1 (C_{arom}-H), 132.3 (**C**$_{aroom}$-C_3), 158.9 (C_{aroom}-O), 171.2 (**C**$OOCH_2$), 174.6 (**C**$OOCH_3$). HRMS: Calculated for $[C_{19}H_{27}NNaO_8]^+$: 404.1685 (M^++Na); found: 404.1675. The ee (98%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_1=35.26 min, τ_2=45.21 min. $[\alpha]_D^{20}$: +5.3 (*c*=0.5, $CHCl_3$).

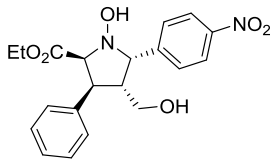
2.2 Synthesis of 1-hydroxypyrrolidine adducts 6a-c



General Procedure C for the Preparation of 1-Hydroxypyrroldine Adducts **6a-c**:

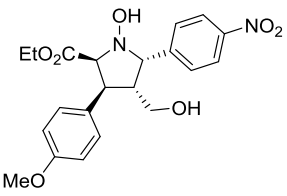
The corresponding nitrone **1i-j** (0.20 mmol) and 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea **5a** (0.04 mmol) were added to a solution of (2*S*)-2-[diphenyl[(trimethilsilyl)oxy]methyl]pyrrolidine **3a** (0.04 mmol) and the corresponding α,β-unsaturated aldehyde **2a, 2c** (0.20 mmol) in dry CH_2Cl_2 (0.4 mL) in an screw capped vial equipped with a magnetic stirring bar. The reaction mixture was stirred at room temperature for 16h. To the crude reaction mixture $NaBH_4$ (0.80 mmol) was added. The reaction was stirred at room temperature for 4 hours, and then 4 mL of water were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 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 (*n*-pentane/Et_2O 1:1 to 3:7) to afford pure alcohols **6a-c**.

The racemic standards, prepared in order to find HPLC separation conditions were synthesized according to aforementioned procedures using racemic mixture of enantiomers of catalyst **3a** (*R* and *S*).



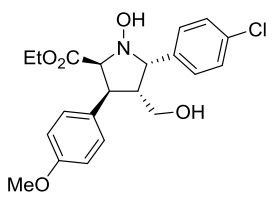
Ethyl (2R,3S,5S)-1-hydroxy-4-(hydroxymethyl)-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (6a). Following the general procedure **C**, **6a** (61 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2a** (32 mg, 0.24 mmol) and nitrone **1i** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%) and thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) using CH_2Cl_2 (0.4 mL) as solvent for 16h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 79%. d.r. 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.14* (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 3.19-3.33 (m, 2H, C**H**$_2$OH), 3.35-3.50 (m,

1H, C_4-H), 3.64 (dd, *J* = 10.1, 7.4 Hz, 1H, C_3-H), 3.81-4.01 (m, 2H, $CH_3C\mathbf{H_2}$), 4.12-4.27* (m, 2H, $CH_3C\mathbf{H_2}$), 4.47 (d, *J* = 7.4 Hz, 1H, C_2-H), 5.04 (s, 1H, NOH), 5.40 (d, *J* = 10.6 Hz, 1H, C_5-H), 5.50* (s, 1H, NOH), 7.28-7.41 (m, 5H, C_6H_5), 7.71 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.25 (d, *J* = 8.7 Hz, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 13.9 ($\mathbf{C}H_3CH_2$), 14.2* ($\mathbf{C}H_3CH_2$), 45.9 (C_4), 46.0 (C_3), 46.6* (C_4), 49.9* (C_3), 60.8 (CH_2OH), 60.9* (CH_2OH), 61.4* ($COO\mathbf{C}H_2$), 62.1 ($COO\mathbf{C}H_2$), 70.1 (C_5), 72.7 (C_2), 73.7* (C_2), 123.6 (C_{arom}-H), 123.9* (C_{arom}-H), 127.8* (C_{arom}-H), 127.9 (C_{arom}-H), 128.3 (C_{arom}-H), 128.8 (C_{arom}-H), 129.0* (C_{arom}-H), 129.0* (C_{arom}-H), 129.4 (C_{arom}-H), 136.5 ($\mathbf{C}_{arom}$-C_3), 147.4 (C_{arom}-NO_2), 147.5 ($\mathbf{C}_{arom}$-C_5), 147.4* ($\mathbf{C}_{arom}$-C_5), 148.6* (C_{arom}-NO_2), 170.5 (CO), 171.9* (CO). IR ($CHCl_3$): 3432 (O-H st), 2952 (C-H st), 1730 (C=O st), 1598 (C=C st), 1519 (NO_2 st), 1246 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{23}N_2O_6]^+$: 387.1556 (M^++H); found: 387.1561. The ee (96%) was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_1=9.22 min, τ_2=30.65 min.



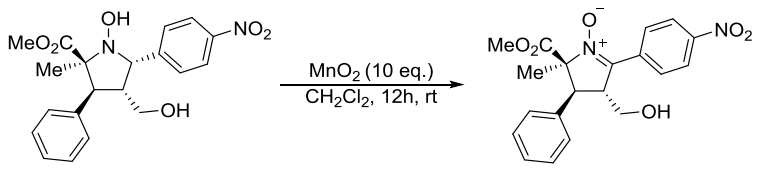
Ethyl (2R,3S,5S)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)pyrrolidine-2-carboxylate (6b). Following the general procedure **C**, **6b** (61 mg, 0.15 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1i** (50 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%) and thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) using CH_2Cl_2 (0.4 mL) as solvent for 16h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 74%. d.r. 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 0.96 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H_3}CH_2$), 1.15* (t, *J* = 7.1 Hz, 3H, $C\mathbf{H_3}CH_2$), 3.12-3.31 (m, 2H, $C\mathbf{H_2}OH$), 3.31-3.46* (m, 1H, C_4-H), 3.57 (dd, *J* = 10.2, 7.3 Hz, C_3-H), 3.82 (s, 1H, CH_3O), 3.87-4.03 (m, 2H, $CH_3C\mathbf{H_2}$), 4.06-4.25* (m, 2H, $CH_3C\mathbf{H_2}$), 4.17* (d, *J* = 9.7 Hz, 2H, C_2-H), 4.42 (d, *J* = 7.4 Hz, 1H, C_2-H), 5.05 (s, 1H, NOH), 5.37 (d, *J* = 10.5 Hz, 1H, C_5-H), 5.49* (s, 1H, NOH), 6.85 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.92* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.22(d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.29* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.65-7.73 (m, 2H, C_{arom}-H),8.18-8.27 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereomer resonances, d.r. 1:1) δ 14.0 ($\mathbf{C}H_3CH_2$), 14.2* ($\mathbf{C}H_3CH_2$), 45.3 (C_4), 45.6* (C_4), 46.3 (C_3), 50.0* (C_3), 55.5 (CH_3O), 60.8 (CH_2OH), 60.9* (CH_2OH), 61.3* ($COO\mathbf{C}H_2$), 62.1 ($COO\mathbf{C}H_2$), 70.1 (C_5), 72.6* (C_5), 72.8 (C_2), 73.9* (C_2), 114.2 (C_{arom}-H), 114.4* (C_{arom}-H), 123.6 (C_{arom}-H), 123.9* (C_{arom}-H), 128.4* (C_{arom}-H), 128.8* (C_{arom}-H), 129.0* ($\mathbf{C}_{arom}$-C_3), 129.4 (C_{arom}-H), 129.4 (C_{arom}-H), 130.0 ($\mathbf{C}_{arom}$-C_3), 147.5 (C_{arom}-NO_2), 147.7* ($\mathbf{C}_{arom}$-C_5), 148.6* (C_{arom}-NO_2), 159.1* (C_{arom}-O), 159.2 (C_{arom}-O), 170.6 (CO), 171.9* (CO). IR ($CHCl_3$): 3426 (O-H st), 2941 (C-H st), 1729 (C=O st), 1605 (C=C st), 1515 (NO_2

st), 1346 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{25}N_2O_7]^+$: 417.1262 (M^++H); found: 417.1669. The ee (97%) was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_1=12.37 min, τ_2=30.14 min. $[\alpha]_D^{20}$: +5.8 (*c*=0.15, $CHCl_3$).



Ethyl (2R,3S,5S)-5-(4-chlorophenyl)-1-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)pyrrolidine-2-carboxylate (6c). Following the general procedure **C**, **6c** (64 mg, 0.16 mmol) was isolated as a pale yellow oil, starting from aldehyde **2c** (40 mg, 0.24 mmol) and nitrone **1j** (48 mg, 0.20 mmol) in the presence of catalyst **3a** (13 mg, 0.04 mmol, 20 mol%) and thiourea **5a** (20 mg, 0.04 mmol, 20 mol%) using CH_2Cl_2 (0.4 mL) as solvent for 16h and after reduction with $NaBH_4$ (30 mg, 0.80 mmol). Yield: 79%. d.r. 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereomer resonances) δ 0.96 (t, *J* = 7.1 Hz, 3H, C**H$_3$**CH_2), 1.29* (t, *J* = 7.1 Hz, 3H, C**H$_3$**CH_2), 3.20-3.34 (m, 2H, C**H$_2$**OH), 3.45 (d, *J* = 7.3, 3.5 Hz, 1H, C_4-H), 3.46-3.59 (m, 1H, C_3-H), 3.79 (s, 1H, CH_3O), 3.80* (s, 1H, CH_3O), 3.85-4.03 (m, 2H, CH_3C**H$_2$**), 4.05-4.19* (m, 2H, CH_3C**H$_2$**), 4.25* (d, *J* = 6.9 Hz, 1H, C_2-H), 4.39 (d, *J* = 7.4 Hz, 1H, C_2-H), 4.99 (s, 1H, NOH), 5.23 (d, *J* = 9.3 Hz, 1H, C_5-H), 5.49* (s, 1H, NOH), 6.80-6.92 (m, 2H, C_{arom}-H), 7.17-7.49 (m, 6H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (* indicates minor diastereomer resonances, d.r. 1:1) δ 14.0 (**C**H_3CH_2), 45.2 (C_4), 46.2 (C_3), 55.4 (CH_3O), 60.6 (CH_2OH), 62.5 (COO**C**H_2), 69.9 (C_5), 72.7 (C_2), 114.1 (C_{arom}-H), 114.3* (C_{arom}-H), 128.9 (C_{arom}-H), 129.4 (C_{arom}-H), 129.7 (C_{arom}-H), 130.5 (C_{arom}-Cl), 133.5 (**C**$_{arom}$-C_3), 138.0 (**C**$_{arom}$-C_5), 159.1 (C_{arom}-O), 170.7 (CO). IR ($CHCl_3$): 3414 (O-H st), 2930 (C-H st), 1730 (C=O st), 1612 (C=C st), 1514 (NO_2 st), 1250 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{25}ClNO_5]^+$: 406.1421 (M^++H); found: 406.1428. The ee (98%) was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (75:25)]; flow rate 1.0 mL/min; τ_1=12.01 min, τ_2=15.77 min. $[\alpha]_D^{20}$: +8.6 (*c*=1.0, $CHCl_3$). The stereostructure of **5c** was established assuming the same configuration at C-3, C-4 and C-5. The relative configuration at C-2 was then established by X-ray analysis (CCDC Number: 1522262).

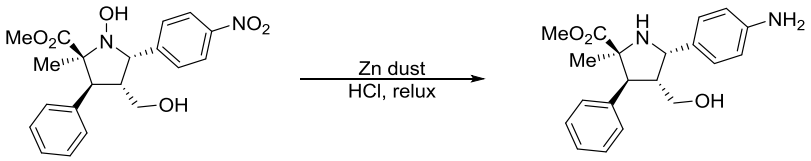
2.3 Preparation of the cyclic nitrone 7a



4a **7a**

(2S,3S,4R)-4-(hydroxymethyl)-2-(methoxycarbonyl)-2-methyl-5-(4-nitrophenyl)-3-phenyl-3,4-dihydro-2H-pyrrole 1-oxide (7a). To a solution of **4a (**38 mg, 0.10 mmol) in CH_2Cl_2 (0.2 mL), MnO_2 activated (100 mg, 1.0 mmol) was added. The mixture was stirred for 12h at room temperature. Then the crude mixture was filtered through a short pad of silica gel yielding the pure product **7a** (38 mg, 0.10 mmol) as a yellow solid. Yield: 99%. d.r. > 20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H, CH_3C_2), 3.39 (s, 3H, CH_3O), 3.57-3.68 (m, 1H, C_3-H), 3.72 (d, *J* = 8.8 Hz, 1H, C_2-H), 4.00 (dt, *J* = 11.3, 3.3 Hz, 1H, C**H$_a$**H$_b$), 4.09 (dt, *J* = 8.6, 3.1 Hz, 1H, CH$_a$**H$_b$**), 7.26-7.34 (m, 2H, C_{arom}-H), 7.34-7.43 (m, 3H, C_{arom}-H), 8.25-8.38 (m, 4H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (**C**H$_3$C$_2$), 48.4 (C_3), 51.3 (C_4), 52.9 (CH_3O), 60.0 (CH_2), 85.4 (C_2), 123.8 (C_{arom}-H), 128.8 (C_{arom}-H), 128.9 (C_{arom}-H), 129.1 (C_{arom}-H), 134.6 (C_{arom}-C_5), 134.7 (C_5), 141.6 (C_{arom}-C_3), 148.0 (C_{arom}-N), 168.6 (CO). IR ($CHCl_3$): 3322 (O-H st), 2955 (C-H st), 1731 (C=O st), 1605 (C=C st), 1518 (NO_2 st), 1344 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{21}N_2O_6]^+$: 385.1400 (M^++H); found: 385.1405. $[\alpha]_D^{20}$: +144.9 (*c*=1.0, $CHCl_3$).

2.4 Preparation of *N*-H pyrrolidine 8a

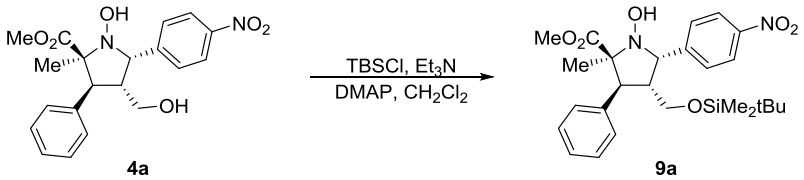


4a **8a**

Methyl (2S,3S,4R,5S)-5-(4-aminophenyl)-4-(hydroxymethyl)-2-methyl-3-phenylpyrrolidine-2-carboxylate (8a). To a suspension of **4a** (38 mg, 0.10 mmol) in H_2O (2 mL), HCl conc. (1mL) and Zn dust (260 mg, 4.0 mmol) were added. The mixture was heated to reflux for 3h until the solution turned from yellow to colorless. The mixture was cooled and basified to pH > 12 with aqueous NaOH 2.5 M, extracted with Et_2O (5 x 5mL), dried over anhydrous Na_2SO_4, filtrated, evaporated and purified by flash column chromatography on triethylamine deactivated SiO_2 (PE/EtOAc 3:7 to 0:100) to afford pure **8a** (26 mg, 0.08 mmol) as a pale yellow oil. Yield: 77%. d.r. > 20:1. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.76 (s, 3H, CH_3C), 3.02 (dtd, *J* = 11.6, 6.0, 3.1 Hz, 1H, C_4-H), 3.14 (d, *J* = 9.7 Hz, 1H, C_3-H), 3.21-3.36 (m, 5H, CH_2O, CH_3O), 3.52* (s, 3H, CH_3O), 5.04 (d, *J* = 8.5 Hz, 1H, C_5-H), 6.59-6.75 (m, 2H, C_{arom}-H), 7.13-7.36 (m, 7H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2 (C_2**C**H_3), 49.9 (C_4), 51.5 (C_3), 57.4 (CH_3O), 62.4 (CH_2O), 62.7 (C_5), 70.0 (C_2), 115.4 (C_{arom}-H), 127.4 (C_{arom}-H), 128.5 (C_{arom}-H), 132.0 (C_{arom}-H), 138.8 (C_{arom}-C_5), 145.8 (C_{arom}-C_3), 148.6 (C_{arom}-NH_2), 176.7 (CO). IR ($CHCl_3$): 3551 (NH_2 st), 3350 (O-H st), 2945 (C-H st), 1720 (C=O st), 1623 (C=C st), 1516 (N-H δ), 1281 (C-O st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{25}N_2O_3]^+$: 341.1865 (M^++H); found: 341.1874. $[\alpha]_D^{20}$: +62.1 (*c*=1.0, $CHCl_3$).

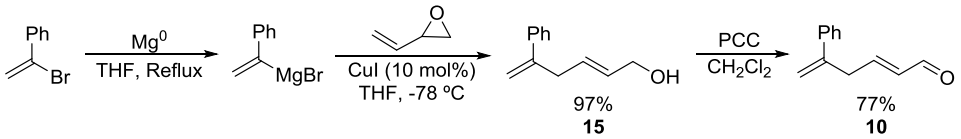
2.5 Preparation of *O*-protected 1-hydroxypyrrolidine 9a

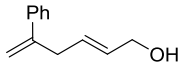


Methyl (2S,3S,4R,5S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-hydroxy-2-methyl-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (9a). To a solution of **4a** (38 mg, 0.10 mmol) and 4-(dimethylamino)pyridine (1 mg, 0.01 mmol) in CH_2Cl_2 at room temperature, tert-buthyldimethylsilyl chloride (30 mg, 0.20 mmol) and triethylamine (28 µL ,0.20 mmol) were added. The mixture was stirred at room temperature for 12h. Then, the solvent was evaporated and the crude mixture was purified by flash column chromatography (PE/EtOAc 9:1 to 7:3) to afford pure **9a** (45 mg, 0.09 mmol) as a colorless oil. Yield: 90%. d.r. > 20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.41 (s, 3H, SiC**H$_3$**CH_3), -0.40 (s, 3H, $SiCH_3$C**H$_3$**), 0.63 (s, 9H, $C(CH_3)_3$), 1.56 (s, 3H, CH_3C), 3.00-3.19 (m, 3H, C_3-H, CH_2), 3.33 (tdd, *J* = 10.8, 6.1, 4.0 Hz, 1H, C_4-H), 3.51 (s, 3H, CH_3O), 3.74* (s, 3H, CH_3O), 4.88 (s, 1H, NOH), 5.24-5.35 (m 1H, C_5-H), 7.15-7.36 (m, 5H, C_{arom}-H), 7.62-7.77 (m, 2H, C_{arom}-H), 8.13-8.25 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.9 ($SiCH_3$), 18.0 (C_2**C**H_3), 22.0 (**C**$(CH_3)_3$), 25.8 (C(**C**$H_3)_3$), 45.6 (C_4), 51.6 (C_3), 53.6 (CH_3O), 61.3 (CH_2O), 70.4 (C_5), 75.4 (C_2), 123.1 (C_{arom}-H), 127.9 (C_{arom}-H), 128.6 (C_{arom}-H), 129.8 (C_{arom}-H), 136.5 (C_{arom}-C_3), 147.2 (C_{arom}-NO_2), 148.6 (C_{arom}-C_5), 172.4 (CO). IR ($CHCl_3$): 3479 (O-H st), 2952 (C-H st), 1729 (C=O st), 1602 (C=C st), 1520 (NO_2 st), 1345 (NO_2 st), 1252 (Si-CH_3 δ sy), 1109 (Si-O st), 836 (Si-CH_3 γ) cm^{-1}. HRMS: Calculated for $[C_{26}H_{36}N_2O_6Si]^+$: 501.2421 (M^++H); found: 501.2420. $[\alpha]_D^{20}$: +18.2 (*c*=1.0, $CHCl_3$).

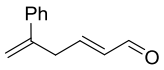
3. FAVORING TRIENAMINE ACTIVATION THROUGH UNCONJUGATED DIENALS

3.1 Synthesis of the starting materials





(*E*)-5-phenyl-hexa-2,5-dien-1-ol (15). Following an adapted literature procedure,[8] to a solution of copper cyanide (128 mg, 1.4 mmol) and racemic 2-vinyl oxirane (1.15 mL, 14.0 mmol) in dry THF (11 mL) at -78 ºC under inert atmosphere was added dropwise the α -styryl magnesium bromide prepared from α-bromostyrene (2.2 mL, 16.8 mmol) and magnesium powder (450 mg) 18.5 mmol) in THF (17 mL). After stirring for 1.5 hours, the reaction was quenched with 20 mL of HCl (1 M), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) to afford pure (*E*)-5-phenyl-hexa-2,5-dien-1-ol **15** (2.34 g, 13.4 mmol) as a pale yellow oil. Yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20-3.336 (m, 2H, CC**H**$_2$C), 4.10 (t, *J* = 5.0 Hz, 2H, C**H**$_2$OH), 5.09 (dd, *J* = 2.6, 1.3 Hz, 1H, C=C**H**$_{cis}$H$_{trans}$), 5.39 (d, *J* = 0.5 Hz, 1H, C=CH$_{cis}$**H**$_{trans}$), 5.72-5.80 (m, 2H, C**H**=C**H**), 7.26-7.37 (m, 3H, C_{arom}-H), 7.40-7.47 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 37.9 (C**C**H$_2$C), 63.5 (**C**H$_2$OH), 113.2 (C=**C**H$_2$), 126.0 (C_{arom}-H), 127.5 (C_{arom}-H), 128.3 (C_{arom}-H), 130.2 (**C**H=CHCH$_2$O), 131.0 (CH=**C**HCH$_2$O), 140.7 (C_{arom}), 146.3 (**C**C$_6$H$_5$). IR (neat): 3332 (O-H st) cm^{-1}. HRMS: Calculated for $[C_{12}H_{13}]^+$: 157.1017 $[(M\text{-}OH)^+]$; found: 157.1009. MS (70 eV) *m/z* (%): 174 (8, $[M^+]$), 156 (94), 143 (100), 128 (93), 115 (66), 103 (88), 91 (45), 77 (45).

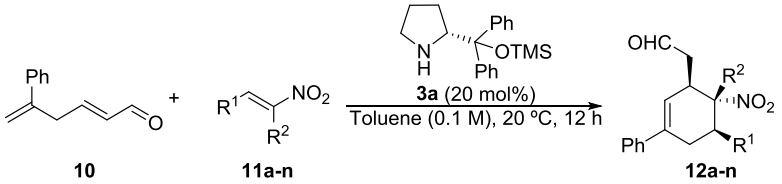


(*E*)-phenylhexa-2,5-dienal (10). Pyridinium chlorocromate (4.64 mmol) was added in one portion to a solution of (*E*)-5-phenyl-hexa-2,5-dien-1-ol **15** (2.85 mmol) in CH_2Cl_2 (6 mL) at room temperature, the reaction mixture was stirred for 1 hour. The crude was directly subjected to flash chromatography (hexanes/EtOAc gradient from 19:1 to 9:1) affording the (*E*)-phenylhexa-2,5-dienal **10** (375

[8] Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Scheleif, W. A.; Huff, J. R.; Anderson, P. A. *J. Med. Chem.* **1993**,*36*, 2300.

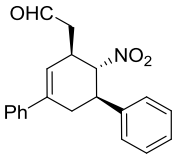
mg, 2.2 mmol) as a yellow oil. Yield 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (dt, *J* = 6.6, 1.2 Hz, 2H, CC**H**$_2$C), 5.17 (dd, *J* = 2.1, 1.1 Hz, 1H, C=C**H**$_{cis}$H$_{trans}$), 5.52 (s, 1H, C=CH$_{cis}$**H**$_{trans}$), 6.20 (ddt, *J* = 15.6, 7.9, 1.6 Hz, 1H, C**H**CHO), 6.91 (dt, *J* = 15.6, 6.6 Hz, 1H, C**H**CH$_2$), 7.28-7.46 (m, 5H, C_{arom}-H), 9.52 (d, *J* = 7.9 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 38.4 (C**C**H$_2$C), 114.9 (**C**H$_2$=C), 125.9 (C_{arom}-H), 128.0 (C_{arom}-H), 128.5 (C_{arom}-H), 134.2 (**C**HCHO), 139.7 (C_{arom}), 143.9 (**C**C$_6$H$_5$), 155.4 (**C**HCH$_2$), 193.7 (CHO). IR (neat): 1685 (C=O st), 1625 (C=C st) cm^{-1}. HRMS: Calculated for [$C_{12}H_{13}O$]$^+$: 173.0966 [(M+H)$^+$]; found: 173.0959. MS (70 eV) *m/z* (%): 172 (28, [M$^+$]), 157 (32), 143 (47), 128 (100), 115 (34), 103 (70), 91 (14), 77 (38).

3.2 Synthesis of the Cyclohexenyl Acetaldehyde Adducts 12a-n

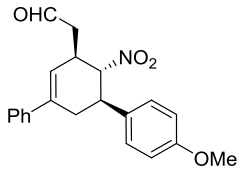


General Procedure D for the Preparation of Cyclohexenyl Acetaldehyde Adducts **12a-n**:

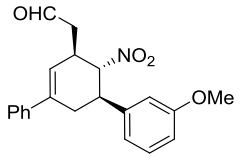
The corresponding nitroolefin **11a-n** (0.20 mmol) was added to a solution of (2*R*)-2-[diphenyl[(trimethilsilyl)oxy]methyl]pyrrolidine **3a** (0.04 mmol) and (*E*)-phenylhexa-2,5-dienal **10** (0.26 mmol) in toluene (2 mL) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred in a thermostatic bath at 20 ºC for 12 hours. Then the crude reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (hexanes/EtOAc gradient from 19:1 to 9:1) affording the corresponding tetrasubstituted cyclohexenyl adduct **12a-n**.



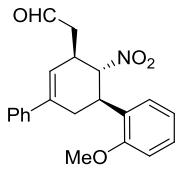
2-((1'*R*,5'*R*,6'*S*)-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12a). Following the general procedure **D**, **12a** (63 mg, 0.19 mmol) was isolated as a yellow oil, starting from *trans*-β-nitrostyrene **11a** (30 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 99%. dr: 13:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63-2.99 (m, 4H, C**H**$_2$CHO, CH_2C), 3.62-3.73 (m, 2H, C**H**C$_6$H$_5$, C**H**CH$_2$CHO), 4.91 (dd, *J* = 11.6, 10.2 Hz, 1H, $CHNO_2$), 5.92 (s, 1H, CH=C), 7.28-7.38 (m, 10H, C_{arom}-H), 9.82 (s, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.8 (**C**H$_2$CC$_6$H$_5$), 37.1 (**C**HCH$_2$CHO), 45.3 (**C**HC$_6$H$_5$), 45.9 (**C**H$_2$CHO), 91.8 ($CHNO_2$), 122.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.4 (C_{arom}-H), 127.9 (C_{arom}-H), 127.9 (**C**H=C), 128.5 (C_{arom}-H), 129.0 (C_{arom}-H), 137.1 (**C**=CH), 139.1 (C_{arom}), 139.4 (C_{arom}), 198.9 (CHO). IR (neat): 1722 (C=O st), 1546 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{20}O]^+$: 275.1436 (M^+-H_2O); found: 275.1437. MS (70 eV) *m/z* (%): 274 (81, [M^+-NO_2]), 256 (46), 231 (86), 215 (27), 128 (27), 115 (33), 91 (100), 77 (20). The ee (94%) was determined on the reduced compound **13a**. $[\alpha]_D^{20}$: -15.8 (*c*=1.0, CH_2Cl_2).



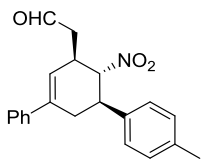
2-((1'*R*,5'*R*,6'*S*)-4-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12b). Following the general procedure **D**, **12b** (65 mg, 0.19 mmol) was isolated as a white solid, starting from *trans*-4-methoxy-β-nitrostyrene **11b** (36 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 93%. dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63-2.96 (m, 4H, C**H**$_2$CHO, CH_2C), 3.56-3.69 (m, 2H, CHAr, C**H**CH_2CHO), 3.81 (s, 3H, CH_3), 4.86 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.93 (dt, *J* = 3.0, 1.4 Hz, 1H, CH=C), 6.85-6.95 (m, 2H, C_{arom}-H), 7.19-7.25 (m, 2H, C_{arom}-H), 7.27-7.43 (m, 5H, C_{arom}-H), 9.81 (t, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.8 (**C**$H_2CC_6H_5$), 37.2 (**C**HCH_2CHO), 44.6 (CHAr), 46.0 (**C**H_2CHO), 55.2 (CH_3), 92.2 ($CHNO_2$), 114.4 (C_{arom}-H), 122.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.9 (C_{arom}-H), 128.4 (C_{arom}-H), 128.5 (**C**H=C), 131.0 (C_{arom}), 137.2 (**C**=CH), 139.4 (C_{arom}), 159.2 (C_{arom}-O), 199.0 (CHO). IR (CH_2Cl_2): 1720 (C=O st), 1547.6 (NO_2 st), 1372 (NO_2 st). HRMS: Calculated for $[C_{21}H_{22}NO_4]^+$: 352.1549 (M^++H); found: 352.1541. MS (70 eV) *m/z* (%): 304 (36, [M^+-NO_2]), 261 (55), 121 (100), 115 (13), 91 (14), 77 (10). M.p**.** (hexanes, EtOAc): 144-145 ºC. The ee (93%) was determined on the reduced compound **13b** (see below). $[\alpha]_D^{20}$: -8.4 (*c* = 1.0, CH_2Cl_2).



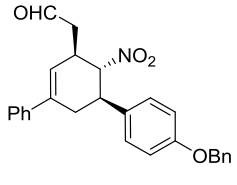
2-((1'*R*,5'*R*,6'*S*)-3-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12c). Following the general procedure **D**, **12c** (63 mg, 0.18 mmol) was isolated as a white solid, starting from *trans*-3-methoxy-β-nitrostyrene **11c** (36 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 91%. dr: 16:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63-2.99 (m, 4H, C**H**$_2$CHO, CH_2C), 3.55-3.72 (m, 2H, CHAr, C**H**CH_2CHO), 3.80 (s, 3H, CH_3), 4.90 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.91 (dt, *J* = 3.2, 1.5, 1H, CH=C), 6.77-6.92 (m, 3H, C_{arom}-H), 7.27-7.39 (m, 6H, C_{arom}-H), 9.75-9.86 (m, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.7 (**C**$H_2CC_6H_5$), 37.2 (**C**HCH_2CHO), 45.3 (CHAr), 45.9 (**C**H_2CHO), 55.2 (CH_3), 91.7 ($CHNO_2$), 113.0 (C_{arom}-H), 113.5 (C_{arom}-H), 119.5 (C_{arom}-H), 122.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.9 (C_{arom}-H), 128.5 (C_{arom}-H), 130.0 (**C**H=C), 137.1 (**C**=CH), 139.4 (C_{arom}), 140.7 (C_{arom}), 159.9 (C_{arom}-O), 199.0 (CHO). IR (CH_2Cl_2): 1720 (C=O st), 1547 (NO_2 st), 1378 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{22}NO_4]^+$: 352.1549 ([M+H^+]; found: 352.1556. MS (70 eV) *m/z* (%): 304 (40, [M^+-NO_2]), 261 (59), 121 (100), 91 (14). M.p. (hexanes, EtOAc): 91-92 ºC. The ee (90%) was determined on the reduced compound **13c** (see below). $[\alpha]_D^{20}$: -20.0 (*c*=1.0, CH_2Cl_2).



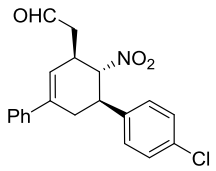
2-((1'*R*,5'*R*,6'*S*)-2-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12d). Following the general procedure **D**, **12d** (65 mg, 0.18 mmol) was isolated as a white solid, starting from *trans*-2-methoxy-β-nitrostyrene **11d** (36 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 92%. dr: 12:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58-3.06 (m, 4H, C**H**$_2$CHO, CH_2C), 3.57-3.74 (m, 1H, C**H**CH_2CHO), 3.83-4.11 (m, 4H , CHAr, CH_3), 5.18-5.33 (m, 1H, $CHNO_2$), 5.91 (q, *J* = 1.9 Hz, 1H, CH=C), 6.86-6.99 (m, 2H, C_{arom}-H), 7.14-7.42 (m, 7H, C_{arom}-H), 9.79-9.86 (m, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.4 (**C**$H_2CC_6H_5$), 37.0 (**C**HCH_2CHO), 46.1 (CHAr), 46.1 (CH_2CHO), 55.5 (CH_3), 89.7 ($CHNO_2$), 111.4 (C_{arom}-H), 121.0 (C_{arom}-H), 122.6 (C_{arom}-H), 125.2 (C_{arom}-H), 126.8 (C_{arom}), 127.8 (C_{arom}-H), 127.8 (C_{arom}-H), 128.4 (C_{arom}-H), 128.9 (**C**H=C), 137.4 (**C**=CH), 139.6 (C_{arom}-C), 157.4 (C_{arom}-O), 199.2 (CHO). IR (CH_2Cl_2): 1723 (C=O st), 1546 (NO_2 st), 1376 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{21}O_2]^+$: 305.1542 ($[M]^+$-NO_2); found: 305.1530. MS (70 eV) *m/z* (%): 304 (78, [M^+-NO_2]), 286 (49), 261 (100), 121 (71), 91 (44). M.p**.** (hexanes, EtOAc): 149-150 ºC. The ee (97%) was determined on the reduced compound **13d** (see below). $[\alpha]_D^{20}$: -2.4 (*c*=1.0, CH_2Cl_2).



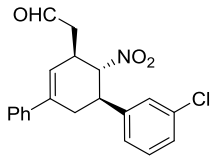
2-((1'*R*,5'*R*,6'*S*)-4-methyl-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12e). Following the general procedure **D**, **12e** (57 mg, 0.17 mmol) was isolated as a white solid, starting from *trans*-4-methyl-β-nitrostyrene **11e** (33 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 85%. dr: 19:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.54-3.06 (m, 4H, C**H**$_2$CHO, CH_2C), 3.47-3.85 (m, 2H, CHAr, C**H**CH_2CHO), 4.89 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.93 (dt, *J* = 3.0, 1.5 Hz, 1H, CH=C), 7.14-7.23 (m, 4H, C_{arom}-H), 7.26-7.41 (m, 5H, C_{arom}-H), 9.82 (t, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (CH_3), 35.8 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 44.9 (CHAr), 45.9 (**C**H_2CHO), 91.9 ($CHNO_2$), 122.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.2 (C_{arom}-H), 127.9 (**C**H=C), 128.5 (C_{arom}-H), 129.6 (C_{arom}-H), 136.0 (**C**$_{arom}$-CH), 137.1 (**C**=CH), 137.6 (C_{arom}-CH_3), 139.4 (**C**$_{arom}$-C), 199.0 (CHO). IR (CH_2Cl_2): 1716 (C=O st), 1547 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{21}O]^+$: 289.1592 ($[M]^+$-NO_2); found: 289.1585. MS (70 eV) *m/z* (%): 288 (77, [M^+-NO_2]), 270 (27), 245 (78), 215 (17), 105 (100), 91 (28), 77 (14). M.p. (hexanes, EtOAc): 124-125 ºC. The ee (92%) was determined on the reduced compound **13e** (see below). $[\alpha]_D^{20}$: 15.1 (*c*=1.0, CH_2Cl_2).



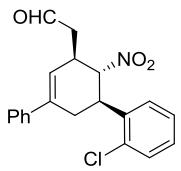
2-((1'*R*,5'*R*,6'*S*)-4-(benzyloxy)-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12f). Following the general procedure **D**, **12f** (84 mg, 0.20 mmol) was isolated as a yellow oil, starting from *trans*-4-benzyloxy-β-nitrostyrene **11f** (52 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 98%. dr: 16:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58-2.97 (m, 4H, C**H**$_2$CHO, CH_2C), 3.51-3.81 (m, 2H, CHAr, C**H**CH_2CHO), 4.85 (dd, *J* = 11.6, 10.1 Hz, 1H, $CHNO_2$), 5.05 (s, 2H, CH_2O) 5.92 (dt, *J* = 3.1, 1.5 Hz, 1H, CH=C), 6.93-7.01 (m, 2H, C_{arom}-H), 7.18-7.25 (m, 2H, C_{arom}-H), 7.28-7.50 (m, 10H, C_{arom}-H), 9.75-9.89 (m, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.8 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 44.6 (CHAr), 46.0 (CH_2CHO), 70.0 (CH_2-O), 92.1 ($CHNO_2$), 115.3 (C_{arom}-H), 122.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.5 (C_{arom}-H), 127.9 (C_{arom}-H), 128.0 (C_{arom}-CH), 128.5 (C_{arom}-H), 128.5 (C_{arom}-H), 128.6 (C_{arom}-H), 131.3 (**C**H=C), 136.8 (**C**$_{arom}$-CH_2), 137.2 (**C**=CH), 139.5 (**C**$_{arom}$-C), 158.4 (C_{arom}-O), 199.0 (CHO). IR (neat): 1712 (C=O st), 1547 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{27}H_{25}O_2]^+$: 381.1855 ([M]$^+$-NO_2); found: 381.1836. MS (70 eV) *m/z* (%): 375 (53, [M$^+$- C_4H_3]), 284 (100), 254 (19), 91 (78). The ee (96%) was determined on the reduced compound **13f** (see below). $[\alpha]_D^{20}$: -6.4 (*c*=1.0, CH_2Cl_2).



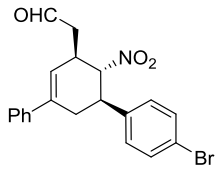
2-((1'*R*,5'*R*,6'*S*)-4-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12g). Following the general procedure **D**, **12g** (71 mg, 0.20 mmol) was isolated as a white solid, starting from *trans*-4-chloro-β-nitrostyrene **11g** (37 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 92%. dr: 14:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59-3.07 (m, 4H, C**H**$_2$CHO, CH_2C), 3.53-3.74 (m, 2H, CHAr, C**H**CH_2CHO), 4.89 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.93 (q, *J* = 2.3, 1.7 Hz, 1H, CH=C), 7.22-7.27 (m, 2H, C_{arom}-H), 7.30-7.39 (m, 7H, C_{arom}-H), 9.83 (d, *J* = 1.2 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.7 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 44.8 (CHAr), 45.9 (**C**H_2CHO), 91.6 ($CHNO_2$), 122.9 (C_{arom}-H), 125.3 (C_{arom}-H), 128.0 (**C**H=C), 128.6 (C_{arom}-H), 128.8 (C_{arom}-H), 129.2 (C_{arom}-H), 133.8 (C_{arom}-Cl), 136.9 (**C**=CH), 137.6 (**C**$_{arom}$-CH), 139.3 (C_{arom}-C), 198.8 (CHO). IR (CH_2Cl_2): 1720 (C=O st), 1540 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{19}ClO]^+$: 309.1046 ([M]$^+$-NO_2); found: 309.1052. MS (70 eV) *m/z* (%): 308 (94, [M$^+$-NO_2]), 290 (52), 265 (88), 125 (100), 91 (49), 28 (35). M.p**.** (hexanes, EtOAc): 160-161 ºC. The ee (90%) was determined on the reduced compound **13g** (see below). $[\alpha]_D^{20}$: -20.2 (*c*=1.0, CH_2Cl_2).



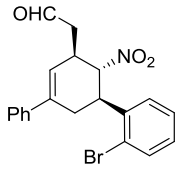
2-((1'*R*,5'*R*,6'*S*)-3-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12h). Following the general procedure **D**, **12h** (67 mg, 0.19 mmol) was isolated as a yellow oil, starting from *trans*-3-chloro-β-nitrostyrene **11h** (37 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 94%. dr: 12:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61-3.04 (m, 4H, C**H**$_2$CHO, CH_2C), 3.52-3.81 (m, 2H, CHAr, C**H**CH_2CHO), 4.91 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.83-6.01 (m, 1H, CH=C), 7.19 (ddd, *J* = 5.7, 3.4, 1.9 Hz, 1H, C_{arom}-H), 7.29-7.40 (m, 8H, C_{arom}-H), 9.83 (d, *J* = 1.1 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.7 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 45.0 (CHAr), 45.9 (**C**H_2CHO), 91.4 ($CHNO_2$), 122.8 (C_{arom}-H), 125.3 (C_{arom}-H), 125.7 (C_{arom}-H), 127.7 (C_{arom}-H), 128.0 (C_{arom}-H), 128.2 (C_{arom}-H), 128.6 (C_{arom}-H), 130.3 (**C**H=C), 134.8 (C_{arom}-Cl), 136.9 (**C**=CH), 139.3 (**C**$_{arom}$-CH), 141.2 (**C**$_{arom}$-C), 198.8 (CHO). IR (neat): 1723 (C=O st), 1547 (NO_2 st), 1373 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{18}ClO]^+$: 309.1046 ($[M]^+$-NO_2); found: 309.1044. MS (70 eV) *m/z* (%): 308 (87, [M^+-NO_2]), 290 (49), 265 (83), 125 (100), 91 (50), 28 (88). The ee (93%) was determined on the reduced compound **13h** (see below). $[\alpha]_D^{20}$: -16.3 (*c*=1.0, CH_2Cl_2).



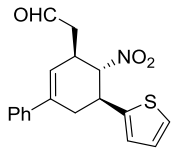
2-((1'*R*,5'*R*,6'*S*)-2-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12i). Following the general procedure **D**, **12i** (63 mg, 0.18 mmol) was isolated as a white solid, starting from *trans*-2-chloro-β-nitrostyrene **11j** (37 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 88%. dr: 14:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53-3.10 (m, 4H, C**H**$_2$CHO, CH_2C), 3.63-3.78 (bs, 1H, C**H**CH_2CHO), 4.40 (bs, 1H, CHAr), 5.07 (bs, 1H, $CHNO_2$), 5.94 (q, *J* = 2.0 Hz, 1H, CH=C), 7.19-7.45 (m, 9H, C_{arom}-H), 9.83 (t, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.0 (**C**$H_2CC_6H_5$), 37.2 (**C**HCH_2CHO), 40.5 (CHAr), 45.9 (**C**H_2CHO), 90.0 ($CHNO_2$), 122.8 (C_{arom}-H), 125.2 (C_{arom}-H), 126.4 (C_{arom}-H), 127.5 (C_{arom}-H), 128.0 (C_{arom}-H), 128.5 (C_{arom}-H), 128.8 (C_{arom}-H), 130.3 (**C**H=C), 134.1 (C_{arom}-Cl), 136.8 (**C**$_{arom}$-CH), 136.9 (**C**=CH), 139.3 (**C**$_{arom}$-C), 198.9 (CHO). IR (CH_2Cl_2): 1720 (C=O st), 1547 (NO_2 st), 1376 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{19}ClO]^+$: 309.1046 ($[M]^+$-NO_2); found: 309.1046. MS (70 eV) *m/z* (%): 308 (79, [M^+-NO_2]), 290 (56), 265 (70), 125 (49), 91 (53), 28 (100). M.p. (hexanes, EtOAc): 124-125 ºC. The ee (96%) was determined on the reduced compound **13i** (see below). $[\alpha]_D^{20}$: 15.1 (*c*=1.0, CH_2Cl_2).



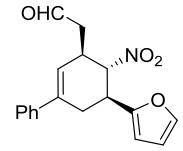
2-((1'*R*,5'*R*,6'*S*)-4-bromo-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12j). Following the general procedure **D**, **12j** (73 mg, 0.18 mmol) was isolated as a bright yellow solid, starting from *trans*-4-bromo-β-nitrostyrene **11j** (46 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 92%. dr: 13:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60-2.97 (m, 4H, C**H**$_2$CHO, CH_2C), 3.53-3.73 (m, 2H, C**H**CH_2CHO, CHAr), 4.87 (dd, *J* = 11.7, 10.1 Hz, 1H, $CHNO_2$), 5.90 (td, *J* = 2.4, 1.0 Hz, 1H, CH=C), 7.11-7.22 (m, 2H, C_{arom}-H), 7.24-7.39 (m, 5H, C_{arom}-H), 7.42-7.54 (m, 2H, C_{arom}-H), 9.78-9.85 (m, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.6 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 44.8 (CHAr), 45.9 (**C**H_2CHO), 91.5 ($CHNO_2$), 121.9 (C_{arom}-Br), 122.9 (C_{arom}-H), 125.3 (C_{arom}-H), 128.0 (**C**H=C), 128.6 (C_{arom}-H), 129.1 (C_{arom}-H), 132.2 (C_{arom}-H), 136.9 (**C**=CH), 138.1 (C_{arom}-CH), 139.3 (**C**$_{arom}$-C), 198.8 (CHO). IR (CH_2Cl_2): 1713 (C=O st), 1547.6 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{18}BrO]^+$: 353.0541 ($[M]^+$-NO_2); found: 353.0525. MS (70 eV) *m/z* (%): 354 (40, [M^+-NO_2]), 336 (26), 309 (78), 230 (59), 169 (39), 115 (31), 91 (30), 28 (100). M.p. (hexanes, EtOAc): 169-170 ºC. The ee (96%) was determined on the reduced compound **13j** (see below). $[\alpha]_D^{20}$: -21.7 (*c*=1.0, CH_2Cl_2).



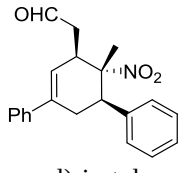
2-((1'*R*,5'*R*,6'*S*)-2-bromo-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12k). Following the general procedure **D**, **12k** (65 mg, 0.16 mmol) was isolated as a bright yellow solid, starting from *trans*-2-bromo-β-nitrostyrene **11k** (46 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 81%. dr: 13:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49-3.09 (m, 4H, C**H**$_2$CHO, CH_2C), 3.62-3.79 (m, 1H, C**H**CH_2CHO), 4.36 (td, *J* = 11.5, 5.4 Hz, 1H, CHAr), 5.06 (t, *J* = 10.9 Hz, 1H, $CHNO_2$), 5.92 (q, *J* = 1.9 Hz, 1H, CH=C), 7.07-7.20 (m, 1H, C_{arom}-H), 7.27-7.40 (m, 7H, C_{arom}-H), 7.59 (dd, *J* = 8.3, 1.0 Hz, 1H, C_{arom}-H), 9.83 (t, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.1 (**C**$H_2CC_6H_5$), 37.3 (**C**HCH_2CHO), 43.4 (CHAr), 45.8 (**C**H_2CHO), 90.1 ($CHNO_2$), 122.8 (C_{arom}-H), 124.8 (C_{arom}-Br), 125.3 (C_{arom}-H), 126.5 (C_{arom}-H), 128.0 (C_{arom}-H), 128.2 (C_{arom}-H), 128.5 (**C**H=C), 129.1 (C_{arom}-H), 133.6 (C_{arom}-H), 136.9 (**C**=CH), 138.6 (C_{arom}-CH), 139.2 (**C**$_{arom}$-C), 198.9 (CHO). IR (CH_2Cl_2): 1716 (C=O st), 1547 (NO_2 st), 1382 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{18}BrO]^+$: 353.054 ($[M]^+$-NO_2); found: 353.0529. MS (70 eV) *m/z* (%): 352 (36, [M^+-NO_2]), 309 (26), 230 (51), 169 (37), 115 (29), 91 (29), 28 (100). M.p. (hexanes, EtOAc): 143-144 ºC. The ee (92%) was determined on the reduced compound **13k** (see below). $[\alpha]_D^{20}$: 11.2 (*c*=1.0, CH_2Cl_2).



2-((3*R*,4*S*,5*S*)-4-nitro-5-(thiophen-2-yl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetaldehyde (12l). Following the general procedure **D**, **12l** (57 mg, 0.17 mmol) was isolated as a yellow oil, starting from 2-(2-nitrovinyl)thiophene **11l** (31 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 87%. dr: 13:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50-3.14 (m, 4H, C**H**$_2$CHO, CH_2C), 3.67 (dddt, *J* =8.1, 6.0, 3.8, 2.3 Hz, 1H, C**H**CH_2CHO), 3.99 (td, *J* = 11.4, 5.5 Hz, 1H, CHAr), 4.77 (dd, *J* = 11.4, 10.1 Hz, 1H, $CHNO_2$), 5.91 (t, *J* = 1.7 Hz, 1H, CH=C), 6.94-6.98 (m, 2H, $C_{Heteroarom}$-H), 7.20-7.26 (m, 1H, $C_{Heteroarom}$-H), 7.28-7.42 (m, 5H, C_{arom}-H), 9.80 (dd, *J* = 1.4, 0.7 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 36.4 (**C**$H_2CC_6H_5$), 37.1 (**C**HCH_2CHO), 40.5 (CHAr), 46.0 (**C**H_2CHO), 93.2 ($CHNO_2$), 122.8 (C_{arom}-H), 124.8 (**C**$_{Heteroarom}$-H), 125.3 (C_{arom}-H), 125.9 (**C**$_{Heteroarom}$-H), 127.1 (**C**$_{Heteroarom}$-H), 128.0 (**C**H=C), 128.6 (C_{arom}-H), 136.8 (**C**=CH), 139.3 (**C**$_{arom}$-C), 141.8 (**C**$_{Heteroarom}$-CH), 198.9 (CHO). IR (neat): 1721 (C=O st), 1547 (NO_2 st), 1371 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{18}H_{17}NO_3S]^+$: 353.054 ([M+H$^+$]); found: 328.1023. MS (70 eV) *m/z* (%): 280 (81, [M$^+$-NO_2]), 237 (100), 203 (30), 97 (87). The ee (97%) was determined on the reduced compound **13l** (see below). $[\alpha]_D^{20}$: -21.8 (*c*=1.0, CH_2Cl_2).

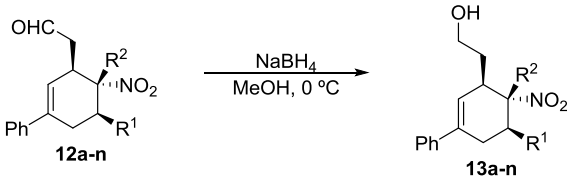


2-((3*R*,4*S*,5*S*)-5-(furan-2-yl)-4-nitro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetaldehyde (12m). Following the general procedure **D**, **12m** (50 mg, 0.16 mmol) was isolated as a bright yellow solid, starting from 2-(2-nitrovinyl)furane **11m** (28 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 80%. dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57-3.08 (m, 4H, C**H**$_2$CHO, CH_2C), 3.65 (dddt, *J* = 10.0, 7.8, 3.8, 1.7 Hz, 1H, C**H**CH_2CHO), 3.80 (td, *J* = 11.0, 6.2 Hz, 1H, CHAr), 4.84 (dd, *J* = 11.4, 10.0 Hz, 1H, $CHNO_2$), 5.88 (td, *J* = 2.4, 1.2 Hz 1H, CH=C), 6.20 (dd, *J* = 3.3, 0.8 Hz, 1H, $C_{Heteroarom}$-H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H, $C_{Heteroarom}$-H), 7.28-7.47 (m, 6H, $C_{Heteroarom}$-H, C_{arom}-H), 9.79 (d, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.1 (**C**$H_2CC_6H_5$), 36.4 (**C**HCH_2CHO), 38.5 (CHAr), 45.9 (**C**H_2CHO), 90.2 ($CHNO_2$), 107.4 ($C_{Heteroarom}$-H), 110.4 ($C_{Heteroarom}$-H), 122.5 (C_{arom}-H), 125.2 (C_{arom}-H), 127.9 (**C**H=C), 128.5 (C_{arom}-H), 136.4 (**C**=CH), 139.4 (**C**$_{arom}$-C), 142.5 ($C_{Heteroarom}$-H), 151.9 (**C**$_{Heteroarom}$-CH), 198.8 (CHO). IR (CH_2Cl_2): 1720 (C=O st), 1547 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{18}H_{17}NO_4]^+$: 312.1236 ([M+H$^+$]); found: 312.1240. MS (70 eV) *m/z* (%): 264 (77, [M$^+$-NO_2]), 221 (100), 178 (34), 81 (58). M.p. (hexanes, EtOAc): 87-88 ºC. The ee (89%) was determined on the reduced compound **13m** (see below). $[\alpha]_D^{20}$: -10.5 (*c*=1.0, CH_2Cl_2).



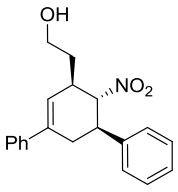
2-((1'*R*,5'*R*,6'*S*)-4,6'-dimethyl-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)acetaldehyde (12n). Following the general procedure **D**, **12i** (42 mg, 0.12 mmol) was isolated as a yellow oil, starting from *trans*-β-methyl-β-nitrostyrene **11n** (33 mg, 0.20 mmol), (*E*)-5-phenylhexa-2,5-dienal **10** (45 mg, 0.26 mmol) and **3a** (13 mg, 0.04 mmol) in toluene (2 mL) as solvent. Yield: 64%. dr: 16:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H, CH_3), 2.39-2.63 (m, 2H, CH_2C), 2.82-3.07 (m, 2H, C**H**$_2$CHO), 3.90 (dd, *J* = 11.5, 6.2 Hz, 1H, C**H**CH_2CHO), 4.20 (d, *J* = 10.5 Hz, 1H, CHAr), 5.87 (q, *J* = 1.9 Hz, 1H, CH=C), 7.23-7.43 (m, 10H, C_{arom}-H), 9.83 (dd, *J* = 2.0, 0.8 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.8 (CH_3), 32.4 (**C**$H_2CC_6H_5$), 40.9 (**C**HCH_2CHO), 44.0 (CHAr), 49.2 (**C**H_2CHO), 94.0 (CNO_2) 123.5 (C_{arom}-H), 125.2 (C_{arom}-H), 127.9 (C_{arom}-H), 128.3 (**C**H=C), 128.6 (C_{arom}-H), 128.7 (C_{arom}-H), 128.8 (C_{arom}-H), 136.5 (**C**$_{arom}$-CH), 136.9 (**C**=CH), 139.3 (**C**$_{arom}$-C), 199.1 (CHO). IR (neat): 1723 (C=O st), 1536 (NO_2 st), 1389 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{21}O]^+$: 289.1592 ($[M]^+$-NO_2); found: 289.1594. MS (70 eV) *m/z* (%): 288 (77, $[M^+$-$NO_2]$), 270 (27), 245 (78), 215 (17), 105 (100), 91 (28), 77 (14). The ee (96%) was determined on the reduced compound **13i** (see below). $[\alpha]_D^{20}$: -70.0 (*c*=1.0, CH_2Cl_2).

3.3 Synthesis of the Cyclohexenyl Alcohol Adducts 13a-n

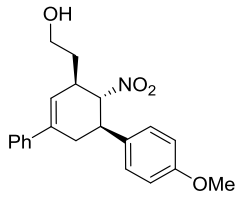


General Procedure E for the Reduction of Cyclohexenyl Acetaldehyde Adducts **12a-n** *to the corresponding Alcohols* **13a-n**:

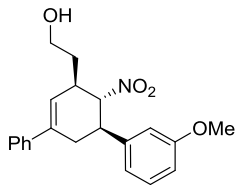
To a solution of aldehyde **12a-n** (0.10 mmol) in MeOH (3 mL) at 0 ºC $NaBH_4$ (0.15 mmol) was added. The mixture was stirred at 0 ºC for 10 min, then 4 mL of saturated solution of NH_4Cl were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc 7:3) to afford pure alcohol **13a-n**. The racemic standards, prepared in order to find HPLC separation conditions were synthesized according to aforementioned procedures using racemic mixture of enantiomers of catalyst **3a** (*R* and *S*).



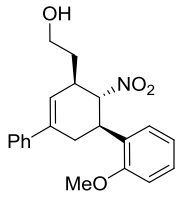
2-((1'*R*,5'*R*,6'*S*)-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13a). Following the general procedure **E**, **13a** (60 mg, 0.18 mmol) was isolated as a white solid, starting from the acetaldehyde **12a** (63 mg, 0.19 mmol) and $NaBH_4$ (11 mg, 0.29 mmol) in MeOH (3 mL) as solvent. Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-2.00 (m, 2H, CHC**H**$_2$CH$_2$), 2.71-2.98 (m, 2H, CH_2C), 3.29-3.42 (m, 1H, C**H**CH$_2$CH$_2$), 3.54 (td, *J* = 11.5, 5.8 Hz, 1H, CHC$_6$H$_5$), 3.78 (t, *J* = 5.8 Hz, 2H, CH_2O), 4.89 (dd, *J* = 11.5, 10.2 Hz, 1H, $CHNO_2$), 6.03 (s, 1H, CH=C), 7.23-7.44 (m, 10H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.9 (**C**H$_2$CC$_6$H$_5$), 35.8 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.8 (**C**HC$_6$H$_5$), 59.5 (CH_2O), 92.8 ($CHNO_2$), 123.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.4 (C_{arom}-H), 127.7 (C_{arom}-H), 127.8 (**C**H=C), 128.5 (C_{arom}-H), 128.9 (C_{arom}-H), 136.4 (**C**=CH), 139.4 (C_{arom}-CH), 139.8 (C_{arom}-C). IR (CH_2Cl_2): 3387 (O-H st), 2883 (C-H st), 1546 (NO_2 st), 1376 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{20}H_{21}O$]$^+$: 277.1592 (M^+-NO_2); found: 277.1579. MS (70 eV) *m/z* (%): 272 (100, [M^+-C_4H_3]), 257 (13), 228 (10), 165 (58), 28 (22). M.p. (hexanes, EtOAc): 120-121 ºC. The ee (94%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=18.92 min, τ_2=28.54 min. $[\alpha]_D^{20}$: -12.0 (*c*=1.0, CH_2Cl_2).



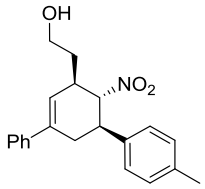
2-((1'*R*,5'*R*,6'*S*)-4-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13b). Following the general procedure **E**, **13b** (46 mg, 0.13 mmol) was isolated as a white solid, starting from the acetaldehyde **12b** (47 mg, 0.13 mmol) and $NaBH_4$ (8 mg, 0.20 mmol) in MeOH (3 mL) as solvent. Yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.98 (m, 2H, CHC**H**$_2$CH$_2$), 2.70-2.94 (m, 2H, CH_2C), 3.27-3.41 (m, 1H, C**H**CH$_2$CH$_2$), 3.52 (td, *J* = 11.5, 5.7 Hz, 1H, CHAr), 3.76-3.87 (m, 5H, CH_2O, CH_3), 4.87 (dd, *J* = 11.6, 10.0 Hz, 1H, $CHNO_2$), 6.06 (bs, 1H, CH=C), 6.82-6.92 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.16-7.23 (m, 1H, C_{arom}-H), 7.25-7.42 (m, 5H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.0 (**C**H$_2$C), 35.8 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.0 (**C**HAr), 55.2 (CH_3), 59.6 (CH_2O), 93.1 ($CHNO_2$), 114.3 (C_{arom}-H), 123.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.7 (**C**H=C), 128.5 (C_{arom}-H), 128.5 (C_{arom}-H), 131.3 (**C**$_{arom}$-CH), 136.5 (**C**=CH), 139.8 (**C**$_{arom}$-C), 159.0 (C_{arom}-O). IR (CH_2Cl_2): 3401 (O-H st), 2923 (C-H st), 1547 (NO_2 st), 1249 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}O_2]^+$: 307.1698 (M^+-NO_2); found: 307.1683. MS (70 eV) *m/z* (%): 312 (38, [M^+-C_3H_4]), 282 (100), 254 (8), 238 (8), 28 (47). M.p. (hexanes, EtOAc): 81-82 ºC. The ee (93%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_1=15.83 min, τ_2=26.41 min. $[\alpha]_D^{20}$: -9.5 (*c*=1.0, CH_2Cl_2).



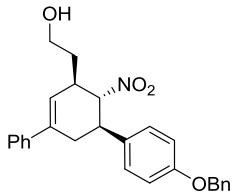
2-((1'*R*,5'*R*,6'*S*)-3-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13c). Following the general procedure **E**, **13c** (52 mg, 0.15 mmol) was isolated as a white solid, starting from the acetaldehyde **12c** (62 mg, 0.18 mmol) and $NaBH_4$ (10 mg, 0.27 mmol) in MeOH (3 mL) as solvent. Yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.95 (m, 2H, CHC**H**$_2$CH$_2$), 2.70-2.95 (m, 2H, CH_2C), 3.26-3.42 (m, 1H, C**H**CH$_2$CH$_2$), 3.56 (td, *J* = 11.5, 5.7 Hz, 1H), 3.78-3.86 (m, 5H, CH_2O, CH_3), 4.92 (dd, *J* = 11.6, 10.1 Hz, 1H, $CHNO_2$), 6.07 (t, *J* = 1.7 Hz, 1H, CH=C), 6.79-6.90 (m, 3H, C_{arom}-H), 7.22-7.41 (m, 6H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.9 (**C**H$_2$C), 35.7 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.7 (**C**HAr), 55.2 (CH_3), 59.5 (CH_2O), 92.6 ($CHNO_2$), 112.9 (C_{arom}-H), 113.5 (C_{arom}-H), 119.6 (C_{arom}-H), 123.7 (C_{arom}-H), 125.2 (C_{arom}-H), 127.7 (**C**H=C), 128.5 (C_{arom}-H), 129.9 (C_{arom}-H), 136.4 (**C**=CH), 139.8 (**C**$_{arom}$-CH), 141.0 (**C**$_{arom}$-C), 159.8 (C_{arom}-O). IR (CH_2Cl_2): 3257 (O-H st), 2920 (C-H st), 1548 (NO_2 st), 1372 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}O_2]^+$: 307.1698 (M^+-NO_2); found: 307.1689. MS (70 eV) *m/z* (%): 302 (46, [M^+-C_4H_3]), 207 (7), 83 (7), 28 (100). M.p. (hexanes, EtOAc): 104-105 ºC. The ee (90%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_1=15.32 min, τ_2=18.78 min. $[\alpha]_D^{20}$: -10.1 (*c*=1.0, CH_2Cl_2).



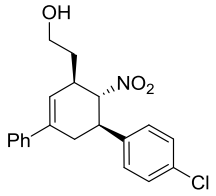
2-((1'*R*,5'*R*,6'*S*)-2-methoxy-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13d). Following the general procedure **E**, **13d** (39 mg, 0.11 mmol) was isolated as a white solid, starting from the acetaldehyde **12d** (42 mg, 0.18 mmol) and $NaBH_4$ (7 mg, 0.18 mmol) in MeOH (3 mL) as solvent. Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74-1.98 (m, 2H, CHC**H**$_2$CH$_2$), 2.77-3.07 (m, 2H, CH$_2$C), 3.27-3.39 (m, 1H, C**H**CH$_2$CH$_2$), 3.78-3.95 (m, 5H, CH$_2$O, CH$_3$), 5.29 (t, *J* = 10.8 Hz, 1H, CHNO$_2$), 6.09 (bs, 1H, CH=C), 6.88-7.00 (m, 2H, C$_{arom}$-H), 7.17-7.46 (m, 7H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ, 33.7 (**C**H$_2$C), 35.2 (CH**C**H$_2$CH$_2$), 39.5 (**C**HCH$_2$CH$_2$), 42.9 (**C**HAr), 55.6 (CH$_3$), 59.7 (CH$_2$O), 90.7 (CHNO$_2$), 111.5 (C$_{arom}$-H), 121.0 (C$_{arom}$-H), 123.7 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 127.2 (**C**$_{arom}$-CH), 127.6 (**C**H=C), 128.4 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 128.9 (C$_{arom}$-H), 136.7 (**C**=CH), 140.1 (**C**$_{arom}$-C), 157.6 (C$_{arom}$-O). IR (CH_2Cl_2): 3347 (O-H st), 2945 (C-H st), 1545 (NO_2 st), 1381 (NO_2 st) cm^{-1} HRMS: Calculated for $[C_{21}H_{23}O_2]^+$: 307.1698 (M^+-NO_2); found: 307.1689. MS (70 eV) *m/z* (%): 302 (58, [M^+-C_4H_3]), 207 (6), 165 (4), 83 (11), 28 (100). M.p. (hexanes, EtOAc): 121-122 ºC. The ee (97%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=26.54 min, τ_2=35.49 min. $[\alpha]_D^{20}$: 10.9 (*c*=1.0, CH_2Cl_2).



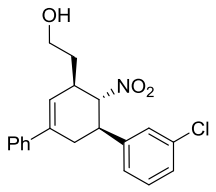
2-((1'*R*,5'*R*,6'*S*)-4-methyl-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13e). Following the general procedure **E**, **13e** (43 mg, 0.13 mmol) was isolated as a white solid, starting from the acetaldehyde **12h** (50 mg, 0.14 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) in MeOH (3 mL) as solvent. Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.96 (m, 2H, CHC**H**$_2$CH$_2$), 2.33 (s, 3H, CH$_3$), 2.70-2.97 (m, 2H, CH$_2$C), 3.27-3.40 (m, 1H, C**H**CH$_2$CH$_2$), 3.54 (td, *J* = 11.4, 5.8 Hz, 1H, CHAr), 3.84 (t, *J* = 6.6 Hz, 2H, CH$_2$O), 4.91 (dd, *J* = 11.6, 10.1 Hz, 1H, CHNO$_2$), 6.06 (td, *J* = 2.3, 1.0 Hz, 1H, CH=C), 7.11-7.20 (m, 4H, C$_{arom}$-H), 7.24-7.41 (m, 5H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (CH$_3$), 35.0 (**C**H$_2$C), 35.9 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.4 (CHAr), 59.7 (CH$_2$O), 92.9 (CHNO$_2$), 123.8 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 127.3 (C$_{arom}$-H), 127.7 (**C**H=C), 128.5 (C$_{arom}$-H), 129.6 (C$_{arom}$-H), 136.3 (**C**=CH), 136.6 (**C**$_{arom}$-CH$_3$), 137.5 (**C**$_{arom}$-CH), 139.8 (**C**$_{arom}$-C). IR (CH_2Cl_2): 3389 (O-H st), 2920 (C-H st), 1551 (NO_2 st), 1379 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}O]^+$: 291.1749 (M^+-NO_2); found: 291.1757. MS (70 eV) *m/z* (%): 286 (100, [M^+-C_4H_3]), 271 (13), 228 (8), 165 (9), 119 (6), 28 (82). M.p. (hexanes, EtOAc): 80-81 ºC. The ee (93%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=26.17 min, τ_2=34.86 min. $[\alpha]_D^{20}$ -8.9 (*c*=1.0, CH_2Cl_2).



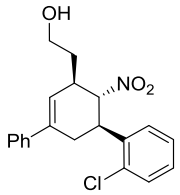
2-((1'*R*,5'*R*,6'*S*)-4-(benzyloxy)-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13f). Following the general procedure **E**, **13f** (75 mg, 0.17 mmol) was isolated as a white solid, starting from the acetaldehyde **2f** (84 mg, 0.19 mmol) and $NaBH_4$ (11 mg, 0.29 mmol) in MeOH (3 mL) as solvent. Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-2.02 (m, 2H, CHC**H**$_2$CH$_2$), 2.70-2.99 (m, 2H, CH_2C), 3.31-3.43 (m, 1H, C**H**CH$_2$CH$_2$), 3.56 (td, *J* = 11.5, 5.7 Hz, 1H, CHAr), 3.84 (t, *J* = 6.4 Hz, 2H, CH_2OH), 4.90 (dd, *J* = 11.6, 10.0 Hz, 1H, $CHNO_2$), 5.07 (s, 2H, PhCH$_2$), 6.09 (d, *J* = 2.1 Hz, 1H, CH=C), 6.95-7.02 (m, 2H, C_{arom}-H), 7.23 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.27-7.52 (m, 10H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.0 (**C**H$_2$C), 35.9 (CH**C**H$_2$CH$_2$), 39.7 (**C**HCH$_2$CH$_2$), 45.1 (CHAr), 59.6 (CH_2O), 70.1 (PhCH$_2$), 93.1 ($CHNO_2$), 115.2 (C_{arom}-H), 123.8 (C_{arom}-H), 125.2 (C_{arom}-H), 127.5 (C_{arom}-H), 127.7 (**C**H=C), 128.0 (C_{arom}-H), 128.5 (C_{arom}-H), 128.5 (C_{arom}-H), 128.6 (C_{arom}-H), 131.6 (**C**$_{arom}$-CH), 136.5 (**C**=CH), 136.9 (**C**$_{arom}$-CH$_2$), 139.9 (**C**$_{arom}$-C), 158.4 (C_{arom}-O). IR (CH_2Cl_2): 3386 (O-H st), 2955 (C-H st), 1548 (NO_2 st), 1379 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{27}H_{27}O_2]^+$: 383.2011 (M^+-NO_2); found: 383.2014. MS (70 eV) *m/z* (%): 336 (14, [M^+-C_7H_7]), 154 (8), 91 (100). M.p. (hexanes, EtOAc): 144-145 ºC. The ee (91%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=28.67 min, τ_2=61.54 min. $[\alpha]_D^{20}$ -7.5 (*c*=1.0, CH_2Cl_2).



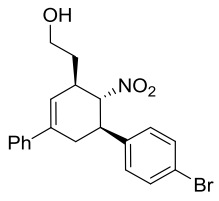
2-((1'*R*,5'*R*,6'*S*)-4-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13g). Following the general procedure **E**, **13g** (47 mg, 0.13 mmol) was isolated as a white solid, starting from the acetaldehyde **12g** (50 mg, 0.14 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) in MeOH (3 mL) as solvent. Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-200 (m, 2H, CHC**H**$_2$CH$_2$), 2.67-2.99 (m, 2H, CH_2C), 3.30-3.43 (m, 1H, C**H**CH$_2$CH$_2$), 3.59 (td, *J* = 11.6, 5.6 Hz, 1H, CHAr), 3.80-3.92 (m, 2H, CH_2O), 4.93 (dd, *J* = 11.7, 10.0 Hz, 1H, $CHNO_2$), 6.09 (dd, *J* = 2.5, 1.1 Hz, 1H, CH=C), 7.22-7.42 (m, 9H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.8 (**C**H$_2$C), 35.7 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.2 (CHAr), 59.5 (CH_2O), 92.6 ($CHNO_2$), 123.8 (C_{arom}-H), 125.2 (C_{arom}-H), 127.8 (**C**H=C), 128.5 (C_{arom}-H), 128.8 (C_{arom}-H), 129.1 (C_{arom}-H), 133.7 (C_{arom}-Cl), 136.3 (**C**=CH), 137.8 (**C**$_{arom}$-CH), 139.6 (**C**$_{arom}$-C). IR (CH_2Cl_2): 3386 (O-H st), 3059 (C-H st), 1547 (NO_2 st), 1376 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{20}H_{20}ClO]^+$: 311.1203 (M^+-NO_2); found: 311.1192. MS (70 eV) *m/z* (%): 306 (100, [M^+-C_4H_3]), 239 (18), 165 (12), 119 (12). M.p. (hexanes, EtOAc): 127-128 ºC. The ee (90%) was determined by HPLC using a *Chiralpak ID-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=25.32 min, τ_2=46.44 min. $[\alpha]_D^{20}$ -11.9 (*c*=1.0, CH_2Cl_2).



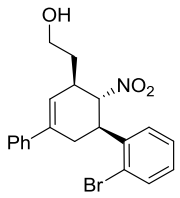
2-((1'*R*,5'*R*,6'*S*)-3-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13h). Following the general procedure **E**, **13h** (43 mg, 0.12 mmol) was isolated as a white solid, starting from the acetaldehyde **12h** (46 mg, 0.13 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) in MeOH (3 mL) as solvent. Yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.99 (m, 2H, CHC**H**$_2$CH$_2$), 2.68-2.99 (m, 2H, CH$_2$C), 3.27-3.41 (m, 1H, C**H**CH$_2$CH$_2$), 3.56 (td, *J* = 11.5, 5.6 Hz, 1H, CHAr), 3.83 (t, *J* = 6.3 Hz, 2H, CH$_2$O), 4.92 (dd, *J* = 11.7, 10.0 Hz, 1H, CHNO$_2$), 6.07 (td, *J* = 2.3, 0.9 Hz, 1H, CH=C), 7.14-7.22 (m, 1H, C$_{arom}$-H), 7.26-7.41 (m, 8H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.8 (**C**H$_2$C), 35.7 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.4 (CHAr), 59.5 (CH$_2$O), 92.4 (CHNO$_2$), 123.7 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 125.7 (C$_{arom}$-H), 127.7 (**C**H=C), 127.8 (C$_{arom}$-H), 128.1 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 130.2 (C$_{arom}$-H), 134.7 (C$_{arom}$-Cl), 136.2 (**C**=CH), 139.6 (**C**$_{arom}$-CH), 141.4 (**C**$_{arom}$-C). IR (CH_2Cl_2): 3376 (O-H st), 2926 (C-H st), 1546 (NO_2 st), 1376 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{20}H_{20}ClO$]$^+$: 311.1203 (M$^+$-NO_2); found: 311.1213. MS (70 eV) *m/z* (%): 306 (100, [M$^+$-C_4H_3]), 239 (14), 165 (16), 119 (16). M.p. (hexanes, EtOAc): 110-111 ºC. The ee (93%) was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=37.55 min, τ_{minor}=42.31 min. $[\alpha]_D^{20}$ -8.9 (*c*=1.0, CH_2Cl_2).



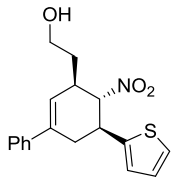
2-((1'*R*,5'*R*,6'*S*)-2-chloro-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13i). Following the general procedure **E**, **13i** (56 mg, 0.16 mmol) was isolated as a colorless oil, starting from the acetaldehyde **12i** (60 mg, 0.17 mmol) and $NaBH_4$ (10 mg, 0.26 mmol) in MeOH (3 mL) as solvent. Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74-1.98 (m, 2H, CHC**H**$_2$CH$_2$), 2.44-2.69 (m, 1H, C**H**$_a$H$_b$C), 2.85-3.03 (m, 1H, CH$_a$**H**$_b$C), 3.28-3.43 (m, 1H, C**H**CH$_2$CH$_2$), 3.85 (td, *J* = 6.4, 1.6 Hz, 2H, CH$_2$O), 4.23-4.49 (m, 1H, CHAr), 5.01-5.16 (m, 1H, CHNO$_2$), 6.08 (q, *J* = 1.9 Hz, 1H, CH=C), 7.14-7.49 (m, 9H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.8 (**C**H$_2$C), 35.2 (CH**C**H$_2$CH$_2$), 39.8 (**C**HCH$_2$CH$_2$), 41.0 (CHAr), 59.6 (CH$_2$O), 91.0 (CHNO$_2$), 123.8 (C$_{arom}$-H), 125.3 (C$_{arom}$-H), 126.8 (C$_{arom}$-H), 127.5 (C$_{arom}$-H), 127.8 (**C**H=C), 128.5 (C$_{arom}$-H), 128.8 (C$_{arom}$-H), 130.2 (C$_{arom}$-H), 134.2 (C$_{arom}$-Cl), 136.3 (**C**=CH), 137.2 (**C**$_{arom}$-CH), 139.7 (**C**$_{arom}$-C). IR (neat): 3368 (O-H st), 2970 (C-H st), 1549 (NO_2 st), 1375 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{20}H_{20}ClO$]$^+$: 311.1203 (M$^+$-NO_2); found: 311.1190. MS (70 eV) *m/z* (%): 306 (72, [M$^+$-C_4H_3]), 239 (8), 165 (8), 119 (6), 28 (100). The ee (96%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=21.85 min, τ_2=26.27 min. $[\alpha]_D^{20}$ 20.4 (*c*=1.0, CH_2Cl_2).



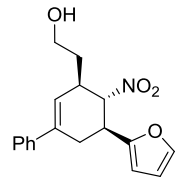
2-((1'*R*,5'*R*,6'*S*)-4-bromo-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13j). Following the general procedure **E**, **13j** (42 mg, 0.10 mmol) was isolated as a white solid, starting from the acetaldehyde **12j** (43 mg, 0.11 mmol) and $NaBH_4$ (6 mg, 0.16 mmol) in MeOH (3 mL) as solvent. Yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-2.00 (m, 2H, CHC**H**$_2$CH$_2$), 2.64-3.01 (m, 2H, CH$_2$C), 3.34 (dtt, *J* = 10.0, 5.2, 2.6 Hz, 1H, **C**HCH$_2$CH$_2$), 3.56 (td, *J* = 11.6, 5.6 Hz, 1H, CHAr), 3.78-3.90 (m, 2H, CH$_2$O), 4.90 (dd, *J* = 11.7, 10.1 Hz, 1H, CHNO$_2$), 6.06 (dt, *J* = 2.9, 1.4 Hz, 1H, CH=C), 7.12-7.20 (m, 2H, Carom-H), 7.24-7.40 (m, 5H, Carom-H), 7.44-7.52 (m, 2H, Carom-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.8 (**C**H$_2$C), 35.7 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 45.3 (CHAr), 59.5 (CH$_2$O), 92.5 (CHNO$_2$), 121.8 (C$_{arom}$-Br), 123.8 (C$_{arom}$-H), 125.2 (C$_{arom}$-H), 127.8 (**C**H=C), 128.5 C$_{arom}$-H), 129.2 C$_{arom}$-H), 132.1 (C$_{arom}$-H), 136.3 (**C**=CH), 138.4 (**C**$_{arom}$-CH), 139.6 (**C**$_{arom}$-C). IR (CH_2Cl_2): 3393 (O-H st), 2920 (C-H st), 1545 (NO_2 st), 1379 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{20}H_{20}BrO$]$^+$: 355.0698 (M$^+$-NO_2); found: 355.0681. MS (70 eV) *m/z* (%): 350 (5, [M$^+$-C_4H_3]), 303 (93), 265 (100), 229 (37), 215 (35), 165 (40), 128 (54), 115 (59), 91 (75), 77 (38). M.p. (hexanes, EtOAc): 139-140 ºC. The ee (96%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=28.10 min, τ_2=60.59 min. $[\alpha]_D^{20}$ 10.7 (*c*=1.0, CH_2Cl_2).



2-((1'*R*,5'*R*,6'*S*)-2-bromo-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13k). Following the general procedure **E**, **13k** (52 mg, 0.37 mmol) was isolated as a yellow oil, starting from the acetaldehyde **12k** (56 mg, 0.14 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) in MeOH (3 mL) as solvent. Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74-2.02 (m, 2H, CHC**H**$_2$CH$_2$), 2.45-2.66 (m, 1H, C**H**$_a$H$_b$C), 2.98 (dd, *J* = 17.9, 5.1 Hz, 1H, CH$_a$**H**$_b$C), 3.29-3.47 (m, 1H, **C**HCH$_2$CH$_2$), 3.86 (tt, *J* = 6.2, 3.0 Hz, 2H, CH$_2$O), 4.32 (td, *J* = 11.6, 5.4 Hz, 1H, CHAr), 4.99-5.21 (m, 1H, CHNO$_2$), 6.08 (d, *J* = 2.3 Hz, 1H, CH=C), 7.13 (td, *J* = 7.5, 6.9 Hz, 1H, C$_{arom}$-H), 7.23-7.44 (m, 7H, C$_{arom}$-H), 7.58 (dd, *J* = 8.0, 1.1 Hz, 1H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.7 (**C**H$_2$C), 35.2 (CH**C**H$_2$CH$_2$), 39.8 (**C**HCH$_2$CH$_2$), 43.8 (CHAr), 59.6 (CH$_2$O), 91.0 (CHNO$_2$), 123.8 (C$_{arom}$-H), 124.8 (C$_{arom}$-Br), 125.2 (C$_{arom}$-H), 126.8 (C$_{arom}$-H), 127.7 (**C**H=C), 128.1 (C$_{arom}$-H), 128.5 (C$_{arom}$-H), 129.0 (C$_{arom}$-H), 133.5 (C$_{arom}$-H), 136.3 (**C**=CH), 138.8 (**C**$_{arom}$-CH), 139.6 (**C**$_{arom}$-C). IR (neat): 3364 (O-H st), 2930 (C-H st), 1548 (NO_2 st), 1368 (NO_2 st) cm^{-1}. HRMS: Calculated for [$C_{20}H_{20}BrO$]$^+$: 355.0698 (M$^+$-NO_2); found: 355.0698. MS (70 eV) *m/z* (%): 350 (41, [M$^+$-C_4H_3]), 239 (8), 207 (6), 165 (6), 28 (100). The ee (93%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=19.84 min, τ_2=23.14 min. $[\alpha]_D^{20}$ 15.2 (*c*=0.7, CH_2Cl_2).

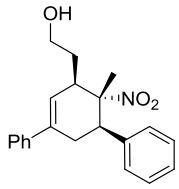


2-((3*R*,4*S*,5*S*)-4-nitro-5-(thiophen-2-yl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)ethanol (13l). Following the general procedure **E**, **13l** (36 mg, 0.11 mmol) was isolated as a yellow oil, starting from the acetaldehyde **12l** (40 mg, 0.12 mmol) and $NaBH_4$ (7 mg, 0.18 mmol) in MeOH (3 mL) as solvent. Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.97 (m, 2H, CHC**H**$_2$CH$_2$), 2.77-2.95 (m, 1H, C**H**$_a$H$_b$C), 3.05 (dddd, *J* = 17.6, 5.5, 1.9, 1.0 Hz, 1H, CH$_a$**H**$_b$C), 3.36 (dddd, *J* = 12.0, 6.1, 3.3, 1.4 Hz, 1H, **C**HCH$_2$CH$_2$), 3.78-3.87 (m, 2H, CH$_2$O), 3.93 (td, *J* = 11.5, 5.5 Hz, 1H, CHAr), 4.80 (dd, *J* = 11.4, 10.1 Hz, 1H, CHNO$_2$), 6.05 (td, *J* = 2.4, 0.9 Hz, 1H, CH=C), 6.92-6.99 (m, 2H, C$_{Heteroarom}$-H), 7.22-7.25 (m, 1H, C$_{Heteroarom}$-H), 7.28-7.43 (m, 5H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 35.0 (**C**H$_2$C), 36.5 (CH**C**H$_2$CH$_2$), 39.6 (**C**HCH$_2$CH$_2$), 41.0 (CHAr), 59.6 (CH$_2$O), 94.2 (CHNO$_2$), 123.8 (C$_{arom}$-H), 124.7 (C$_{Heteroarom}$-H), 125.3 (C$_{arom}$-H), 125.8 (C$_{Heteroarom}$-H), 127.0 (C$_{Heteroarom}$-H), 127.8 (**C**H=C), 128.6 (C$_{arom}$-H), 136.1 (**C**=CH), 139.7 (C$_{arom}$-C), 142.1 (**C**$_{Heteroarom}$-CH). IR (neat): 3368 (O-H st), 2923 (C-H st), 1548 (NO$_2$ st), 1372 (NO$_2$ st) cm^{-1}. HRMS: Calculated for [C$_{18}$H$_{19}$OS]$^+$: 283.1157 (M$^+$-NO$_2$); found: 283.1161. MS (70 eV) *m/z* (%): 278 (96, [M$^+$-C$_4$H$_3$]), 245 (18), 215 (30), 165 (23), 115 (28), 91 (100). The ee (97%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=26.77 min, τ_2=34.14 min. $[\alpha]_D^{20}$ -6.8 (*c* = 0.5, CH_2Cl_2).



2-((3*R*,4*S*,5*S*)-5-(furan-2-yl)-4-nitro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)ethanol (13m). Following the general procedure **E**, **13m** (31 mg, 0.10 mmol) was isolated as a white solid, starting from the acetaldehyde **12m** (36 mg, 0.11 mmol) and $NaBH_4$ (7 mg, 0.18 mmol) in MeOH (3 mL) as solvent. Yield: 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.96 (m, 2H, CHC**H**$_2$CH$_2$), 2.85-3.08 (m, 2H, CH$_2$C), 3.34 (dtt, *J* = 10.0, 4.1, 2.0 Hz, 1H, **C**HCH$_2$CH$_2$), 3.76 (td, *J* = 11.3, 6.4 Hz, 1H, CHAr), 3.85 (t, *J* = 5.5 Hz, 2H, CH$_2$O), 4.90 (dd, *J* = 11.5, 10.1 Hz, 1H, CHNO$_2$), 6.05 (dt, *J* = 2.5, 1.2 Hz, 1H, CH=C), 6.18-6.26 (m, 1H, C$_{Heteroarom}$-H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H, C$_{Heteroarom}$-H), 7.30-7.46 (m, 6H, C$_{arom}$-H, C$_{Heteroarom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.3 (**C**H$_2$C), 34.9 (CH**C**H$_2$CH$_2$), 39.0 (**C**HCH$_2$CH$_2$), 39.0 (CHAr), 59.6 (CH$_2$O), 91.3 (CHNO$_2$), 107.3 (C$_{Heteroarom}$-H), 110.3 (C$_{Heteroarom}$-H), 123.6 (C$_{arom}$-H), 125.5 (C$_{arom}$-H), 127.8 (**C**H=C), 128.5 (C$_{arom}$-H), 135.9 (**C**=CH), 139.8 (**C**$_{arom}$-C), 142.4 (C$_{Heteroarom}$-H), 152.2 (**C**$_{Heteroarom}$-CH). IR (CH_2Cl_2): 3376 (O-H st), 2920 (C-H st), 1548 (NO$_2$ st), 1376 (NO$_2$ st) cm^{-1}. HRMS: Calculated for [C$_{18}$H$_{19}$O$_2$]$^+$: 267.1385 (M$^+$-NO$_2$); found: 267.1379. MS (70 eV) *m/z* (%): 248 (22, [M$^+$-C$_5$H$_5$]), 206 (10), 144 (100), 115 (58), 91 (19). M.p. (hexanes, EtOAc): 95-96 ºC. The ee (89%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-

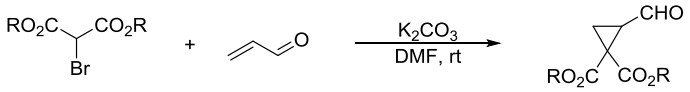
PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=26.95 min, τ_2=34.13 min. $[\alpha]_D^{20}$ -18.2 (*c*=1.0, CH_2Cl_2).



2-((1'*R*,5'*R*,6'*S*)-6'-methyl-6'-nitro-1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-5'-yl)ethanol (13n). Following the general procedure **E**, **13n** (30 mg, 0.09 mmol) was isolated as a yellow oil, starting from the acetaldehyde **12n** (34 mg, 0.10 mmol) and $NaBH_4$ (6 mg, 0.15 mmol) in MeOH (3 mL) as solvent. Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3H, CH_3), 1.54-1.67 (m, 2H, CHC**H**$_2$CH$_2$), 2.79-3.05 (m, 2H, CH_2C), 3.66-3.76 (m, 1H, **C**HCH$_2$CH$_2$), 3.77-3.91 (m, 2H, CH_2O), 6.07 (td, *J* = 2.1, 1.3 Hz, 1H, CH=C), 7.20-7.27 (m, 2H C_{arom}-H), 7.29-7.39 (m, 6H, C_{arom}-H), 7.40-7.48 (m, 2H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3 (CH_3), 32.4 (**C**H$_2$C), 33.0 (CH**C**H$_2$CH$_2$), 43.3 (**C**HCH$_2$CH$_2$), 49.5 (CHAr), 60.3 (CH_2O), 95.0 (CNO_2), 124.5 (C_{arom}-H), 125.2 (C_{arom}-H), 127.7 (**C**H=C), 128.1 (C_{arom}-H), 128.5 (C_{arom}-H), 128.6 (C_{arom}-H), 128.7 (C_{arom}-H), 135.7 (**C**$_{arom}$-CH), 137.2 (**C**=CH), 139.8 (**C**$_{arom}$-C). IR (neat): 3368 (O-H st), 2923 (C-H st), 1533 (NO_2 st), 1389 (NO_2 st) cm^{-1}. HRMS: Calculated for $[C_{21}H_{23}O]^+$: 291.1749 (M^+-NO_2); found: 291.1758. MS (70 eV) *m/z* (%): 290 (23, [M^+-NO_2]), 245 (34), 215 (8), 165 (11), 128 (10), 105 (22), 28 (100). The ee (96%) was determined by HPLC using a *Chiralpak IE-3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.90 mL/min; τ_1=38.05 min, τ_2=40.74 min. $[\alpha]_D^{20}$ -69.2 (*c*=1.0, CH_2Cl_2).

4. *N*-HETEROCYCLIC CARBENE-CATALYZED [4+2] CYCLOADDITION REACTION

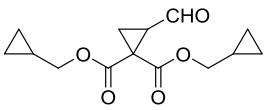
4.1 Synthesis of 2-formylcyclopropane-1,1-dicarboxylate derivatives 16a-f



16a-f

General Procedure F for the Preparation of 2-formylcyclopropane-1,1-dicarboxylate derivatives **16a-f**:

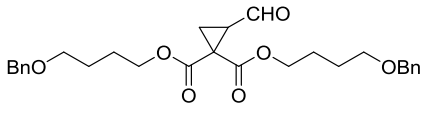
2-Formylcyclopropane-1,1-dicarboxylate derivatives were prepared according to literature procedures[9] as follows. The corresponding dialkylbromomalonate (2.0 mmol, 1 equiv) was added over a solution of freshly distilled acrolein (2.4 mmol, 1.2 equiv) in DMF (0.2 M, 10 mL) at room temperature and K_2CO_3 (4 mmol, 2 equiv) was then added. The reaction was stirred for 5 h, then diluted with Et_2O (20 mL) and quenched with glacial AcOH and water until pH=7. The aqueous layer was extracted with Et_2O (5 × 20 mL). The organic layers were washed with brine (3 × 20 mL), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) to afford the corresponding 2-formylcyclopropane-1,1-dicarboxylate **16a-f**. Spectroscopic data for **16a**,[9] **16b**,[10] **16c**,[11] **16d**,[12] were in agreement with those reported in the literature.



Bis(cyclopropylmethyl) 2-formylcyclopropane-1,1-dicarboxylate (16e). Following the general procedure **F**, **16e** (771 mg, 1.65 mmol) was isolated as colorless oil, using bis(cyclopropylmethyl) 2-bromomalonate (580 mg, 2.0 mmol), acrolein (0.11 mL, 2.4 mmol) and K_2CO_3 (550 mg, 4.0 mmol). Yield: 56%. Rf (hexanes/EtOAc 6:4): 0.55. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (ddd, *J* = 6.4, 4.6, 2.0, Hz, 4H, 2 × $C_{2'}$-**H**$_a$H$_b$, 2 × $C_{3'}$-**H**$_a$H$_b$), 0.49-0.58 (m, 4H, $C_{2'}$-H$_a$**H**$_b$, 2 × $C_{3'}$-H$_a$**H**$_b$), 1.09 (tt, *J* = 9.1, 3.9, 2H, 2 × $C_{1'}$-H), 1.78 (dd, *J* = 8.8, 5.0 Hz, 1H, C**H**$_a$H$_b$), 2.04 (dd, *J* = 6.9, 5.0 Hz, 1H, CH$_a$**H**$_b$), 2.70 (ddd, *J* = 8.8, 6.9, 4.6 Hz, C**H**CHO), 3.86-4.11 (m, 4H, OCH_2), 9.26 (d, *J*

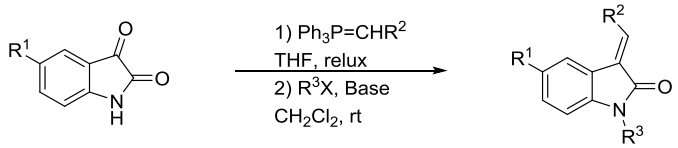
[9] Dias, D. A.; Kerr, M. A. *Org. Lett.*, **2009**, *11*, 3694.
[10] Benjamin, D.; Sherry, B. D.; Fürstner, A. *Chem. Commun.* **2009**, 7116.
[11] Nishikate, T.; Noda, Y.; Fujimoto, R; Ishikawa, S. *Chem. Commun.* **2015**, *51*, 12843.
[12] Du, D.; Li, L.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 4379.

= 4.6 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.2, 3.2, 3.3, 3.3 (2 × $C_{2'}$, 2 × $C_{3'}$), 9.5 ($C_{1'}$), 19.2 (C_3), 34.8 (C_2), 37.7 (C_1), 71.0 (CH_2O), 166.0 (COO) 167.9 (COO), 196.3 (CHO). IR (neat): 3005 (C-H st), 2955 (C-H st), 1715 (C=O st), 1259, 1196 (C-O st) cm^{-1}. MS (EI) m/z (%): 195 (9), 55 (100). HRMS (ESI+): Calculated for $[C_{14}H_{18}O_5Na]^+$: 289.1052 $[(M+Na)^+]$; found: 289.1040.



Bis(4-(benzyloxy)butyl) 2-formylcyclopropane-1,1-dicarboxylate (16f). Following the general procedure **F**, **16f** (771 mg, 1.65 mmol) was isolated as a colorless oil, using bis(4-(benzyloxy)butyl) 2-bromomalonate (1.1 g, 2.0 mmol), acrolein (0.11 mL, 2.4 mmol) and K_2CO_3 (550 mg, 4.0 mmol). Yield: 86%. Rf (hexanes/EtOAc 6:4): 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61-1.82 (m, 9H, C**H**$_2$C*H*$_2$CH$_2$O, C_3-**H**$_a$H$_b$), 2.03-2.08 (m, 1H, C_3-H$_a$**H**$_b$), 2.74 (ddd, *J* = 8.8, 6.9, 4.4 Hz, 1H, C_1-H) 3.48 (td, *J* = 6.1, 1.9 Hz, 4H, BnOC**H**$_2$), 4.19 (td, *J* = 5.7, 5.0, 3.2 Hz, 4H, CO_2CH_2), 4.49 (s, 4H, C**H**$_2$Ph), 7.27-7.39 (m, 10H, C_{arom}-H), 9.32 (d, *J* = 4.4 Hz, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.4 (C_3), 25.4, 25.4 (CO_2CH_2**C**H$_2$), 26.1, 26.1 (BnOCH$_2$**C**H$_2$), 34.8 (C_2), 37.8 (C_1), 66.1 (CO_2**C**H$_2$), 66.3 (CO_2**C**H$_2$), 69.5 (BnO**C**H$_2$), 69.6 (BnO**C**H$_2$), 72.9 (Ph**C**H$_2$), 127.6 (C_{arom}-H), 128.4 (C_{arom}-H), 138.4 (**C**$_{arom}$-C), 165.9 (COO), 167.9 (COO), 196.3 (CHO). IR (neat): 2955 (C-H st), 2858 (C-H st), 1736 (C=O st), 1263, 1199 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for $[C_{28}H_{34}O_7Na]^+$: 505.2202 $[(M+Na)^+]$; found: 505.2206.

4.2 Synthesis of isatin derivatives 17a-l



17a-c, 17f-l

General Procedure G for the Preparation of isatin derivatives **17a-c, 17f-l**:

N-(*tert*-butoxycarbonyl)alkylideneoxindole derivatives were prepared according to an addapted literature procedure.[13] To a solution of the corresponding alkyltriphenylphosphonium halide (3.0 mmol, 1 equiv), synthesized from the alkyl halide and triphenylphosphine, in THF (10 mL, 0.3 M) at 0 ºC, sodium hydride (3.15 mmol, 1.05 equiv), as dispersion in mineral oil, was added. The reaction was stirred at room temperature for 1 h. Then, the corresponding isatine (2.85 mmol, 0.95 equiv) was added as a solid and the mixture was refluxed for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL), the organic layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 1:1) to afford the *N*-H alkylideneoxindole derivative. To a solution of the corresponding *N*-H alkylideneoxindole derivative (2.5 mmol, 1.0 equiv) and 4-dimethylaminopyridine (0.125 mmol, 0.05 equiv) in CH_2Cl_2 (8 mL, 0.3 M) at room temperature di-*tert*-butyl dicarbonate (3.0 mmol, 1.2 equiv) was added in one portion. The reaction was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and directly purified by flash column chromatography (hexanes/EtOAc gradient 19:1 to 9:1) to afford the *N*-(*tert*-butoxycarbonyl)alkylideneoxindole derivative. Spectroscopic data for **17a**,[14] **17g-h**,[15] **17j,**[16] **17k-l**,[17] were in agreement with those reported in the literature.

N-(benzyloxycarbonyl)alkylideneoxindole derivative **17b**[16] was prepared following general procedure **G** using benzyl-chloroformate (3.0 mmol, 1.2 equiv) and trilethylamine (3.0 mmol, 1.2 equiv) instead of di-*tert*-butyl dicarbonate. Spectroscopic data were in agreement with those reported in the literature.

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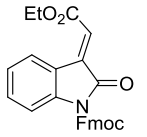
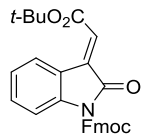
13 Manoni, F.; Connon, S. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2628.
14 Cao, S.-H.; Zhang, X.-C.; Wei, Y.; Shi, M. *Eur. J. Org. Chem*. **2011**, 2668.
15 Tan, B.; Hernández-Torres, G.; Barbas III, C. F. *J. Am. Chem. Soc*. **2011**, *133*, 12354.
16 Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 15212.
17 Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. *Chem. Eur. J*. **2012**, *18*, 6737.

N-(acetyl)alkylideneoxindole derivative **17f**[18] was prepared following general procedure **G** using acetic anhydride (3.0 mmol, 1.2 equiv) instead of di-*tert*-butyl dicarbonate. Spectroscopic data were in agreement with those reported in the literature.

N-(9-fluorenylmethoxycarbonyl)alkylideneoxindole derivatives **17c**, **17i** were prepared following general procedure **G** using 9-fluorenylmethoxycarbonyl chloride (3.0 mmol, 1.2 equiv) and *N*,*N*-diisopropylethylamine (2.75 mmol, 1.1 equiv) instead of di-*tert*-butyl dicarbonate.



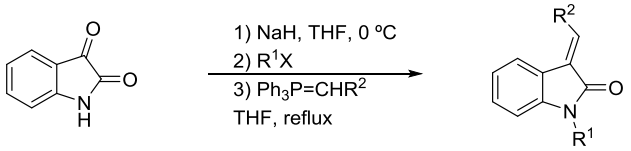
(9*H*-fluoren-9-yl)methyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (17c). Following the general procedure **G**, **17c** (900 mg, 2.05 mmol) was isolated as a yellow solid, using isatine (420 mg, 2.85 mmol) and (carbethoxymethylene)triphenylphosphorane (1.05g, 3.0 mmol). Yield: 82%. Rf (hexanes/EtOAc 8:2): 0.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 4.32-4.45 (m, 3H, CH$_2$C*H*, CH$_3$C*H*$_2$O), 4.70 (d, *J* = 7.1 Hz, 2H, CHC*H*$_2$O), 6.99 (s, 1H, C$_3$=CH), 7.20 (td, *J* = 7.7, 1.1 Hz, 1H, C$_5$-H), 7.31-7.47 (m, 5H, C$_6$-H, C$_{arom}$-H), 7.74 (d, 1H, *J* = 8.2 Hz, C$_7$-H), 7.79 (ddd, *J* = 6.8, 4.2, 1.2 Hz, 4H, C$_{arom}$-H), 8.70 (dd, *J* = 7.9, 1.4 Hz, 1H, C$_4$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (*C*H$_3$CH$_2$O), 43.5 (*C*HCH$_2$), 61.4 (CH$_3$*C*H$_2$O), 69.2 (CH*C*H$_2$), 115.0 (C$_7$-H), 120.0 (C$_{arom}$-H), 120.2 (C$_{3a}$), 123.6 (C$_4$-H), 124.9 (C$_5$-H), 125.3, 127.3, 127.9 (C$_{arom}$-H), 128.3 (C$_6$-H), 132.8 (C$_3$=*C*H), 135.9 (C$_3$), 141.2 (*C*$_{arom}$-C), 141.3 (C$_{7a}$), 143.7 (*C*$_{arom}$-C), 150.4 (NCO), 165.2 (C$_2$), 165.5 (*C*OOEt). IR (neat): 2973 (C-H st), 1731 (C=O st), 1706 (C=O st), 1188 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for [$C_{27}H_{21}NO_5Na$]$^+$: 462.1317 [(M+Na)$^+$]; found: 462.1317. M.p. (hexanes/EtOAc): 175-177 ºC.



(9*H*-fluoren-9-yl)methyl (*E*)-3-(2-(tert-butoxy)-2-oxoethylidene)-2-oxoindoline-1-carboxylate (17i). Following the general procedure **G**, **17i** (930 mg, 2.0 mmol) was isolated as a pale yellow solid, using isatine (420 mg, 2.85 mmol) and (*tert*-butoxyarbonylmethylene)triphenylphosphorane (1.12 g, 3.0 mmol). Yield: 70%. Rf (hexanes/EtOAc 6:4): 0.55. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H, C(CH$_3$)$_3$), 4.42 (t, *J* = 7.0 Hz, 1H, C*H*CH$_2$), 4.70 (d, *J* = 7.1 Hz, 2H, CHC*H*$_2$), 6.96 (s, 1H, C$_3$=CH), 7.21 (td, *J* = 7.7, 1.1 Hz, 1H, C$_5$-H), 7.32-7.48 (m, 5H, C$_6$-H, C$_{arom}$-H), 7.72-7.84 (m, 5H, C$_7$-H, C$_{arom}$-H), 8.67 (dd, *J* = 7.9, 1.4 Hz, 1H, C$_4$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.1 (C(*C*H$_3$)$_3$), 46.6 (*C*HCH$_2$), 69.2 (CH*C*H$_2$), 82.3 (*C*(CH$_3$)$_3$), 115.0 (C$_7$-H), 120.0 (C$_{arom}$-H), 120.4 (C$_{3a}$), 124.9 (C$_4$-H), 125.4 (C$_{arom}$-H), 126.0 (C$_5$-H), 127.3 (C$_{arom}$-H), 128.0 (C$_{arom}$-H), 128.1 (C$_6$-H), 132.5 (C$_3$=*C*H), 134.9 (C$_3$), 141.1 (C$_{arom}$-C), 141.4 (C$_{7a}$), 143.4 (C$_{arom}$-C),150.5 (NCO), 164.6 (C$_2$), 165.8 (*C*OO*t*-Bu). IR

[18] Wang, L.; Zhang, D.; Li, J.; Xu, G.; Sun, J. *RSC Adv*. **2014**, *4*, 44193.

(neat): 2977 (C-H st), 1732 (C=O st), 1712 (C=O st), 1146 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for $[C_{29}H_{25}NO_5Na]^+$: 490.1630 $[(M+Na)^+]$; found: 490.1646. M.p. (hexanes/EtOAc): 144-146 ºC.

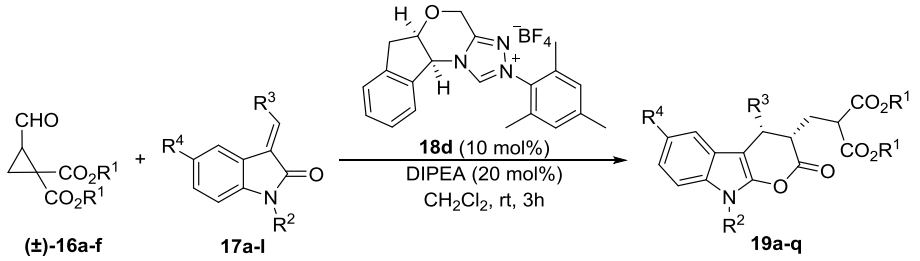


General Procedure H for the Preparation of isatin derivatives **17d-e**:

N-(alkyl)-alkylideneoxindole derivatives **17d**[19] and **17e**[16] were prepared in two steps according to an addapted literature procedure,[20] as follows. 1st step: To a solution of isatin (5.0 mmol, 1 equiv) in anhydrous DMF (10 ml, 0.5 M) at 0 °C, sodium hydride (60% dispersion in oil, 6.0 mmol, 1.2 equiv) was added in one portion and stirred for 1 h. The corresponding alkyl halide (7.5 mmol, 1.5 equiv) was added and the reaction was stirred at 0 °C for 30 min. The reaction mixture was then poured into saturated aqueous solution of NH_4Cl and extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with water (3 × 15 mL) and brine (20 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude *N*-alkyl isatin product which was purified by column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3). 2nd step: To a solution of the corresponding alkyltriphenylphosphonium halide (3.0 mmol, 1 equiv), synthesized from the alkyl halide and triphenylphosphine, in THF (10 mL, 0.3 M) at 0 ºC, sodium hydride (3.15 mmol, 1.05 equiv), as dispersion in mineral oil, was added. The reaction was stirred at room temperature for 1 h. Then, the previously synthesized *N*-alkyl isatine (2.85 mmol, 0.95 equiv) was added as a solid and the mixture was refluxed for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL), the organic layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 1:1) yielding the *N*-(alkyl)-alkylideneoxindole derivatives **17d-e**. Spectroscopic data were in agreement with those reported in the literature.

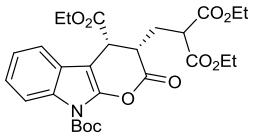
[19] Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem. Int. Ed*. 2011, **50**, 9124.
[20] B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* 2011, **133**, 20611.

4.3 Synthesis of [2,3-*b*]indole adducts 19a-q



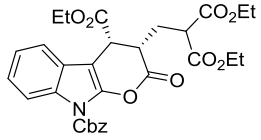
General Procedure I for the Preparation of [2,3-b]indole adducts **19a-q**:

Into as oven-dryed, screw-capped vial equipped with a magnetic stir bar, the triazolium salt **18d** (0.02 mmol, 0.1 equiv) was weighed. The vial was capped with a septum cap and purged with argon for 5 min. Then, to the vial under positive argon pressure, were successively added CH_2Cl_2 (1 mL), *N*,*N*-diisopropylethylamine (0.04 mmol, 0.2 equiv), the corresponding formilcyclopropane dicarboxylate **16a-l** (0.30 mmol, 1.5 equiv) in solution of CH_2Cl_2 (1 mL) via syringe, and the corresponding 3-methylene-2-oxindol **17a-f** (0.20 mmol, 1.0 equiv) was added as a solid removing the septum cap and stirred at 23 ºC for 3 h. The crude reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (hexanes/EtOAc gradient from 19:1 to 9:1), affording the corresponding adducts **19a-q**. Racemic samples were obtained following the same protocol but with 2-(pentafluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate **18a** (0.1 mmol, 0.1 equiv) as catalyst.

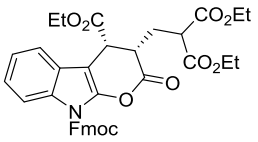


9-(*tert*-Butyl) 4-ethyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-b]indole-4,9(2*H*)-dicarboxylate (19a). Following the general procedure **I**, **19a** (100 mg, 0.19 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 94%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2CH_3)_2$), 1.28 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2CH_3)_2$), 1.67 (s, 9H, $C(CH_3)_3$), 2.16 (ddd, *J* = 14.1, 9.1, 4.7 Hz, 1H, C_3-CH_aH_b), 2.69 (ddd, *J* = 14.1, 8.3, 5.9 Hz, 1H, C_3-CH_aH_b), 3.08 (ddd, *J* = 8.3, 6.1, 4.7 Hz, 1H, C_3-H), 3.81 (dd, *J* = 9.1, 5.9 Hz, 1H, C_3-CH_2CH), 4.05 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.07-

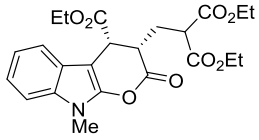
4.29 (m, 6H, C_4-$CO_2C\mathbf{H}_2$, $CH(CO_2C\mathbf{H}_2CH_3)_2$), 7.23-7.31 (m, 2H, C_6-H, C_7-H), 7.43-7.50 (m, 1H, C_5-H), 8.05-8.13 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9 (C_4-$CO_2CH_2\mathbf{C}H_3$), 14.0 ($CH(CO_2CH_2\mathbf{C}H_3)_2$), 27.4 ($C_3$-$\mathbf{C}H_aH_b$), 28.0 ($C(\mathbf{C}H_3)_3$), 39.3 ($C_4$), 40.3 ($C_3$), 49.6 ($C_3$-$CH_2\mathbf{C}H$), 61.7 ($CH(CO_2\mathbf{C}H_2CH_3)_2$), 61.8 ($C_4$-$CO_2\mathbf{C}H_2$), 85.0 ($\mathbf{C}(CH_3)_3$), 93.0 ($C_{4a}$), 115.3 ($C_8$), 117.6 ($C_5$), 123.6 ($C_6$), 123.6 ($C_7$), 124.5 ($C_{4b}$), 131.5 ($C_{8a}$), 144.4 (NCO), 148.1 ($C_{9a}$), 166.8 ($C_2$), 168.6, 168.9 ($CH(\mathbf{C}O_2Et)_2$), 169.9 ($C_4$-$\mathbf{C}O_2$). IR (neat): 2984 (C-H st), 1794 (C=O st), 1731 (C=O st), 1148 (C-O st) cm^{-1}. MS (EI) m/z (%): 281 (25), 207 (71), 169 (100), 133 (74), 104 (39), 91 (43), 77 (52), 51 (60). HRMS (ESI+): Calculated for $[C_{27}H_{34}NO_{10}]^+$: 532.2183 $[(M+H)^+]$; found: 532.2192. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=7.06 min, τ_2=8.46 min (>99%). $[\alpha]_D^{20}$: -7.3 (*c*=1.0, CH_2Cl_2).



9-Benzyl 4-ethyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19b). Following the general procedure **I**, **19b** (89 mg, 0.16 mmol) was isolated as a yellow oil, using benzyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17b** (70 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 79%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2C\mathbf{H}_3$), 1.26 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 1.28 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 2.17 (ddd, *J* = 14.1, 9.1, 4.6 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.70 (ddd, *J* = 14.2, 8.3, 5.8 Hz, 1H, C_3-$CH_a\mathbf{H}_b$), 3.09 (ddd, *J* = 8.3, 6.1, 4.6 Hz, 1H, C_3-H), 3.82 (dd, *J* = 9.1, 5.8 Hz, 1H, C_3-$CH_2C\mathbf{H}$), 4.06 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.09-4.27 (m, 6H, C_4-$CO_2C\mathbf{H}_2$, $CH(CO_2C\mathbf{H}_2CH_3)_2$), 5.50 (s, 1H, $PhC\mathbf{H}_2O$), 7.23-7.32 (m, 2H, C_6-H, C_7-H), 7.33-7.50 (m, 4H, C_{arom}-H), 7.52-7.58 (m, 2H, C_{arom}-H, C_5-H), 8.10-8.19 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.0 (C_4-$CO_2CH_2\mathbf{C}H_3$, $CH(CO_2CH_2\mathbf{C}H_3)_2$), 27.5 ($C_3$-$\mathbf{C}H_2$), 39.3 ($C_4$), 40.4 ($C_3$), 49.6 ($C_3$-$CH_2\mathbf{C}H$), 61.8 ($CH(CO_2\mathbf{C}H_2CH_3)_2$), 61.9 ($C_4$-$CO_2\mathbf{C}H_2$), 69.1 ($Ph\mathbf{C}H_2O$), 93.6 ($C_{4a}$), 115.4 ($C_8$), 117.7 ($C_5$), 123.9 ($C_6$), 124.0 ($C_7$), 124.6 ($C_{4b}$), 128.2 ($C_{arom}$-H), 128.6 ($C_{arom}$-H), 128.7 ($C_{arom}$-H), 131.5 ($\mathbf{C}_{arom}$-C), 134.7 ($C_{8a}$), 144.2 ($C_{9a}$), 149.6 (NCO), 166.7 ($C_2$), 168.6, 168.9 ($CH(\mathbf{C}O_2Et)_2$), 169.7 ($C_4$-$\mathbf{C}O_2$). IR (neat): 2984 (C-H st), 1778 (C=O st), 1738 (C=O st), 1148 (C-O st) cm^{-1}. MS (EI) m/z (%): 339 (7), 280 (28), 271 (39), 251 (29), 207 (100), 170 (54), 141 (23), 115 (44), 91 (51), 79 (33), 77 (28), 51 (26). HRMS (ESI-): Calculated for $[C_{30}H_{30}NO_{10}]^-$: 564.1870 $[(M-H)^-]$; found: 564.1867. The ee (85%) was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=17.03 min, τ_2=31.32 min. $[\alpha]_D^{20}$: +46.7 (*c*=1.0, CH_2Cl_2).

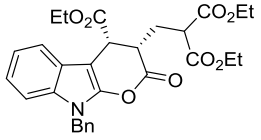


9-((9*H*-Fluoren-9-yl)methyl) 4-ethyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19c). Following the general procedure **I**, **19c** (131 mg, 0.20 mmol) was isolated as a yellow oil, using (9*H*-fluoren-9-yl)methyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17c** (88 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 99%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2C\mathbf{H}_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 1.31 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 2.23 (ddd, *J* = 14.0, 9.0, 4.6 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.76 (ddd, *J* = 14.3, 8.4, 5.8 Hz, 1H, C_3-$CH_a\mathbf{H}_b$), 3.18 (ddd, *J* = 8.4, 6.1, 4.6 Hz, 1H, C_3-H), 3.88 (dd, *J* = 9.0, 5.8 Hz, 1H, C_3-$CH_2C\mathbf{H}$), 4.10 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.12-4.31 (m, 6H, C_4-$CO_2C\mathbf{H}_2$, $CH(CO_2C\mathbf{H}_2CH_3)_2$), 4.42 (t, *J* = 6.6 Hz, 1H, $C\mathbf{H}CH_2O$), 4.80 (qd, *J* = 10.7, 6.6 Hz, 2H, $CHC\mathbf{H}_2O$), 7.15-7.51 (m, 7H, C_5-H, C_6-H, C_7-H, C_{arom}-H), 7.77-7.89 (m, 5H, C_8-H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 ($CH(CO_2CH_2\mathbf{C}H_3)_2$), 27.4 ($C_3$-$\mathbf{C}H_2$), 39.2 ($C_4$), 40.4 ($C_3$), 46.6 ($\mathbf{C}HCH_2O$), 49.5 ($C_3$-$CH_2\mathbf{C}H$), 61.8 ($CH(CO_2\mathbf{C}H_2CH_3)_2$), 61.9 ($CH(CO_2\mathbf{C}H_2CH_3)_2$), 69.4 ($CH\mathbf{C}H_2O$), 93.7 ($C_{4a}$), 115.4 ($C_8$), 117.6 ($C_5$), 120.0, 120.0 ($C_{arom}$-H), 123.9 ($C_6$), 124.0 ($C_7$), 124.5 ($C_{4b}$), 125.1, 125.2, 127.3, 127.9 (C_{arom}-H), 131.5 (C_{8a}), 141.3, 141.3, 143.1 ($\mathbf{C}_{arom}$-C), 144.0 (C_{9a}), 149.7 (NCO), 166.6 (C_2), 168.6, 168.9 ($CH(\mathbf{C}O_2Et)_2$), 169.7 (C_4-$\mathbf{C}O_2$). (neat): 2977 (C-H st), 1792 (C=O st), 1730 (C=O st), 1168 (C-O st) cm^{-1}. MS (EI) m/z (%): 178 (100), 176 (24), 152 (13), 89 (10), 76 (14). HRMS (ESI-): Calculated for $[C_{37}H_{34}O_{10}]^-$: 652.2183 $[(M-H)^-]$; found: 652.2149. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=35.53 min, τ_2=75.43 min (>99%). $[\alpha]_D^{20}$: +39.9 (*c*=1.0, CH_2Cl_2).

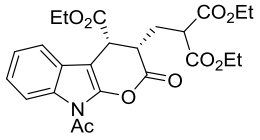


Diethyl 2-(((3*S*,4*R*)-4-(ethoxycarbonyl)-9-methyl-2-oxo-2,3,4,9-tetrahydropyrano[2,3-*b*]indol-3-yl)methyl)malonate (19d). Following the general procedure **I**, **19d** (44 mg, 0.10 mmol) was isolated as a yellow oil, using ethyl (*E*)-2-(1-methyl-2-oxoindolin-3-ylidene)acetate **17d** (46 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 49%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2C\mathbf{H}_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 1.29 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 2.17 (ddd, *J* = 14.1, 8.8, 4.9 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.72 (ddd, *J*

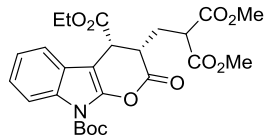
= 14.4, 8.2, 6.2 Hz, 1H, C_3-CH_aH_b), 3.08 (ddd, *J* = 8.2, 5.9, 4.9 Hz, 1H, C_3-H), 3.65 (s, 3H, NCH_3), 3.82 (dd, *J* = 8.8, 6.2 Hz, 1H, C_3-CH_2CH), 4.05-4.14 (m, 3H, C_4-H, C_4-$CO_2CH_2CH_3$), 4.16-4.27 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 7.14-7.22 (m, 2H, C_6-H, C_7-H), 7.23-7.30 (m, 1H, C_5-H), 7.48-7.55 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (C_4-$CO_2CH_2CH_3$, $CH(CO_2CH_2CH_3)_2$), 27.7 (C_3-CH_2), 28.0 (NCH_3), 40.3 (C_4), 40.9 (C_3), 49.7 (C_3-CH_2CH), 61.6 ($CH(CO_2CH_2CH_3)_2$), 61.7 (C_4-CO_2CH_2), 86.5 (C_{4a}), 109.2 (C_8), 117.7 (C_5), 120.8 (C_6), 120.9 (C_7), 124.3 (C_{4b}), 132.3 (C_{8a}), 145.4 (C_{9a}), 167.8 (C_2), 168.7, 169.0 ($CH(CO_2Et)_2$), 170.8 (C_4-CO_2). IR (neat): 2984 (C-H st), 1793 (C=O st), 1731 (C=O st), 1148 (C-O st) cm^{-1}. HRMS (ESI-): Calculated for $[C_{23}H_{27}NO_8]^+$: 446.1815 [$(M-H)^-$]; found: 446.1830. MS (70 eV) *m/z* (%): 445 (10, M^+), 371 (36), 231 (23), 212 (100), 184 (36). The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=16.29 min, τ_2=22.74 min (96%). $[\alpha]_D^{20}$: -13.5 (*c*=1.0, CH_2Cl_2).



Diethyl 2-(((3*S*,4*R*)-9-benzyl-4-(ethoxycarbonyl)-2-oxo-2,3,4,9-tetrahydropyrano[2,3-*b*]indol-3-yl)methyl)malonate (19e). Following the general procedure **I**, **19e** (38 mg, 0.07 mmol) was isolated as a yellow oil, using ethyl (*E*)-2-(1-benzyl-2-oxoindolin-3-ylidene)acetate **17e** (61 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 36%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2CH_3$), 1.27 (m, 6H, $CH(CO_2CH_2CH_3)_2$), 2.18 (ddd, *J* = 14.1, 8.7, 5.0 Hz, 1H, C_3-CH_aH_b), 2.72 (ddd, *J* = 14.1, 8.1, 6.3 Hz, 1H, C_3-CH_aH_b), 3.11 (ddd, *J* = 8.1, 6.0, 5.0 Hz, 1H, C_3-H), 3.81 (dd, *J* = 8.7, 6.3 Hz, 1H, C_3-CH_2CH), 4.07-4.16 (m, 3H, C_4-H, C_4-CO_2CH_2), 4.16-4.30 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 5.26 (s, 2H, $PhCH_2$), 7.08-7.34 (m, 8H, C_6-H, C_7-H, C_8-H, C_6H_5), 7.49-7.56 (m, 1H, C_5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (C_4-$CO_2CH_2CH_3$, $CH(CO_2CH_2CH_3)_2$), 27.7 (C_3-CH_aH_b), 40.3 (C_4), 40.9 (C_3), 45.5 ($C_6H_5CH_2$), 49.6 (C_3-CH_2CH), 61.6 (C_4-CO_2CH_2), 61.8 ($CH(CO_2CH_2CH_3)_2$), 86.9 (C_{4a}), 110.0 (C_8), 117.8 (C_5), 121.0 (C_6), 121.1 (C_7), 123.5 (C_{4b}), 126.8, 127.7, 128.8 (C_{arom}-H), 131.8 (C_{8a}), 136.3 (C_{arom}-C), 145.3 (C_{9a}), 167.6 (C_2), 168.7, 169.0 ($CH(CO_2Et)_2$), 170.7 (C_4-CO_2). IR (neat): 2984 (C-H st), 1793 (C=O st), 1731 (C=O st), 1148 (C-O st) cm^{-1}. MS (EI) m/z (%): 327 (14), 281 (21), 207 (78), 184 (37), 169 (100), 156 (56), 128 (72), 110 (85), 99 (46). HRMS (ESI+): Calculated for $[C_{29}H_{32}NO_8]^+$: 552.2128 [$(M+H)^+$]; found: 552.2119. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=11.98 min, τ_2=19.33 min (87%). $[\alpha]_D^{20}$: -6.8 (*c*=0.5, CH_2Cl_2).

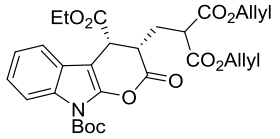


Diethyl 2-(((3*S*,4*R*)-9-acetyl-4-(ethoxycarbonyl)-2-oxo-2,3,4,9-tetrahydropyrano[2,3-*b*]indol-3-yl)methyl)malonate (19f). Following the general procedure **I**, **19f** (46 mg, 0.10 mmol) was isolated as a white solid, using ethyl **17f** (*E*)-2-(1-acetyl-2-oxoindolin-3-ylidene)acetate (52 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 49%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.30. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3H, C_4-$CO_2CH_2C\mathbf{H}_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 1.28 (t, *J* = 7.1 Hz, 3H, $CH(CO_2CH_2C\mathbf{H}_3)_2$), 2.17 (ddd, *J* = 14.5, 8.7, 4.8 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.71 (m, 4H, C_3-$CH_a\mathbf{H}_b$, CH_3CO), 3.14 (ddd, *J* = 8.1, 6.0, 4.8 Hz, 1H, C_3-H), 3.79 (dd, *J* = 8.7, 6.1 Hz, 1H, C_3-$CH_2C\mathbf{H}$), 4.07 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.09-4.30 (m, 6H, C_4-$CO_2C\mathbf{H}_2$, $CH(CO_2C\mathbf{H}_2CH_3)_2$), 7.27-7.34 (m, 2H, C_6-H, C_7-H), 7.42-7.52 (m, 1H, C_5-H), 8.36-8.49 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (C_4-$CO_2CH_2\mathbf{C}H_3$, $CH(CO_2CH_2\mathbf{C}H_3)_2$), 26.4 ($\mathbf{C}H_3CO$), 27.4 ($C_3$-$\mathbf{C}H_2$), 39.3 ($C_4$), 40.3 ($C_3$), 49.5 ($C_3$-$CH_2\mathbf{C}H$), 61.8 ($CH(CO_2\mathbf{C}H_2CH_3)_2$), 62.0 ($C_4$-$CO_2\mathbf{C}H_2$), 93.5 ($C_{4a}$), 116.9 ($C_8$), 117.4 ($C_5$), 124.5 ($C_6$), 124.5 ($C_7$), 124.6 ($C_{4b}$), 131.7 ($C_{8a}$), 143.5 ($C_{9a}$), 166.4 ($C_2$), 168.4 ($CH_3\mathbf{C}O$) 168.6, 168.9 ($CH(\mathbf{C}O_2Et)_2$), 169.9 ($C_4$-$\mathbf{C}O_2$). IR (neat): 2980 (C-H st), 1726 (C=O st) cm^{-1}. MS (EI) m/z (%): 327 (14), 184 (44), 169 (83), 156 (71), 128 (60), 110 (100), 99 (38). HRMS (ESI+): Calculated for $[C_{24}H_{28}NO_9]^+$: 474.1764 $[(M+H)^+]$; found: 474.1767. M.p. (hexanes, EtOAc): 101-103ºC. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=21.80 min, τ_2=23.76 min (90%). $[\alpha]_D^{20}$: -11.6 (*c*=1.0, CH_2Cl_2).

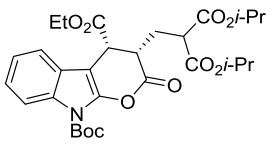


9-(*tert*-butyl) 4-ethyl (3*S*,4*R*)-3-(3-methoxy-2-(methoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19g). Following the general procedure **I**, **19g** (86 mg, 0.17 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), dimethyl 2-formylcyclopropane-1,1-dicarboxylate **16b** (56 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 85%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 1.65 (s, 9H, $C(CH_3)_3$), 2.15 (ddd, *J* = 14.1, 9.3, 4.5 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.67 (ddd, *J* = 14.3, 8.5, 5.6 Hz, 1H, C_3-$CH_a\mathbf{H}_b$), 3.04 (ddd, *J* = 8.5, 6.1, 4.4 Hz, 1H, C_3-H), 3.72 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 3.85 (dd, *J* = 9.2, 5.6 Hz, 1H, C_3-$CH_2C\mathbf{H}$), 4.02 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.04-4.18 (m, 2H, $CH_3C\mathbf{H}_2$), 7.21-

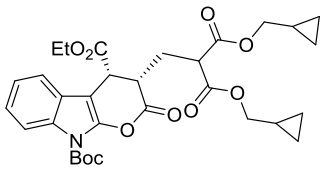
7.29 (m, 2H, C_6-H, C_7-H), 7.42-7.48 (m, 1H, C_5-H), 8.04-8.11 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (C_4-$CO_2CH_2\mathbf{C}H_3$), 27.4 (C_3-$\mathbf{C}H_2$), 28.1 ($C(\mathbf{C}H_3)_3$), 39.3 (C_4), 40.5 (C_3), 49.3 (C_3-$CH_2\mathbf{C}H$), 52.8 ($CH(CO_2\mathbf{C}H_3)_2$), 61.9 (C_4-$CO_2\mathbf{C}H_2$), 85.1 ($\mathbf{C}(CH_3)_3$), 93.0 (C_{4a}), 115.3 (C_8), 117.7 (C_5), 123.6 (C_6), 123.7 (C_7), 124.4 (C_{4b}), 131.5 (C_{8a}), 144.5 (NCO), 148.1 (C_{9a}), 166.8 (C_2), 169.1, 169.4 ($CH(\mathbf{C}O_2CH_3)_2$), 169.9 (C_4-$\mathbf{C}O_2$). IR (neat): 2984 (C-H st), 1795 (C=O st), 1736 (C=O st), 1146 (C-O st) cm^{-1}. MS (EI) m/z (%): 329 (37), 281 (36), 218 (45), 207 (87), 172 (100), 132 (54), 91 (43), 77 (53), 55 (20). HRMS (ESI-): Calculated for $[C_{25}H_{28}NO_{10}]^-$: 502.1713 $[(M-H)^-]$; found: 502.1718. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=8.13 min, τ_2=10.40 min (99%). $[\alpha]_D^{20}$: +42.7 (*c*=1.0, CH_2Cl_2).



9-(*tert*-butyl) 4-ethyl (3*S*,4*R*)-3-(3-(allyloxy)-2-((allyloxy)carbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19h). Following the general procedure **I**, **19h** (96 mg, 0.17 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), diallyl 2-formylcyclopropane-1,1-dicarboxylate **16c** (71 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 86%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 1.68 (s, 9H, $C(CH_3)_3$), 2.19 (ddd, *J* = 14.1, 9.2, 4.5 Hz, 1H, C_3-$C\mathbf{H}_aH_b$), 2.72 (ddd, *J* = 14.3, 8.4, 5.7 Hz, 1H, C_3-$CH_a\mathbf{H}_b$), 3.08 (ddd, *J* = 8.4, 6.1, 4.6 Hz, 1H, C_3-H), 3.91 (dd, *J* = 9.2, 5.7 Hz, 1H, C_3-$CH_2C\mathbf{H}$), 4.04 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.06-4.23 (m, 2H, $CH_3C\mathbf{H}_2$), 4.65 (ddt, *J* = 8.6, 4.3, 1.4 Hz, 4H, 2 × $C\mathbf{H}_2CH=CH_2$), 5.25 (dt, *J* = 10.4, 1.3 Hz, 2H, 2 × $CH_2CH=C\mathbf{H}_aH_b$), 5.33 (ddd, *J* = 17.2, 3.7, 1.6 Hz, 2H, 2 × $CH_2CH=CH_a\mathbf{H}_b$), 5.80-5.99 (m, 2H, 2 × $CH_2C\mathbf{H}=CH_aH_b$), 7.24-7.32 (m, 2H, C_6-H, C_7-H), 7.43-7.50 (m, 1H, C_5-H), 8.07-8.15 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 ($\mathbf{C}H_3CH_2$), 27.7 (C_3-$\mathbf{C}H_2$), 28.1 ($C(\mathbf{C}H_3)_3$), 39.3 (C_4), 40.4 (C_3), 49.5 (C_3-$CH_2\mathbf{C}H$), 61.9 ($CH_3\mathbf{C}H_2$), 66.3, 66.3 (2 × $\mathbf{C}H_2CH=CH_2$), 85.0 ($\mathbf{C}(CH_3)_3$), 93.0 (C_{4a}), 115.3 (C_8), 117.6 (C_5), 118.9, 119.0 (2 × $CH_2CH=\mathbf{C}H_2$), 123.6 (C_6), 123.6 (C_7), 124.4 (C_{4b}), 131.2, 131.3 (2 × $CH_2\mathbf{C}H=CH_2$), 131.5 (C_{8a}), 144.4 (NCO), 148.1 (C_{9a}), 166.8 (C_2), 168.2, 168.5 ($CH(\mathbf{C}O_2Allyl)_2$), 169.9 (C_4-$\mathbf{C}O_2$). IR (neat): 2987 (C-H st), 1792 (C=O st), 1732 (C=O st), 1146 (C-O st) cm^{-1}. MS (EI) m/z (%): 585 (1), 281 (34), 271 (57), 243 (26), 215 (30), 207 (100), 170 (96), 141 (31), 115 (51), 77 (43), 55 (14). HRMS (ESI+): Calculated for $[C_{24}H_{34}NO_{10}]^+$: 556.2183 $[(M+H)^+]$; found: 556.2183. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=21.69 min, τ_2=31.69 min (98%). $[\alpha]_D^{20}$: -23.3 (*c*=1.0, CH_2Cl_2).

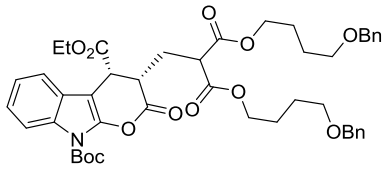


9-(*tert*-butyl) 4-ethyl (3*S*,4*R*)-3-(3-isopropoxy-2-(isopropoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19i). Following the general procedure **I**, **19i** (7 mg, 0.01 mmol) was isolated as a yellow oil, using tert-butyl (E)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), diisopropyl 2-formylcyclopropane-1,1-dicarboxylate **16d** (73 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 6%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.32 (m, 15H, C**H**$_3$CH$_2$, 2 × CH(C**H**$_3$)$_2$), 1.68 (s, 9H, C(CH$_3$)$_3$), 2.14 (ddd, *J* = 14.2, 9.2, 4.9 Hz, 1H, C$_3$-C**H**$_a$H$_b$), 2.67 (ddd, *J* = 14.3, 8.2, 6.0 Hz, 1H, C$_3$-CH$_a$**H**$_b$), 3.08 (ddd, *J* = 8.1, 6.1, 4.7 Hz, 1H, C$_3$-H), 3.73 (dd, *J* = 8.9, 6.0 Hz, 1H, C$_3$-CH$_2$C**H**), 4.04 (d, *J* = 6.1 Hz, 1H, C$_4$-H), 4.08-4.21 (m, 2H, CH$_3$C**H**$_2$), 4.99-5.13 (m, 2H, 2 × C**H**(CH$_3$)$_2$), 7.24-7.32 (m, 2H, C$_6$-H, C$_7$-H), 7.43-7.50 (m, 1H, C$_5$-H), 8.06-8.14 (m, 1H, C$_8$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 21.6, 21.7 (2 × CH(**C**H$_3$)$_2$), 27.4 (C$_3$-**C**H$_2$), 28.1 (C(**C**H$_3$)$_3$), 39.4 (C$_4$), 40.4 (C$_3$), 49.6 (C$_3$-CH$_2$**C**H), 61.9 (CH$_3$**C**H$_2$), 69.4, 69.4 (2 × **C**H(CH$_3$)$_2$), 85.1 (**C**(CH$_3$)$_3$), 93.1 (C$_{4a}$), 115.4 (C$_8$), 117.6 (C$_5$), 123.6 (C$_6$), 123.7 (C$_7$), 124.5 (C$_{4b}$), 131.6 (C$_{8a}$), 144.6 (NCO), 148.2 (C$_{9a}$), 166.9 (C$_2$), 168.3, 168.6 (CH(**C**O$_2$*i*-Pr)$_2$), 169.9 (C$_4$-**C**O$_2$). IR (neat): 2980 (C-H st), 1795 (C=O st), 1730 (C=O st), 1146 (C-O st) cm^{-1}. HRMS (ESI-): Calculated for [$C_{29}H_{36}NO_{10}$]$^-$: 558.2339 [(M-H)$^-$]; found: 558.2344. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=21.85 min, τ_2=31.39 min (99%).



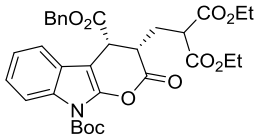
9-(*tert*-butyl) 4-ethyl (3*S*,4*R*)-3-(3-(cyclopropylmethoxy)-2-((cyclopropylmethoxy)carbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19j). Following the general procedure **I**, **19j** (103 mg, 0.18 mmol) was isolated as a yellow oil, using *tert*-butyl (E)-3-(2-ethoxy-2-oxoethylidene)-5-methyl-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), bis(cyclopropylmethyl) 2-formylcyclopropane-1,1-dicarboxylate **16e** (80 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 88%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.45. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (tt, *J* = 4.7, 2.4 Hz, 4H, (2 × C$_{2'}$-**H**$_a$H$_b$, 2 × C$_{3'}$-**H**$_a$H$_b$), 0.51-0.63 (m, 4H, 2 × C$_{2'}$-H$_a$**H**$_b$, 2 × C$_{3'}$-H$_a$**H**$_b$), 1.12 (tt, *J* = 7.8, 3.8 Hz, 2H, 2 × C$_{1'}$-H), 1.20 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.68 (s, 9H, C(CH$_3$)$_3$), 2.11-2.24 (m, 1H, C$_3$-C**H**$_a$H$_b$), 2.72 (ddd, *J* = 14.3, 8.2, 6.0 Hz, 1H, C$_3$-CH$_a$**H**$_b$), 3.10 (dt, *J* = 8.1, 5.2 Hz, 1H, C$_3$-

H), 3.87 (dd, *J* = 9.0, 6.0 Hz, 1H, C_3-CH_2C**H**), 3.99 (dd, *J* = 7.3, 5.3 Hz, 4H, 2 × *c*-$C_3H_5C\mathbf{H}_2$), 4.06 (d, *J* = 6.2 Hz, 1H, C_4-H), 4.08-4.21 (m, 2H, $CH_3C\mathbf{H}_2$), 7.23-7.31 (m, 2H, C_6-H, C_7-H), 7.44-7.49 (m, 1H, C_5-H), 8.06-8.13 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.2 ($C_{2'}$), 3.3 ($C_{3'}$), 9.7 ($C_{1'}$), 14.0 (**C**H_3CH_2), 27.6 (C_3-**C**H_aH_b), 28.1 (C(**C**H_3)$_3$), 39.4 (C_4), 40.4 (C_3), 49.7 (C_3-CH_2**C**H), 61.9 (C_4-CO_2**C**H_2), 70.5, 70.5 (*c*-C_3H_5O**C**H_2), 85.1 (**C**$(CH_3)_3$), 93.1 (C_{4a}), 115.4 (C_5), 117.6 (C_8), 123.6 (C_6), 123.7 (C_7), 124.4 (C_{4b}), 131.5 (C_{8a}), 144.5 (NCO), 148.1 (C_{9a}), 166.8 (C_2), 168.8, 169.1 (CH(**C**O_2CH_2*c*-$C_3H_5)_2$), 169.9 (C_4-**C**O_2). IR (neat): 2984 (C-H st), 1795 (C=O st), 1736 (C=O st), 1149 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for $[C_{31}H_{38}NO_{10}]^+$: 584.2496 $[(M+H)^+]$; found: 584.2494. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=28.05 min, τ_2=44.57 min (99%). $[\alpha]_D^{20}$: -47.6 (*c*=1.0, CH_2Cl_2).

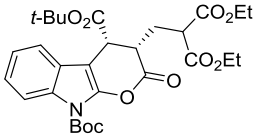


9-(*tert*-butyl) 4-ethyl (3*S*,4*R*)-3-(3-(4-(benzyloxy)butoxy)-2-((4-(benzyloxy)butoxy)carbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19k). Following the general procedure **I**, **19k** (143 mg, 0.18 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17a** (64 mg, 0.20 mmol), bis(4-(benzyloxy)butyl) 2-formylcyclopropane-1,1-dicarboxylate **16g** (145 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 89%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.1 Hz, 3H, C**H**$_3CH_2$), 1.57-1.84 (m, 17H, 2 × $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$, C(C*H*$_3$)$_3$), 2.11-2.26 (m, 1H, C_3-C**H**$_aH_b$), 2.70 (ddd, *J* = 14.3, 8.4, 5.9 Hz, 1H, C_3-CH_a**H**$_b$), 3.09 (dt, *J* = 7.9, 5.0 Hz, 1H, C_3-H), 3.47 (t, *J* = 6.0 Hz, 4H, 2 × BnOC**H**$_2$), 3.85 (dd, *J* = 9.0, 5.8 Hz, 1H, C_3-CH_2C**H**), 4.05 (d, *J* = 6.2 Hz, 1H, C_4-H), 4.09-4.24 (m, 6H, C_4-$CO_2C\mathbf{H}_2CH_3$, 2 × $CO_2C\mathbf{H}_2CH_2$), 4.47 (d, *J* = 4.8 Hz, 4H, 2 × PhC**H**$_2$), 7.23-7.38 (m, 12H, 2 × Ph, C_6-H, C_7-H), 7.43-7.50 (m, 1H, C_5-H), 8.07-8.16 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (**C**H_3CH_2), 25.3, 26.0 ($CH_2\mathbf{C}H_2\mathbf{C}H_2CH_2$), 27.5 ($C_3$-**C**$H_2$), 28.0 (C(**C**$H_3$)$_3$), 39.2 ($C_4$), 40.3 ($C_3$), 49.5 ($C_3$-$CH_2$**C**H), 61.8 ($CH_3\mathbf{C}H_2$), 65.6 $CO_2\mathbf{C}H_2CH_2$), 69.4 (BnO**C**H_2), 72.8 (Ph**C**H_2), 84.9 (**C**$(CH_3)_3$), 93.0 (C_{4a}), 115.2 (C_8), 117.6 (C_5), 123.5 (C_6), 123.6 (C_7), 124.3 (C_{4b}), 127.4, 127.5, 128.2 (C_{arom}-H), 131.4 (C_{8a}), 138.3 (C_{arom}-C), 144.4 (NCO), 148.0 (C_{9a}), 166.8 (C_2), 168.6, 168.9 (CH(**C**$O_2(CH_2)_4OBn)_2$), 169.8 (C_4-**C**O_2). IR (neat): 2941 (C-H st), 1795 (C=O st), 1732 (C=O st), 1146 (C-O st) cm^{-1}. MS (EI) m/z (%): 445 (16), 371 (82), 297 (32), 252 (30), 231 (43), 212 (100), 186 (51), 159 (31), 130 (24), 55 (30). HRMS (ESI-): Calculated for $[C_{45}H_{52}NO_{12}]^-$: 798.3490 $[(M-H)^-]$; found: 798.3492. The ee was determined by HPLC

using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=12.63 min, τ_2=17.16 min (>99%). $[\alpha]_D^{20}$: -24.1 (*c*=1.0, CH_2Cl_2).

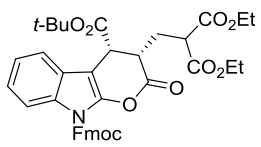


4-Benzyl 9-(*tert*-butyl) (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19l). Following the general procedure **I**, **19l** (97 mg, 0.16 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-(benzyloxy)-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17g** (76 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 82%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.45. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.27 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.68 (s, 9H, C(CH$_3$)$_3$), 2.13 (ddd, *J* = 14.1, 9.1, 4.6 Hz, 1H, C$_3$-C**H**$_a$H$_b$), 2.65 (ddd, *J* = 14.2, 8.4, 5.8 Hz, 1H, C$_3$-CH$_a$**H**$_b$), 3.11 (ddd, *J* = 8.3, 6.0, 4.6 Hz, 1H, C$_3$-H), 3.80 (dd, *J* = 9.1, 5.7 Hz, 1H, C$_3$-CH$_2$C**H**), 4.12 (d, *J* = 6.2 Hz, 1H, C$_4$-H), 4.14-4.29 (m, 4H, 2 × CH$_3$C**H**$_2$), 5.10 (s, 2H, PhC**H**$_2$), 7.18-7.32 (m, 7H, C$_6$-H, C$_7$-H, C$_{arom}$-H), 7.40-7.47 (m, 1H, C$_8$-H), 8.07-8.15 (m, 1H, C$_5$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.0 (**C**H$_3$CH$_2$), 27.4 (C$_3$-**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 39.3 (C$_4$), 40.3 (C$_3$), 49.6 (C$_3$-CH$_2$**C**H), 61.7, 61.7 (CH$_3$**C**H$_2$), 67.5 (Ph**C**H$_2$), 85.0 (**C**(CH$_3$)$_3$), 92.8 (C$_{4a}$), 115.3 (C$_8$), 117.6 (C$_5$), 123.6 (C$_6$), 124.3 (C$_7$), 124.7 (C$_{4b}$), 128.1, 128.3, 128.4 (C$_{arom}$-H), 131.5 (C$_{8a}$), 134.8 (**C**$_{arom}$-C), 144.5 (C$_{9a}$), 148.1 (NCO), 166.7 (C$_2$), 168.6, 168.9 (CH(**C**O$_2$Et)$_2$), 169.8 (C$_4$-**C**O$_2$). IR (neat): 2980 (C-H st), 1793 (C=O st), 1732 (C=O st), 1146 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for $[C_{32}H_{35}NO_{10}Na]^+$: 616.2159 [(M+Na)$^+$]; found: 616.2177. M.p. (hexanes, CH_2Cl_2): 122-124 ºC. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=9.31 min, τ_2=16.27 min (99%). $[\alpha]_D^{20}$: +54.1 (*c*=1.0, CH_2Cl_2).



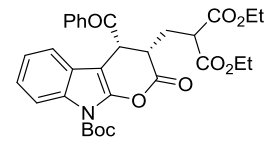
Di-*tert*-butyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19m). Following the general procedure **I**, **19m** (109 mg, 0.19 mmol) was isolated as a pale yellow oil, using *tert*-butyl (*E*)-3-(2-(tert-butoxy)-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17h** (69 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 97%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.28 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.37 (s, 9H, C$_4$-CO$_2$C(CH$_3$)$_3$), 1.68 (s, 9H,

$NCO_2C(CH_3)_3$), 2.19 (ddd, *J* = 14.1, 8.8, 5.0 Hz, 1H, C_3-C**H**$_a$H$_b$), 2.71 (ddd, *J* = 14.4, 8.1, 6.2 Hz, 1H, C_3-CH$_a$**H**$_b$), 3.02 (ddd, *J* = 8.0, 6.1, 5.0 Hz, 1H, C_3-H), 3.80 (dd, *J* = 8.7, 6.2 Hz, 1H, C_3-CH$_2$C**H**), 3.92 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.12-4.28 (m, 6H, C_4-CO_2C**H**$_2$, 2 × CH_3C**H**$_2$), 7.21-7.35 (m, 2H, C_6-H, C_7-H), 7.41-7.49 (m, 1H, C_5-H), 8.05-8.13 (m, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (**C**H$_3$CH$_2$), 27.4 (C_3-**C**H$_2$), 27.8 (NCO_2C(**C**H$_3$)$_3$), 28.1 (CO_2C(**C**H$_3$)$_3$), 39.4 (C_4), 41.4 (C_3), 49.6 (C_3-CH$_2$**C**H), 61.7, 61.8 (CH$_3$**C**H$_2$), 83.1 (C_4-CO_2**C**), 85.0 (NCO_2**C**), 93.4 (C_{4a}), 115.2 (C_8), 117.6 (C_5), 123.5 (C_6), 123.6 (C_7), 124.5 (C_{4b}), 131.5 (C_{8a}), 144.4 (C_{9a}), 148.2 (NCO), 167.0 (C_2), 168.7, 169.0 (CH(**C**O$_2$Et)$_2$), 169.1 (C_4-**C**O$_2$). IR (neat): 2984 (C-H st), 1795 (C=O st), 1730 (C=O st), 1149 (C-O st) cm^{-1}. MS (EI) m/z (%): 281 (3), 227 (42), 207 (19), 173 (73), 160 (54), 127 (85), 98 (60), 73 (45), 55 (100). HRMS (ESI+): Calculated for $[C_{29}H_{37}NO_{10}Na]^+$: 582.2315 $[(M+Na)^+]$; found: 582.2316. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=5.79 min, τ_2=7.20 min (99%). $[\alpha]_D^{20}$: -9.7 (*c*=1.0, CH_2Cl_2).

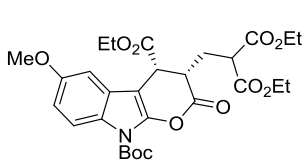


9-((9*H*-Fluoren-9-yl)methyl) 4-(*tert*-butyl) (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19n). Following the general procedure **I**, **19n** (112 mg, 0.16 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **17i** (94 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 82%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.39 (s, 9H, $C(CH_3)_3$), 2.22 (ddd, *J* = 14.0, 8.7, 4.9 Hz, 1H, C_3-C**H**$_a$H$_b$), 2.74 (ddd, *J* = 14.4, 8.2, 6.2 Hz, 1H, C_3-CH$_a$**H**$_b$), 3.04-3.12 (m, 1H, C_3-H), 3.83 (dd, *J* = 8.7, 6.2 Hz, 1H, C_3-CH$_2$C**H**), 3.94 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.16-4.29 (m, 4H, 2 × CH_3C**H**$_2$), 4.43 (t, *J* = 6.7 Hz, 1H, C**H**CH$_2$O), 4.69-4.87 (m, 2H, CHC**H**$_2$O), 7.09-7.52 (m, 8H, C_{arom}-H), 7.74-7.94 (m, 4H, C_{arom}-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (**C**H$_3$CH$_2$), 27.5 (C_3-**C**H$_2$), 27.9 (C(**C**H$_3$)$_3$), 39.4 (C_4), 41.6 (C_3), 46.7 (**C**HCH$_2$O), 49.6 (C_3-CH$_2$**C**H), 61.8, 61.8 (CH$_3$**C**H$_2$), 69.5 (CH**C**H$_2$O), 83.3 (**C**(CH$_3$)$_3$), 94.1 (C_{4a}), 115.4 (C_8), 117.7 (C_5), 120.1, 120.1 (C_{arom}-H), 123.9 (C_6), 124.1 (C_7), 124.7 (C_{4b}), 125.2, 125.3, 127.4, 128.0 (C_{arom}-H), 131.6 (C_{8a}), 141.4, 141.4, 143.2, 143.3 (**C**$_{arom}$-C), 144.0 (C_{9a}), 149.8 (NCO), 166.8 (C_2), 168.7, 168.9 (CH(**C**O$_2$Et)$_2$), 169.0 (C_4-**C**O$_2$). IR (neat): 2980 (C-H st), 1795 (C=O st), 1731 (C=O st), 1151 (C-O st) cm^{-1}. MS (EI) m/z (%): 178 (100), 152 (11), 76 (8). HRMS (ESI+): Calculated for $[C_{39}H_{39}NO_{10}Na]^+$: 704.2472 $[(M+Na)^+]$; found: 704.2474. The ee was

determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=21.83 min, τ_2=55.60 min (>99%). $[\alpha]_D^{20}$: -22.9 (*c*=1.0, CH_2Cl_2).

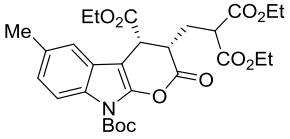


Diethyl 2-(((3*S*,4*R*)-4-benzoyl-9-(*tert*-butoxycarbonyl)-2-oxo-2,3,4,9-tetrahydropyrano[2,3-*b*]indol-3-yl)methyl)malonate (19o). Following the general procedure **I**, **19o** (68 mg, 0.12 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-2-oxo-3-(2-oxo-2-phenylethylidene)indoline-1-carboxylate **17j** (70 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 60%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$) 1.26 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 1.67 (s, 9H, C(CH$_3$)$_3$), 2.05-2.15 (m, 1H, C$_3$-C**H**$_a$H$_b$), 2.64 (ddd, *J* = 13.9, 8.7, 4.9 Hz, 1H, C$_3$-CH$_a$**H**$_b$), 3.13 (ddd, *J* = 8.8, 5.3, 3.7 Hz, 1H, C$_3$-H), 3.87 (dd, *J* = 9.8, 4.8 Hz, 1H, C$_3$-CH$_2$C**H**), 4.14-4.27 (m, 6H, 2 × CH$_3$C**H**$_2$), 5.14 (d, *J* = 6.1 Hz, 1H, C$_4$-H), 7.08-7.25 (m, 3H, C$_6$-H, C$_7$-H, C$_{arom}$-H), 7.49-7.69 (m, 3H, C$_5$-H**,** C$_{arom}$-H), 8.04-8.14 (m, 3H, C$_8$-H, C$_{arom}$-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (**C**H$_3$CH$_2$), 28.0 (C$_3$-**C**H$_2$), 28.1 (C(**C**H$_3$)$_3$), 40.0 (C$_3$), 41.6 (C$_4$), 50.0 (C$_3$-CH$_2$**C**H), 61.8 (CH$_3$**C**H$_2$), 85.0 (**C**(CH$_3$)$_3$), 93.8 (C$_{4a}$), 115.4 (C$_8$), 117.3 (C$_5$), 123.3 (C$_6$), 123.4 (C$_7$), 124.2 (C$_{4b}$), 128.8 (C$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 131.5 (C$_{8a}$), 134.4 (C$_{arom}$-H), 135.8 (C$_{arom}$-C), 145.2 (NCO), 148.1 (C$_{9a}$), 167.7 (C$_2$), 168.9, 169.2 (CH(**C**O$_2$Et)$_2$), 197.8 (C$_4$-**C**O$_2$). IR (neat): 2984 (C-H st), 1793 (C=O st), 1739 (C=O st), 1146 (C-O st) cm^{-1}. HRMS (ESI+): Calculated for $[C_{31}H_{32}NO_9]^+$: 562.2077 $[(M+H)^+]$; found: 562.2078. The ee was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=53.67 min, τ_2=59.34 min (92%). $[\alpha]_D^{20}$: +61.5 (*c*=0.5, CH_2Cl_2).



9-(*tert*-Butyl) 4-ethyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-6-methoxy-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19p). Following the general procedure **I**, **19p** (100 mg, 0.18 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-5-methoxy-2-oxoindoline-1-carboxylate **17k** (69 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 89%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C$_4$-CO$_2$CH$_2$C**H**$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, CH(CO$_2$CH$_2$C**H**$_3$)$_2$), 1.27 (t, *J* = 7.1 Hz, 3H, CH(CO$_2$CH$_2$C**H**$_3$)$_2$), 1.66 (s, 9H, C(CH$_3$)$_3$),

2.15 (ddd, *J* = 14.1, 9.1, 4.6 Hz, 1H, C_3-C**H**$_a$H$_b$), 2.68 (ddd, *J* = 14.3, 8.3, 5.8 Hz, 1H, C_3-CH$_a$**H**$_b$), 3.06 (ddd, *J* = 8.3, 6.1, 4.6 Hz, 1H, C_3-H), 3.80 (dd, *J* = 9.1, 5.8 Hz, 1H, C_3-CH$_2$C**H**), 3.85 (s, 3H, CH_3O), 4.00 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.06-4.26 (m, 6H, C_4-CO_2C**H**$_2$, CH(CO_2C**H**$_2$CH$_3$)$_2$), 6.48 (dd, *J* = 9.0, 2.6 Hz, 1H, C_7-H), 6.92 (d, *J* = 2.5 Hz, 1H, C_5-H), 7.97 (d, *J* = 9.0 Hz, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.0, 14.1 (C_4-CO_2CH_2**C**H$_3$, CH(CO_2CH_2**C**H$_3$)$_2$), 27.5 (C_3-**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 39.3 (C_4), 40.4 (C_3), 49.6 (C_3-CH$_2$**C**H), 55.7 (**C**H$_3$O), 61.8 (CH(CO_2**C**H$_2$CH$_3$)$_2$), 61.9 (C_4-CO_2**C**H$_2$), 84.8 (**C**(CH$_3$)$_3$), 93.0 (C_{4a}), 101.0 (C_5), 111.5 (C_8), 116.3 (C_7), 125.3 (C_{4b}), 125.8 (C_{8a}), 144.8 (NCO), 148.1 (C_{9a}), 156.6 (C_6), 166.8 (C_2), 168.7, 169.0 (CH(**C**O$_2$Et)$_2$), 169.9 (C_4-**C**O$_2$). IR (neat): 2984 (C-H st), 1793 (C=O st), 1732 (C=O st), 1144 (C-O st) cm^{-1}. MS (EI) m/z (%): 243 (15), 215 (16), 169 (100), 156 (25), 141 (22), 123(47), 110 (26), 97 (28). HRMS (ESI+): Calculated for [$C_{28}H_{36}NO_{11}$]$^+$: 562.2288 [(M+H)$^+$]; found: 562.2295. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=9.55 min, τ_2=11.92 min (98%). [α]$_D^{20}$: +19.3 (*c*=1.0, CH_2Cl_2).



9-(*tert*-Butyl) 4-ethyl (3*S*,4*R*)-3-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-6-methyl-2-oxo-3,4-dihydropyrano[2,3-*b*]indole-4,9(2*H*)-dicarboxylate (19q). Following the general procedure **I**, **19q** (93 mg, 0.17 mmol) was isolated as a yellow oil, using *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-5-methyl-2-oxoindoline-1-carboxylate **17l** (64 mg, 0.20 mmol), diethyl 2-formylcyclopropane-1,1-dicarboxylate **16a** (63 mg, 0.30 mmol), triazolium salt **18d** (8.3 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) in CH_2Cl_2 (2 mL) as solvent for 3 h. Yield: 85%. dr: >20:1. Rf (hexanes/EtOAc 8:2): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H, C_4-CO_2CH_2C**H**$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, CH(CO_2CH_2C**H**$_3$)$_2$), 1.28 (t, *J* = 7.1 Hz, 3H, CH(CO_2CH_2C**H**$_3$)$_2$), 1.66 (s, 9H, C(CH$_3$)$_3$), 2.15 (ddd, *J* = 14.1, 9.1, 4.7 Hz, 1H, C_3-C**H**$_a$H$_b$), 2.43 (s, 3H, C_6-CH$_3$), 2.68 (ddd, *J* = 14.3, 8.3, 5.9 Hz, 1H, C_3-CH$_a$**H**$_b$), 3.06 (ddd, *J* = 8.1, 6.1, 4.7 Hz, 1H, C_3-H), 3.81 (dd, *J* = 9.0, 5.9 Hz, 1H, C_3-CH$_2$C**H**), 4.01 (d, *J* = 6.1 Hz, 1H, C_4-H), 4.08-4.27 (m, 6H, C_4-CO_2C**H**$_2$, CH(CO_2C**H**$_2$CH$_3$)$_2$), 7.07 (dd, *J* = 9.0, 2.6 Hz, 1H, C_7-H), 7.23-7.27 (m, 1H, C_5-H), 7.95 (d, *J* = 9.0 Hz, 1H, C_8-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 14.0 (C_4-CO_2CH_2**C**H$_3$, CH(CO_2CH_2**C**H$_3$)$_2$), 21.3 (C_6-**C**H$_3$), 27.4 (C_3-**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 39.3 (C_4), 40.4 (C_3), 49.6 (C_3-CH$_2$**C**H), 61.7, 61.7 (CH(CO_2**C**H$_2$CH$_3$)$_2$), 61.8 (C_4-CO_2**C**H$_2$), 84.8 (**C**(CH$_3$)$_3$), 92.7 (C_{4a}), 115.0 (C_5), 117.6 (C_8), 124.5(C_7), 124.8 (C_{4b}), 129.6 (C_6), 133.2 (C_{8a}), 144.4 (NCO), 148.1 (C_{9a}), 166.9 (C_2), 168.6, 168.9 (CH(**C**O$_2$Et)$_2$), 169.9 (C_4-**C**O$_2$). IR (neat): 2984 (C-H st), 1795 (C=O st), 1731 (C=O st), 1141 (C-O st) cm^{-1}. MS (EI) m/z (%): 186 (14), 169 (55), 140 (80), 112 (42), 85 (100), 84 (71), 68 (36), 55 (32). HRMS (ESI+): Calculated for [$C_{28}H_{36}NO_{10}$]$^+$: 546.2339 [(M+H)$^+$]; found: 546.2341. The ee was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_1=6.87 min, τ_2=8.42 min (99%). [α]$_D^{20}$: +42.0 (*c*=1.0, CH_2Cl_2).

Appendix

Abbreviations, acronyms and symbols[21]

ATR	Attenuated total reflectance
c	Concentration (measured in g/100mL)
C_{arom}	Aromatic carbon
Cat	Catalyst
Conv.	Conversion
D-A	Diels-Alder or Donor-Acceptor
DBFOX	4,6-Dibenzofurandiyl-2,2′-bis(4-phenyl-oxazoline)
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEA	*N*,*N*-Diethyl acetamide
DIPEA	*N*,*N*-Diisopropylethylamine
dpm	Tris(2,2,6,6-tetramethyl-3,5-heptanedionato
dq	Doublet of quartets
E	Electrophile
e.g.	*Exempli gratia* (for example)
ee	Enantiomeric excess
ent	Enantiomer
eq./equiv.	Equivalent
et al.	*Et alii* (and others)
eV	Electron volt
EWG	Electron-withdrawing group
FC	Flash chromatography
FMO	Frontier molecular orbital
Hsp90	Heat Shock protein 90
i.e.	*Id est* (that is)
J	Coupling constant
JAK	Janes kinase
JNK	c-Jun *N*-terminal kinase
L	Levorotatory or ligand
Leu	Leucine
M.p.	Melting point

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

MS	Mass spectrometry or Molecular sieves
n.d.	Not determined
Np	Naphthyl
n.r.	No reaction
P.G.	Protecting group
Pro	Proline
QTOF	Quadrupole-time of flight
R	Alkyl group or substituent
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TTMSS	tris(trimethylsilyl)silane
vs	Versus
X	Halogen, heteroatom or leaving group
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 como catalizadores covalentes en la activación respectiva de cetonas y aldehídos para llevar a cabo transformaciones estereocontroladas está asentándose como área de la química de creciente interés. La metodología implica la formación reversible, a partir de compuestos carbonílicos, de cantidades subestequiometricas de intermedios tipo azometino (enamina o ion iminio) como especies activas. Recientemente, la aplicación del principio de vinilogía a este modo de activación inspiró el descubrimiento de dienamina y trienamina como nuevas estrategias sintéticas para alcanzar la funcionalización de compuestos carbonílicos en γ y ε respectivamente empleando en este caso compuesto carbonilicos poly-insaturados. Simultáneamente, la utilización de Carbenos *N*-Heterociclicos (NHC) como catalizadores se presenta como un área de rápida expansión, sustentada en la habilidad de las especies tipo carbeno para generar intermedios que invierten la reactividad inherente de compuestos carbonílicos, conduciendo en el caso de emplear NHC quirales, a productos enantioenriquecidos.

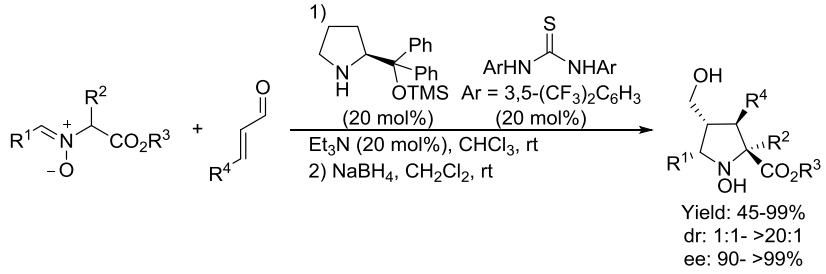
Siguiendo la línea de investigación del grupo en el campo de la organocatálisis asimétrica, la memoria recoge el estudio y desarrollo de diversas metodologías basadas en reacciones de cicloaddición en las que el denominador común es el acceso a intermedios de reacción activados a través de procedimientos poco convencionales utilizando para ello organocatalizadores quirales de diferente naturaleza, los cuales no solo participan generando las especies reactivas, sino que proporcionan un entorno asimétrico conduciendo a la formación de productos enantioenriquecidos.

En un primer capítulo, se muetra 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, describiendo las reacciones que cursan a través de la formación de intermedios tipo enamina, ión iminio y especies vinílogas. Por otro lado, se detallan los modos de activación accesibles mediante el uso de NHC como catalízadores, incluyendo anion acilo, acil azolio, enolato de azolio y homoenolato.

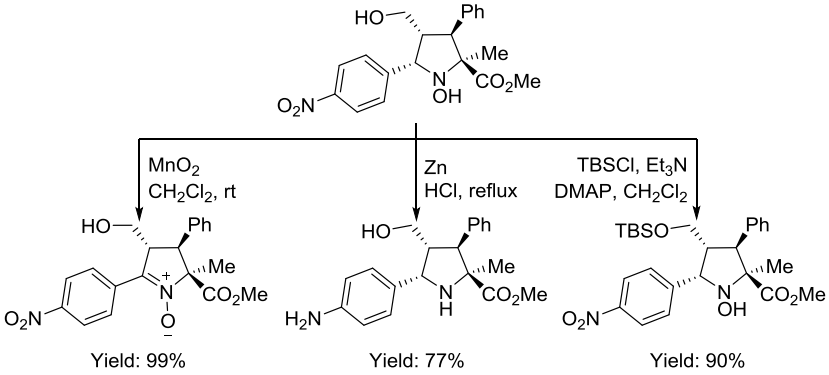
En un segundo capítulo, se presenta la investigación dirigida a explorar la reactividad de iluros de nitrona como 1,3-dipolos en la cicloaddición [3+2] con aldehídos α-β-insaturados activados mediante aminas secundarias quirales *via* ión iminio. Los iluros de nitrona muestran, en este estudio, regioselectividad de C,C-1,3-dipolo, poco convencional comparada con el comportamiento habitual de nitronas como C,O-1,3-dipolos. Para el desarrollo de dicha regioselectividad, fue necesaria la utilización de un sistema catalítico sinergístico que conlleva la presencia de una tiourea aquiral en medio básico para la efectiva generación de la especie iluro de nitrona, junto con un catalizador tipo diphenilprolinol para la activación del enal.

Tras un extenso proceso de exploración de las variables de reacción, se determina que el empleo de 1,3-bis(3,5-bis(trifluorometil)fenil)tiourea y trietilamina junto con trimetilsilil diphenilprolinol como aminocatalizador en cloroformo a temperatura ambiente conducen a la formación de *N*-hidroxipirrolidinas densamente funcionalizadas (Esquema 1), siendo necesaria la reducción de los aductos *in situ* para evitar la epimerización durante su manipulación La metodología se extiende al uso de enales sustituidos con anillos aromáticos con diversos patrones de sustitución y propiedades electónicas, así como a una serie de nitronas, con altos rendimientos, diastereoselectividad variable desde moderada a buena y enantioselectividad excelente.



Esquema 1

Las *N*-hidroxipirrolidinas se someten a transformaciones representaivas de la variabilidad en la reactividad de los diferentes grupos funcionales presentes en dichos compuestos, entre las que se encuentran la reducción a *N*-H pirrolidinas, oxidación a nitronas cíclicas y la protección selectiva del alcohol primario (Esquema 2).

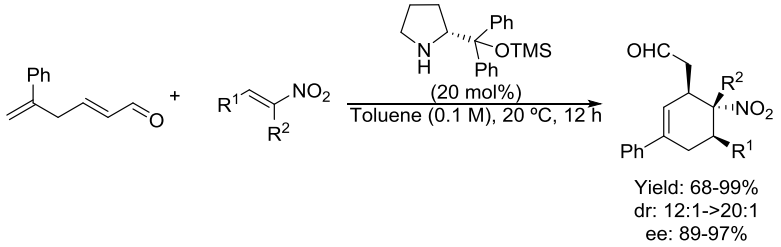


Esquema 2

En un tercer capítulo, con el fin de desarrollar una metodología que permita facilitar la activación de compuestos carbonilicos poliinsaturados mediante aminocatálisis, se aplica el concepto de enamina viníloga seleccionando como sustrato modelo dienales que presenten conjugación interrumpida. Se comprueba que estos sustratos facilitan la formación del intermedio tipo trienamina debido, entre otros factores, a una etapa de condensación del aminocatalizador con el dienal no conjugado favorecida en comparación

con dienales conjugados. Adicionalemnte, tras la condensación, la formación del intermedio trienamina se ve de nuevo favorecida debido a que conlleva la conjugación de todos los dobles enlaces. También se demuestra que, sometidos a las mismas condiciones de reacción, el isómero conjugado del dienal no desarrolla la reactividad que presenta el isómero no-conjugado.

Las trienaminas formadas se enfrentan a nitroolefinas que toman parte en la reacción de cicloaddición tipo Diels-Alder que, tras el correspondiente proceso de optimización de las condiciones de reacción, el cual concluye con el empleo de trimetilsilil diphenilprolinol como aminocatalizador en tolueno a una temperatura controlada de 20 ºC lleva a la formación de ciclohexenos polisustituidos (Esquema 3). La metodología se amplia al uso de nitroolefinas aromáticas con variados patrones de sustitución y propiedades electónicas rindiendo aductos con altos rendimientos y de manera altamente diastereo- y enantioselectiva.

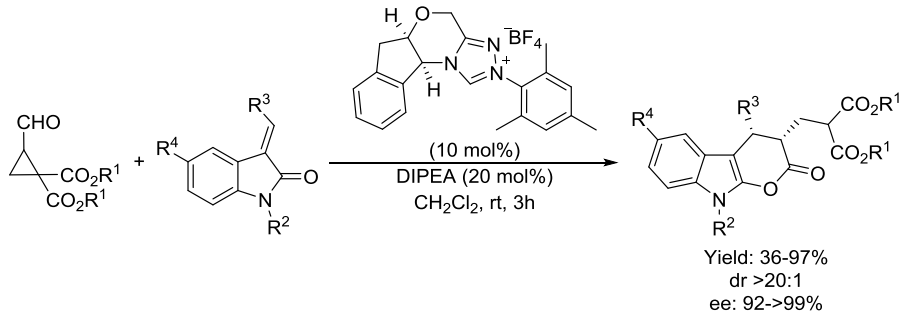


Esquema 3

El cuarto capítulo trata de la generación de especies de ciclopropano Donor-Aceptor, a partir de formilciclopropanos sustituidos con grupos electon-atractores, aprovechando la capacidad que presentan los catalizadores NHC para invertir la polaridad (*umpolung*) de compuestos carbonílicos. Los ciclopropanos Donor-Aceptor experimentan apertura de anillo debido a su inestabilidad termodinámica y cinética, formando, tras una transferencia de proton, enolatos de azolio. Los enolatos de azolio intervienen como especies alqueno

HOMO-activados con alquilideneoxindoles actuando como aceptores tipo Michael en la reacción de cicloadición tipo Diels-Alder con demanda electrónica inversa.

La evaluación de condiciones de reacción lleva al empleo de una sal de triazolio quiral como precursor de la especie carbeno, con *N*,*N*-diisopropiletilamina como base, en dichorometano a temperatura ambiente para la formación de estructuras tipo δ-lactona como 3,4-dihidropirano[2,3-*b*]-indoles (Esquema 4). La metodología se extiende al empleo de formilciclopropanos con variación en los sustituyentes del carboxilato, modificación en el grupo *N*-protector del indol, evaluando varios grupos electroatractores en la posición β del alquilideneoxindo y la sustitución en el anillo aromático, obteniendo aductos como únicos diastereoisomeros en moderado hasta alto rendimiento y enantioselectividad excelente.

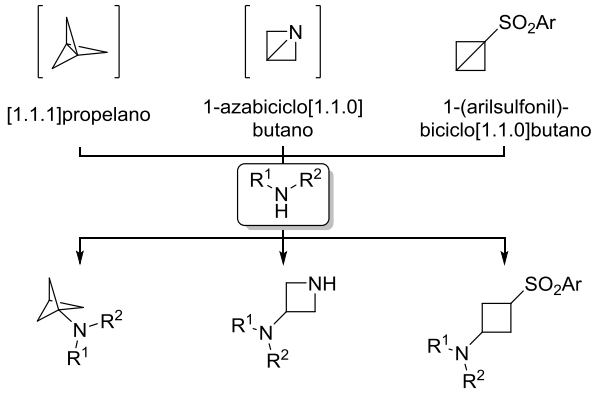


Esquema 4

Finalmente, el capítulo quinto trata de los resultados obtenidos durante una estancia de tres meses en el grupo del profesor Prof. Phil S. Baran, en The Scripps Research Institute (La Jolla, CA). Motivado por el creciente interés de la industria farmacéutica por el desarrollo de metodologías que permitan el rápido acceso a bioisosteres y el difícil acceso a determinadas estructuras de interés farmacológico, como es la biciclo[1.1.1]pentan-1-amina, se plantea el uso de la tensión de anillo como fuerza

impulsora de reacción y originando el desarrollo de transformaciones sintéticas sin precedentes.

En este marco, se estudia una metodología que implica el uso de anillos bicíclicos altamente tensionados, *i.e.* [1.1.1]propelano, 1-azabiciclo[1.1.0]butano y 1-(arilsulfonil)biciclo[1.1.0]butano, los cuales, debido a su naturaleza, presentan una elevada tendencia a experimentar la ruptura del enlace central liberando, en gran medida su tensión. El tipo de reactivo seleccionado para que desencadene la ruptura del enlace central son aminas secundarias que actúan como nucleófilo bajo condiciones de reacción optimizadas para cada sustrato, en una transformación que se asemeja a la reacción de hidroaminación (Esquema 5).



Esquema 5

La reacción de aminación liberadora de tensión se presenta como una potente herramienta sintética para la funcionalización en etapa tardía de compuestos tipo amina, llevando a la formación de productos de elevado interés para la industria farmacéutica

Papers

From part of the work presented in this manuscript the following publications have emerged:

1. *"Regioselectivity Change in the Organocatalytic Enantioselective (3+2) Cycloaddition with Nitrones Through Cooperative H-Bonding Catalysis/Iminium Activation"*

Liher Prieto, Veronica Juste-Navarro, Uxue Uria, Ignacio Delso, Efraim Reyes, Tomas Tejero, Luisa Carrillo, Pedro Merino, and Jose L. Vicario

Chem. Eur. J. DOI: 10.1002/chem.201605350

2. *"Favoring Trienamine Activation through Unconjugated Dienals: Organocatalytic Enantioselective Remote Functionalization of Alkenes"*

Liher Prieto, Garazi Talavera, Uxue Uria, Efraim Reyes, Jose L. Vicario and Luisa Carrillo

Chem. Eur. J. **2014**, *20*, 2145.

3. *"N-Heterocyclic Carbene-Mediated Activation of Formylcyclopropanes. Catalytic Generation of Donor-Acceptor Cyclopropanes and their Reaction with Michael Acceptors"*

Liher Prieto, Eduardo Sánchez-Díez, Uxue Uria, Efraim Reyes, Luisa Carrillo and Jose L. Vicario

Submitted manuscript.

4. *"Strain-Release Amination"*

Ryan Gianatassio, Justin M. Lopchuk, Jie Wang, Chung-Mao Pan, Lara R. Malins, Liher Prieto, Thomas A. Brandt, Michael R. Collins, Gary M. Gallego, Neal W. Sach, Jillian E. Spangler, Huichin Zhu, Jinjiang Zhu, Phil S. Baran

Science **2016**, *351*, 241.

5. *"Strain- Release Heteroatom Functionalization: Development, Scope, and Stereospecificity"*

Justin M. Lopchuk, Kasper Fjelbye, Yu Kawamata, Lara R. Malins, Chung-Mao Pan, Ryan Gianatassio, Jie Wang, Liher Prieto, James Bradow, Thomas A. Brandt, Michael R. Collins, Jeff Elleraas, Jason Ewanicki, William Farrell, Olugbeminiyi O. Fadeyi, Gary M. Gallego, James J. Mousseau, Robert Oliver, Neal W. Sach, Jason K. Smith, Jillian E. Spangler, Huichin Zhu, Jinjiang Zhu, Phil S. Baran

J. Am. Chem. Soc. DOI: 10.1021/jacs.6b13229

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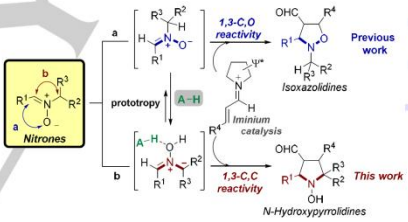
Regioselectivity Change in the Organocatalytic Enantioselective (3+2) Cycloaddition with Nitrones Through Cooperative H-Bonding Catalysis/Iminium Activation.

Liher Prieto,[a] Veronica Juste-Navarro,[b] Uxue Uria,[a] Ignacio Delso,[b] Efraim Reyes,[a] Tomas Tejero,[b] Luisa Carrillo,[a] Pedro Merino,*[b] and Jose L. Vicario*[a]

Dedicated to Prof. Dr. Dieter Enders on the occasion of his 70th birthday

Abstract: The reaction of nitrones with enals under iminium activation can be modulated by using cooperative H-bonding catalysis to induce the participation of a nitrone ylide (C-N-C) instead of the classical C-N-O dipole. As a consequence, *N*-hydroxypyrrolidines, rather than the expected isoxazolidines, are obtained. The reaction proceeds smoothly and high enantioselectivities are observed in all cases. By using the appropriate substrate, polysubstituted pyrrolidines incorporating quaternary stereocenters can be efficiently prepared.

Cycloadditions are powerful reactions that enable the construction of complex molecular architectures through the simultaneous generation of two new bonds.[1] Moreover, the stereochemical requirements associated to cycloaddition processes make this type of reactions very appropriate candidates to develop stereocontrolled variants. In this sense, catalytic and enantioselective (3+2) cycloadditions emerge as very convenient tools for the preparation of stereodefined 5-membered ring heterocyclic scaffolds and in the past few years research has been intense trying to develop catalytic and enantioselective versions with a variety of 1,3-dipoles.[2] In particular, the ability of chiral primary or secondary amines to activate α,β-unsaturated aldehydes or ketones towards their participation as dipolarophiles in (3+2) cycloadditions under the so-called iminium activation manifold[3] has been explored by several authors[4] after the initial discovery of the concept by MacMillan.[5] Specifically this approach has been successfully applied to reactions using nitrones,[6] azomethine ylides[7] and azomethine imines[8] as 1,3-dipoles. Despite these intensive efforts the range of dipoles in which this approach has been employed is still very limited. In particular, nitrones have been widely recognized as one of the most widely used 1,3-dipoles in (3+2) cycloaddition reactions, mainly because these are stable compounds that can be easily synthesized and handled, in comparison with other 1,3-dipoles,[9] and in fact, the 1,3-dipolar cycloaddition between nitrones and enals was the first example of an organocatalytic enantioselective (3+2) cycloaddition under iminium activation.[6a] This reaction enables the direct synthesis of isoxazolidines as single stereoisomers in which the nitrone simultaneously reacts through the C and O termini. As an alternative, we envisaged that this standard 1,3-C,O reactivity of nitrones could be modified to a less conventional 1,3-C,C-type reactivity in (3+2) cycloaddition chemistry using some specific nitrone compounds able to give nitrone ylides, in combination with H-bond cocatalyst,[10] leading to the formation of *N*-hydroxypyrrolidines in a single step (See scheme 1). Moreover, the iminium activation approach could also provide the opportunity to render the overall process enantioselective by the incorporation of a chiral secondary amine as catalyst.



Scheme 1. Bidentate reactivity of nitrones towards (3+2) cycloaddition with enals under cooperative H-bonding catalysis/iminium activation..

We started our work by surveying the viability of the cycloaddition reaction using nitrone **1a** and cinamaldehyde **2a** as a model system (Table 1) introducing an electron-withdrawing group on the α-substituent to the nitrogen atom in the former in order increase the acidity of the adjacent proton that would therefore assist the formation of the required nitrone ylide tautomer. When the reaction was carried out in the presence of the archetypal *O*-TMS diphenylprolinol **3a**, which is recognized as a reliable catalyst for the activation of enals through iminium salt intermediates,[11] no reaction was observed (entry 1) and incorporating benzoic acid as protic additive with the aim to stabilize the nitrone ylide intermediate also led to no reactivity (entry 2). Remarkably, using achiral thiourea **5** as co-catalyst, which had been previously used in other reactions under aminocatalytic activation for the stabilization of ionic intermediates through H-bonding interactions,[12] led to the formation of an *N*-hydroxypyrrolidine adduct, albeit in moderate yield. Importantly, the presence of isoxazolidine cycloadducts

[a] L. Prieto, Dr. U. Uria, Dr. E. Reyes, Dr. L. Carrillo, Prof. J. L. Vicario
Department of Organic Chemistry II
University of the Basque Country (UPV/EHU)
P.O. Box 644, 48080 Bilbao (Spain)
E-mail: joseluis.vicario@ehu.es
[b] V. Juste-Navarro, Prof. T. Tejero, Dr. I. Delso, Prof. P. Merino
Laboratorio de Síntesis Asimétrica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH)
Universidad de Zaragoza-CSIC
Campus San Francisco, 5009 Zaragoza (Spain)
E-mail: pmerino@unizar.es

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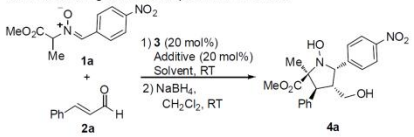
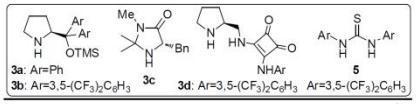
arising from the potential participation of the nitrone as 1,3-C,O dipole was not detected in the crude reaction mixture. The adduct was isolated as a complex mixture of four diastereoisomers that included the presence of the two epimers at C3 (the stereocentre containing the formyl substituent) that appeared during chromatographic purification. In order to avoid this epimerization process, the crude reaction mixture was subjected to *in situ* reduction, observing the clean formation of adduct **4a** in 47% yield and as a 5:1 mixture of diastereoisomers and in which the major one showed a very high e.e. (entry 3).

Table 1. Screening for the best experimental conditions.





Entry	Catalyst	Additive	Solvent	Yield [%][a]	d.r.[b]	e.e. [%][c]
1	**3a**	none	$CHCl_3$	<5	n.d.[d]	n.d.[d]
2	**3a**	$PhCO_2H$	$CHCl_3$	<5	n.d.[d]	n.d.[d]
3	**3a**	**5**	$CHCl_3$	47	5:1	97
4	**3b**	**5**	$CHCl_3$	<5	n.d.[d]	n.d.[d]
5	**3c**	HCl	$MeNO_2$	<5	n.d.[d]	n.d.[d]
6	**3d**	none	$CHCl_3$	40	4:1	20
7[e]	**3a**	**5**	$CHCl_3$	92	5:1	98
8[f]	**3a**	**5**	$CHCl_3$	27	5:1	98
9[e]	**3a**	-	$CHCl_3$	9	2:1	98
10[g]	**3a**	**5**	$CHCl_3$	62	6:1	97
11[e]	**3a**	**5**	CH_2Cl_2	82	3:1	98
12[e]	**3a**	**5**	Toluene	53	4:1	98
13[e]	**3a**	**5**	THF	28	4:1	98
14[e]	**3a**	**5**	EtOAc	22	4:1	97

[a] Yield of pure product after flash column chromatography. [b] Determined by NMR analysis of crude reaction mixture. [c] Determined by HPLC analysis on chiral stationary phase of the corresponding alcohol after reduction (see Supporting Information). [d] n.d.: Not determined [e] Et_3N (20 mol%) was incorporated as additive. [f] Et_3N (40 mol%) was incorporated as additive. [g] Reaction carried out using 1 eq. of **5** and 1 eq. of Et_3N

The use of the bulkier diarylprolinol-based catalyst **3b** under these conditions did not provide any cycloaddition product (entry 4) and the same was observed when we tested the (3+2) reaction with nitrone **1a** under the conditions reported by MacMillan[6a] for the generation of isoxazolidines (entry 5).[13] We also surveyed the possibility of using bifunctional pyrrolidine/squaramide catalyst **3d** but this was unable to provide good enantiocontrol (entry 6). An important improvement was observed when a basic additive such as Et_3N was incorporated (20 mol%) into the reaction scheme, in this case obtaining adduct **4a** in high yield, diastereo- and enantiocontrol after 48h (entry 7).[14] Using a larger amount of base led to poorer yield of **4a** (entry 8) and the same happened when the reaction was carried out in the presence of Et_3N but without thiourea **5** (entry 9), this last experiment demonstrating the key role played by this additive in the stabilization of the nitrone ylide intermediate. The reaction using stoichiometric amounts of both additives was observed to proceed much faster, observing complete conversion after 12h but with a lower isolated yield of **4a** because of some decomposition (entry 10). Finally, other solvents were also surveyed (entries 11-14) without any significant improvement and therefore it was concluded that the conditions summarized in entry 7 of Table 1 were the most appropriate ones for this transformation. It should be highlighted that these conditions enable the generation of nitrone ylides from substrates in which the proton undergoing prototropy is activated by one single electron-withdrawing group, in contrast to what it was previously found for the generation of azomethine ylides, for which the presence of two activating groups is fully necessary to form the ylide.[7a,7k] This is a relevant issue since it also opens the way for the synthesis of pyrrolidines with one single electron-withdrawing substituent at this stereocentre.

Having established a robust experimental protocol for the reaction, we next proceeded to explore the scope of the reaction with respect to the nitrone and the enal reagents. As it can be seen in Table 2, the reaction proceeded efficiently with a family of structurally different β-aryl substituted enals **2a-l**, furnishing the hydroxypyrrolidine adducts **4a-n** in high yields, good diastereoselectivity and excellent e.e (entries 1-14) regardless the electronic nature of the aryl substituent (compare entries 1-7 with entries 9-12) and the position of the substituents at this aryl moiety (compare entries 3, 4 and 7).[16] Also β-heteroaryl substituted enals performed well (entries 6, 13 and 18). In none of these cases the formation of isoxazolidine byproducts were observed in the crude reaction mixture. The reaction also showed a similar level of performance when the structure of the ester moiety of the nitrone was changed (see entries 1-6 *vs* 7-14) and it also proceeded efficiently when nitrones with different substitution patterns at the aryl substituent were employed (entries 15-19), although results indicated that the yield was significantly higher when strongly electron-withdrawing groups were placed at this position (entries 15-18 *vs* entries 19-20). Remarkably, a larger ethyl group at the α-position to the ester moiety of the nitrone also led to excellent results, which points towards the wide tolerance of the reaction towards the incorporation of substituents at this position leading to the formation of a quaternary stereocentre (entry 21). Finally, a glyoxylate-derived nitrone was employed,[17] also illustrating the possible participation of nonaromatic nitrones as substrates (entry 22).[18] A possible limitation to the methodology aroused

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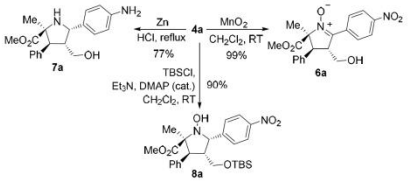
Finally, we also evaluated some possible manipulations of the obtained *N*-hydroxypyrrolidines **4** in order to demonstrate their potential as chiral building blocks in synthesis (Scheme 3). Taking **4a** as representative example, this compound could be easily oxidized to give highly-substituted cyclic nitrone **6a** of high synthetic value.[9a] Moreover, the reduction to the corresponding pyrrolidine **7a** could also be easily accomplished under Zn/HCl conditions. Finally, we also demonstrated the feasibility of the selective protection of the primary alcohol moiety in the presence of the hydroxylamino functionality.



Scheme 3. Some useful transformations on adduct **4a**.

In conclusion, this novel organocatalyzed asymmetric (3+2) cycloaddition of nitrones with α,β-unsaturated aldehydes provides a new entry to the enantioselective synthesis of a variety of highly substituted *N*-hydroxypyrrolidines bearing a quaternary center adjacent to the nitrogen atom.[22] The combined use of organocatalyst **3a** together with thiourea **5** enabled the first successful use of *N*-(alkoxycarbonylmethyl)nitrones in highly enantioselective (3+2) cycloadditions participating as 1,3-C-C dipoles, in an alternative to their well-known 1,3-C,O reactivity.

Acknowledgements

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Keywords: cycloaddition • nitrones • pyrrolidines • organocatalysis • Asymmetric catalysis

[1] (a) S. Kobayashi, K. A. Jørgensen, *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002; (b) P. Wipf, Z. Fang, L. Ferrie, M. Ueda, M. A. A. Walczak, Y. Yan, M. Yang, *Pure Appl. Chem.* **2013**, *85*, 1079; (c) N. Nishiwaki, *Methods and applications of Cycloaddition Reactions in Organic Syntheses*; John Wiley: Hoboken, USA, 2014; (d) M. Vrabel, T. Carell, *Cycloadditions in Bioorthogonal Chemistry*; Springer: Zurich, Switzerland, 2016.

[2] A. Padwa, W. H. Pearson *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry*, John Wiley & sons: New York, USA, 2003. For some reviews see (a) M. Baunach, C. Hertweck, *Angew. Chem., Int. Ed.* **2015**, *54*, 12550. (b) C. Nájera, J. M. Sansano, M. Yus *Org. Biomol. Chem.* **2015**, *13*, 8596. (c) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784; (d) M. Kissane, A. R. Maguire, *Chem. Soc. Rev.* **2010**, *39*, 845; (e) B. Engels, M. Christl, *Angew. Chem., Int. Ed.* **2009**, *48*, 7968. (f) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887; (g) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235; (h) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247.

[3] For some specific revisions focused on the iminium activation manifold see (a) J. B. Brazier, N. C. Tomkinson, *Top. Curr. Chem.* **2010**, *291*, 281. (c) G. Lelais, D. W. C. MacMillan *Aldrichim. Acta* **2006**, *39*, 79. (d) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

[4] Selected reviews on organocatalytic enantioselective cycloadditions: (a) H. Pellissier *Tetrahedron* **2012**, *68*, 2197. (b) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703. (c) J. L. Vicario *Synlett* **2016**, *27*, 1006.

[5] (a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. See also (b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[6] First report (a) W. S. Jen, J. J. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874. Other examples (b) P. H. Poulsen, S. Vergura, A. Monleon, D. K. B. Jørgensen, K. A. Jørgensen *J. Am. Chem. Soc.* **2016**, *138*, 6412. (c) L. Weselinski, E. Kalinowska, J. Jurczak, *Tetrahedron: Asymmetry* **2012**, *23*, 264. (d) T. Otsuki, J. Kumagai, Y. Kohari, Y. Okuyama, E. Kwon, C. Seki, K. Uwai, Y. Mawatari, N. Kobayashi, T. Iwasa, M. Tokiwa, M. Takeshita, A. Maeda, A. Hashimoto, K. Turuga, H. Nakano, *Eur. J. Org. Chem.* **2015**, 7292. (e) J. Aleman, A. Fraile, L. Marzo, J. L. Garcia Ruano, C. Izquierdo, S. Diaz-Tendero, *Adv. Synth. Catal.* **2012**, *354*, 1665. (f) Z.-L. Shen, K. K. K. Goh, C. H. A. Wong, W.-Y. Loo, Y.-S. Yang, J. Lu, T.-P. Loh, *Chem. Commun.* **2012**, *48*, 5856. (g) X. Cai, C. Wang, J. Sun, *Adv. Synth. Catal.* **2012**, *354*, 359. (h) S. S. Chow, M. Nevalainen, C. A. Evans, C. W. Johannes, *Tetrahedron Lett.* **2007**, *48*, 277. (i) A. Puglisi, M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, *Eur. J. Org. Chem.* **2004**, 567. (j) S. Karlsson, H.-E. Hoegberg, *Eur. J. Org. Chem.* **2003**, 2782.

[7] First example (a) J. L. Vicario, S. Reboredo, D. Badia, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. Other examples (b) J. Li, H. Zhao, Y. Zhang, *Synlett* **2015**, *26*, 2745. (c) J.-A. Xiao, Q. Liu, J.-W. Ren, J. Liu, R. G. Carter, X.-Q. Chen, H. Yang, *Eur. J. Org. Chem.* **2014**, 5700. (d) A. Iza, I. Ugarriza, U. Uria, E. Reyes, L. Carrillo, J. L. Vicario, *Tetrahedron* **2013**, *69*, 8878. (e) S. Reboredo, E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, A. de Cozar, F. P. Cossio, *Chem. Eur. J.* **2012**, *18*, 7179. (f) S. Reboredo, J. L. Vicario, D. Badia, L. Carrillo, E. Reyes, *Adv. Synth. Catal.* **2011**, *353*, 3307. (g) N. Fernandez, L. Carrillo, J. L. Vicario, D. Badia, E. Reyes, *Chem. Commun.* **2011**, *47*, 12313. (h) A. Iza, L. Carrillo, J. L. Vicario, D. Badia, E. Reyes, J. I. Martinez, *Org. Biomol. Chem.* **2010**, 8, 2238. (i) A. Fraile, D. M. S. Schietroma, A. Albrecht, R. L. Davis, K. A. Jørgensen, *Chem. Eur. J.* **2012**, *18*, 2773. (j) I. Ibrahem, R. Rios, J. Vesely, A. Còrdova, *Tetrahedron Lett.* **2007**, *48*, 6252. (k) S. Lin, L. Deiana, G.-L. Zhao, J. Sun, A. Cordova, *Angew. Chem. Int. Ed.* **2011**, *50*, 7624.

[8] First example (a) W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding, Y.-C. Chen, *Adv. Synth. Catal.* **2006**, *348*, 1818. See also (b) C. Izquierdo, F. Esteban, A. Parra, R. Alfaro, J. Aleman, A. Fraile, J. L. Garcia Ruano, *J. Org. Chem.* **2014**, *79*, 10417. (c) W. Li, Q. Jia, Z. Du, K. Zhang, J. Wang, *Chem. Eur. J.* **2014**, 20, 4559. (d) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2007**, 46, 7667.

[9] (a) P. Merino, in *Science of Synthesis, Vol. 27* (Eds.: D. Bellus, A. Padwa), George Thieme, Stuttgart, **2004**, pp. 511; update in *Science of Synthesis, Vol. 2010/4* (Ed.: E. Schaumann), George Thieme, Stuttgart, **2011**, pp. 325. For reviews on cycloaddition of nitrones see (b) F. Hu, M. Szostak, *Adv. Synth. Catal.* **2015**, *357*, 2583. (c) K. Rück-Braun, T. H. E. Freysoldt, F. Wierschem, *Chem. Soc. Rev.* **2005**, *34*, 507. (d) K.

Chemistry - A European Journal 10.1002/chem.201605350

V. Gothelf, K. A. Jørgensen, *J. Chem. Soc. Chem. Commun.* **2000**, 1449. (e) P. N. Confalone, E. M. Huie, *Org. React. (N.Y.)* **1988**, *36*, 1

[10] (a) V. Juste-Navarro, I. Delso, T. Tejero, P. Merino, *Chem. Eur. J.* **2016**, *22*, 11527. (b) P. Merino, T. Tejero, A. Diez-Martinez, Z. Gultekin, *Eur. J. Org. Chem.* **2011**, 6567.

[11] (a) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860. (b) S. Meninno, A. Lattanzi, *Chem. Commun.* **2013**, *49*, 3821. (c) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248. (d) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.

[12] (a) E. Reyes, G. Talavera, J. L. Vicario, D. Badia, L. Carrillo, *Angew. Chem. Int. Ed.* **2009**, *48*, 5701. (b) N. Z. Burns, M. R. Witten, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 14578. (c) M. R. Witten, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2014**, *53*, 5912.

[13] *p*-Nitrobenzaldehyde and the corresponding cinamaldehyde-derived nitrone were cleanly isolated after 36h of reaction in both cases.

[14] Other Brønsted bases like DMAP, DBU, DABCO, Na_2CO_3 or LiOAc were tested but without furnishing better results than Et_3N.

[15] The obtained aldehydes showed to be configurationally unstable and epimerization was observed upon manipulation.

[16] In all cases, the minor diastereoisomers obtained were identified to be those with opposite configuration at both C2 and C5 positions

[17] The starting nitrone was employed as a mixture of Z/E diastereoisomers from which only one of them was found to be reactive, which explained the low yield. This behavior is under investigation.

[18] Nitrones derived from aliphatic aldehydes (R^1=alkyl) reacted through undesired 1,2-addition pathway. See also ref. 10

[19] The reaction with tolualdehyde-derived nitrone (R^1=4-MeC_6H_4, R^2=Me, R^3=Me) with cinnamaldehyde provided a 20% conversion after 72h.

[20] CCDC 1511107 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] The reaction performed with slightly better yield in the absence of Et_3N.

[22] While this manuscript was under revision, a related example of a [3+2] cycloaddition between isatin-based nitrone ylides and enals proceeding under iminium activation was reported: Y.-R. Chen, G. Zhan, W. Du, Y.-C. Chen. *Adv. Synth. Catal.* **2016**, *358*, 3759

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Organocatalysis

Favoring Trienamine Activation through Unconjugated Dienals: Organocatalytic Enantioselective Remote Functionalization of Alkenes

Liher Prieto, Garazi Talavera, Uxue Uria, Efraim Reyes,* Jose L. Vicario,* and Luisa Carrillo[a]

Abstract: Unconjugated 2,5-dienals are more reactive substrates than the corresponding fully conjugated α,β,γ,δ-unsaturated aldehydes towards organocatalytic activation through trienamine intermediates. This difference in reactivity has been demonstrated in the Diels–Alder reaction with nitroalkenes, a reaction that proceeds with clean β,ε-selectivity to afford the final products in high yields and stereoselectivities, the related polyconjugated 2,4-dienals being completely unreactive.

The discovery of the proline-catalyzed cross-aldol reaction in 2000 by List, Barbas, and Lerner[1] and of the iminium-activation concept by the research group of MacMillan in the same year[2] established the beginning of one of the most active research fields in chemistry, a field that has revolutionized the area of asymmetric catalysis in the last decade. The possibility for primary or secondary amines to activate enolizable aldehydes or ketones towards a variety of reactions opened the way for their α-functionalization in a catalytic and enantioselective fashion by means of the reversible formation of an enamine[3] or an iminium radical–cation intermediate.[4] In the same line, the β-functionalization of enones and enals is possible through the catalytic formation of an α,β-unsaturated iminium ion.[5] More recently, the combination of these two activation manifolds, along with the principle of vinylogy,[6] has opened the possibility for the remote functionalization of unsaturated aldehydes and ketones, allowing the γ- and the δ-functionalization through dienamine catalysis[7] and vinylogous iminium ion activation,[8] respectively. Much more recently, Jørgensen, Chen, and co-workers have also shown that even a more remote ε-functionalization is also possible by the formation of trienamine intermediates which, if conformationally locked, also allow the selective installation of ε-stereocenters with high degree of stereochemical control.[9]

[a] *L. Prieto, Dr. G. Talavera, Dr. U. Uria, Prof. E. Reyes, Prof. J. L. Vicario, Prof. L. Carrillo*
Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología
Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU
P.O. Box 644, 48080 Bilbao (Spain)
E-mail: efraim.reyes@ehu.es
joseluis.vicario@ehu.es

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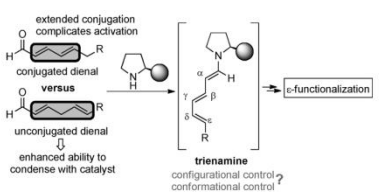
In addition to the different issues that have to be controlled when a stereocenter is generated so far away from the chirality-inducing element, the application of the vinylogy concept in enamine and iminium ion activation also suffers from an additional reactivity problem, which is associated with the covalent nature of the catalyst–substrate interaction. In this sense, the implementation of a reaction through dienamine or trienamine intermediates entails that the conjugation level of the starting material has to increase from that of a simple aldehyde or ketone to that of an α,β-unsaturated or α,β,γ,δ-polyunsaturated aldehyde or ketone, respectively, and this involves a progressive depletion of its reactivity towards condensation with the aminocatalyst. In this context, we herein introduce the use of non-conjugated polyunsaturated aldehydes as more reactive starting materials that have an enhanced tendency to undergo this initial activation step by condensation with the chiral secondary amine catalyst and that also end up in the formation of the same conjugated trienamine intermediate as the one generated with a fully conjugated 2,4-dienal (see Scheme 1). Importantly, this alternative unconjugated dienal substrate has also to be able to be converted into the trienamine intermediate as a single diastereoisomer and with a well-defined geometry for the subsequent reaction to proceed with high stereocontrol, a condition that means all the dynamic equilibria participating in the formation of this intermediate have to end up in a trienamine showing preferential reactivity through one single reactive configuration or conformation.[10] Herein, we present our first results regarding the application of this approach to a Diels–Alder reaction,[11] in which the trienamine intermediate is participating as the diene component and nitroalkenes are used as the dienophile counterparts.[12]



Scheme 1. Conjugated versus unconjugated dienals as substrates for organocatalytic reactions via trienamine intermediates.

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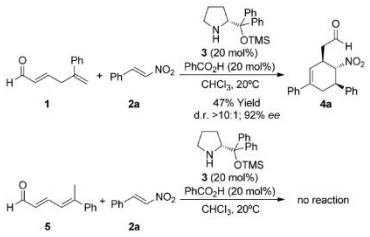
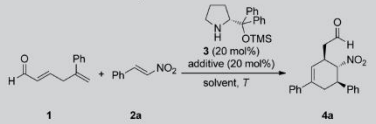
To test our hypothesis, we reacted 2,5-dienal **1** with nitrostyrene (**2a**) in the presence of 20 mol% of *O*-TMS diphenylprolinol **3**, which is a privileged chiral secondary amine catalyst that has shown excellent performance in promoting reactions under enamine, iminium, or dienamine activation, and benzoic acid as a Brønsted acid co-catalyst. This reaction furnished Diels–Alder cycloadduct **4a** in a promising 47% yield and as a single diastereoisomer with 92% *ee*. At the same time, when we carried out the reaction by using conjugated dienal **5** under the same conditions, only the starting materials were recovered after a prolonged reaction time, without any evidence for the formation of product **4a** (Scheme 2).[13]



Scheme 2. Proof of concept experiments.

These two experiments confirmed our initial proposal and led us to further investigate this enhanced reactivity showed by unconjugated dienal **1**. Assuming the excellent performance of catalyst **3** in terms of almost perfect stereocontrol, we therefore focused our efforts on increasing the chemical yield of the process, working with the same set of model reagents (Table 1). We started our studies by testing different solvents; while the use of CH_2Cl_2 (Table 1, entry 2) or a more polar solvent like THF (Table 1, entry 3) led to a notable decrease in the yield of the process, changing the solvent to toluene was found to have a positive effect, **4a** being obtained in a better 66% yield (Table 1, entry 4). We next surveyed the influence of the acid co-catalyst, testing a set of different Brønsted acids (Table 1, entries 5–7). Surprisingly, using additives of either more or less acidic character resulted in poorer conversions, which led us to consider the use of Brønsted bases as co-catalysts (Table 1, entries 8–10). The incorporation of NaOAc resulted in a notable increase in the chemical yield of the reaction, while maintaining the high level of diastereo- and enantioselection (Table 1, entry 8). When other bases such as DBU or DABCO were used (Table 1, entries 9 and 10), **4a** was not detected; the only outcome observed being the complete conversion of **1** into conjugated dienal **5**, which has been shown to be unreactive towards condensation with the catalyst as demonstrated with the preliminary experiment shown in Scheme 2. On the other hand, the reaction in the absence of additive was also found to be very effective, leading to the formation of **4a** in excellent yield and stereocontrol (Table 1, entry 11). Finally, we also evaluated the effect of temperature in the reaction, observing that this was indeed a crucial parameter to be controlled. In fact, whereas carrying out the reaction at a lower temperature led to a decrease in the yield of the reaction without any noticeable improvement in the enantioselectivity (Table 1, entry 12), performing the reaction at a slightly higher temperature resulted in the formation of notable amounts of conjugated dienal byproduct **5**, a transformation that contributed to a poorer yield of **4a** and lower enantioselectivity (Table 1, entry 13).

Table 1. Optimization of experimental conditions using the reaction between **1** and **2a** as model system.[a]



Entry	Solvent	Additive	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	$CHCl_3$	$PhCO_2H$	20	47	>10:1	92
2	CH_2Cl_2	$PhCO_2H$	20	20	>10:1	93
3	THF	$PhCO_2H$	20	8	n.d.[e]	n.d.[e]
4	toluene	$PhCO_2H$	20	66	>10:1	93
5	toluene	$4\text{-}NO_2C_6H_4CO_2H$	20	27	n.d.[e]	n.d.[e]
6	toluene	$4\text{-}MeOC_6H_4CO_2H$	20	41	n.d.[e]	n.d.[e]
7	toluene	$4\text{-}FC_6H_4CO_2H$	20	53	n.d.[e]	n.d.[e]
8	toluene	NaOAc	20	96	>10:1	90
9	toluene	DBU	20	<5	–	–
10	toluene	DABCO	20	<5	–	–
11	toluene	none	20	99	>10:1	94
12	toluene	none	4	67	>10:1	91
13	toluene	none	30	61	>10:1	64

[a] Reactions were carried out in a 0.20 mmol scale of **2a** and 0.26 mmol of **1** using 20 mol% of catalyst **3** in 2.0 mL of solvent at the specified temperature for 12 h. [b] Yield of product **4a** after flash column chromatography purification. [c] Determined by ^1H NMR spectroscopy of crude reaction mixture. [d] Determined by HPLC (see the Supporting Information). [e] n.d.: not determined. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMS=trimethylsilyl.

Having established the best protocol for the reaction, we decided to extend this methodology to nitroalkenes with different substituents (Table 2). Under the optimized conditions, a wide variety of differently substituted cyclohexenes **4a**–**n** were obtained with excellent yields and as single diastereoisomers. In this sense, the reaction performed equally well when nitrostyrene derivatives containing either more electron-rich (Table 2, entries 2–6) or electron-deficient β-aryl moieties (Table 2, entries 7–11) were employed. In the same line, the reaction proceeded satisfactorily without showing important influence with respect to the substitution pattern on the aryl group, maintaining excellent yields and stereoselectivities even if the substituent is located at *ortho*, *meta*, or *para* position (see for example Table 2, entries 2–4 and entries 7–9). Moreover, heteroaryl substituents were also well tolerated (Table 2,

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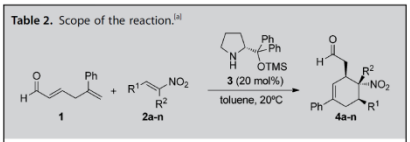
entries 12 and 13). For all the cases tested, the reaction proceeded with excellent enantioselectivity, furnishing the final adducts **4a–n** as highly enantioenriched compounds. Remarkably, α,β-disubstituted nitroalkene **2n** was also found to perform excellently in the reaction (Table 2, entry 14), this example showing the potential of this methodology for the generation of cyclohexenes with a quaternary stereocenter. Notably, as previously mentioned, the temperature of the reaction had to be carefully kept at 20 °C during the entire process by using thermostatized baths, observing that when carrying out the reaction at a higher temperature, yields were significantly affected by the presence of the corresponding fully conjugated dienal, the formation of which is presumably also catalyzed by **3** through trienamine formation/hydrolysis.

Table 2. Scope of the reaction.[a]



Entry	Product	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	Ph	H	99	13:1	94
2	**4b**	4-$MeOC_6H_4$	H	93	>20:1	93
3	**4c**	3-$MeOC_6H_4$	H	91	16:1	90
4	**4d**	2-$MeOC_6H_4$	H	92	12:1	97
5	**4e**	4-MeC_6H_4	H	85	19:1	92
6	**4f**	4-$BnOC_6H_4$	H	98	16:1	96
7	**4g**	4-ClC_6H_4	H	99	14:1	90
8	**4h**	3-ClC_6H_4	H	94	12:1	93
9	**4i**	2-ClC_6H_4	H	88	14:1	96
10	**4j**	4-BrC_6H_4	H	92	13:1	96
11	**4k**	2-BrC_6H_4	H	81	13:1	92
12	**4l**	2-thienyl	H	87	13:1	97
13	**4m**	2-furyl	H	80	>20:1	89
14	**4n**	Ph	Me	64	16:1	96

[a] Reactions were carried out in a 0.20 mmol scale of **2a–n** and 0.26 mmol of **1** using 20 mol% of catalyst **3** in 2.0 mL of toluene at 20 °C for 12 h. [b] Yield of pure isolated product. [c] Determined by ^1H NMR analysis on crude reaction mixture. [d] Determined by HPLC (see the Supporting Information).

The absolute configuration was assigned by single-crystal X-ray analysis of adduct **4e** (Figure 1),[14] the configuration of all other adducts **4a–n** being established by analogy. The structure is consistent with the one previously observed in other [4+2] reactions in which trienamine intermediates derived from linear fully conjugated dienals are participating.[11a–e]

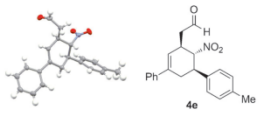


Figure 1. X-ray structure of **4e**.

In conclusion, we have demonstrated that unconjugated dienals in reactions under trienamine activation can be used as alternative substrates for reactions in which the related fully conjugated α,β,γ,δ-unsaturated aldehydes fail to participate. The effect of breaking the conjugation translates into a better ability to condense with the chiral secondary amine catalyst, thus leading to the same vinylogous trienamine intermediate, which is able to react subsequently in a very efficient manner. In this report, we have illustrated the potential of this new methodological approach by implementing a Diels–Alder reaction between these unconjugated dienals and nitroalkenes, the former ones acting as the electron-rich diene counterparts, thus leading to the formation of cyclohexene adducts resulting from the formal ε-activation of the unconjugated olefin moiety. Moreover, we have also demonstrated the ability of the catalyst to induce remote stereoinduction with the same high level of efficiency as exhibited for the cases in which fully conjugated dienals are employed.[15]

Experimental Section

General procedure for the cycloaddition reaction.

Synthesis of 4a–n: The starting nitroolefin **2a–n** (0.20 mmol) was added to a solution of **3** (0.04 mmol) and **1** (0.26 mmol) in toluene (2 mL) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at 20 °C for 12 h, after which the crude reaction mixture was concentrated, directly charged onto silica gel and subjected to flash chromatography (hexane/AcOEt gradient from 19:1 to 9:1), affording the corresponding tetrasubstituted cyclohexenyl adduct **4a–n**.

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Keywords: asymmetric catalysis · cycloaddition · organocatalysis · trienamines · vinylogy

[1] B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[2] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[3] For some reviews on enamine activation, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123; c) T. Kano, K. Maruoka, *Chem. Commun.* **2008**, 5465.
[4] For reviews on SOMO catalysis, see: a) D. W. C. MacMillan, T. D. Beeson in *Science of Synthesis, Asymmetric Organocatalysis, Vol. 1* (Eds.: B. List, K. Maruoka), Georg Thieme Verlag, Stuttgart, **2012**, pp. 271–307; b) P. Renaud, P. Leong, *Science* **2008**, *322*, 55; for a recent example showing the possibility of β-functionalization of simple aldehydes through SOMO catalysis, see: c) M. T. Pirnot, D. A. Rankic, D. B. C. Martin, D. W. C. MacMillan, *Science* **2013**, *339*, 1593.
[5] For some reviews on iminium activation, see: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416; b) G. Lelais, D. W. C. MacMillan,

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Communication

Aldrichimica Acta **2006**, *39*, 79; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[6] a) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1; for two excellent reviews related to the combination of the vinylogy principle with aminocatalysis, see: b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869; c) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287.

[7] D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865.

[8] a) X. Tian, Y. K. Liu, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 6545; *Angew. Chem. Int. Ed.* **2012**, *51*, 6439; b) K. Lee, H. Kim, J. Hong, *Angew. Chem.* **2012**, *124*, 5833; *Angew. Chem. Int. Ed.* **2012**, *51*, 5735; c) L. Dell'Amico, L. Albrecht, T. Naiker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063.

[9] For a pioneering report, see: a) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; for reviews on trienamine catalysis, see: b) E. Arceo, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 5384; *Angew. Chem. Int. Ed.* **2012**, *51*, 5290; c) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709.

[10] For a discussion on the dynamic equilibria participating in trienamine formation and reactivity, see Ref. [9a].

[11] For other reported examples of Diels–Alder reactions under trienamine activation, see: using linear conjugated dienals: a) C. Ma, Z.-J. Jia, J.-X. Liu, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Angew. Chem.* **2013**, *125*, 982; *Angew. Chem. Int. Ed.* **2013**, *52*, 948; b) S.-J. Zhang, J. Zhang, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Org. Lett.* **2013**, *15*, 968; c) H. Jiang, D. Cruz, Y. Li, V. H. Lauridsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 5200; d) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem.* **2011**, *123*, 8797; *Angew. Chem. Int. Ed.* **2011**, *50*, 8638; e) H. Jiang, B. Gschwend, L. Albrecht, S. G. Hansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 9032; using enals with the indole-2,3-quinodimethane moiety: f) Y.-K. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212; g) Y. Liu, M. Nappi, E. C. Escudero-Adan, P. Melchiorre, *Org. Lett.* **2012**, *14*, 1310; using enals with the anthracene moiety h) H. Jiang, C. Rodriguez-Escrich, T. K. Johansen, R. L. Davis, K. A. Jørgensen, *Angew. Chem.* **2012**, *124*, 10417; *Angew. Chem. Int. Ed.* **2012**, *51*, 10271; i) C. Rodríguez-Escrich, R. L. Davis, H. Jiang, J. Stiller, T. K. Johansen, K. A. Jørgensen, *Chem. Eur. J. Chem. Eur J* **2013**, *19*, 2932.

[12] For a previous example of a Diels–Alder reaction with nitroalkenes under trienamine activation see Ref. [11d].

[13] Other conditions and catalysts were also tested, but, in all cases, unreactive starting materials were recovered.

[14] CCDC 971642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] During the submission process of this manuscript, a paper detailing the use of unconjugated dienones as active substrates in trienamine catalysis appeared; the report contained one example of a hetero Diels–Alder reaction under inverse electron demand: X. Feng, Z. Zhou, C. Ma, X. Yin, R. Li, L. Dong, Y.-C. Chen *Angew. Chem.* **2013**, *125, 14423 – 14426; Angew. Chem. Int. Ed.* **2013**, 52, 14173; *Angew. Chem. Int. Ed.* **2013**, *52*, 14173.

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RESEARCH ARTICLE

ORGANIC CHEMISTRY

Strain-release amination

Ryan Gianatassio,[1]* Justin M. Lopchuk,[1]* Jie Wang,[1] Chung-Mao Pan,[1] Lara R. Malins,[1] Liher Prieto,[1] Thomas A. Brandt,[2] Michael R. Collins,[3] Gary M. Gallego,[3] Neal W. Sach,[3] Jillian E. Spangler,[3] Huichin Zhu,[3] Jinjiang Zhu,[3] Phil S. Baran[1]†

To optimize drug candidates, modern medicinal chemists are increasingly turning to an unconventional structural motif: small, strained ring systems. However, the difficulty of introducing substituents such as bicyclo[1.1.1]pentanes, azetidines, or cyclobutanes often outweighs the challenge of synthesizing the parent scaffold itself. Thus, there is an urgent need for general methods to rapidly and directly append such groups onto core scaffolds. Here we report a general strategy to harness the embedded potential energy of effectively spring-loaded C–C and C–N bonds with the most oft-encountered nucleophiles in pharmaceutical chemistry, amines. Strain-release amination can diversify a range of substrates with a multitude of desirable bioisosteres at both the early and late stages of a synthesis. The technique has also been applied to peptide labeling and bioconjugation.

Systematic structural tuning of drug candidates, or leads, is an essential feature of medicinal chemistry research. Exchanging substituents that exhibit similar yet distinct properties in biological environments, termed "bioisosteres," can address a myriad of structural liabilities, circumventing issues such as unwanted metabolic clearance. Such structures also serve to combat the continued challenge of narrowing intellectual property space (*1*). These motifs can be rather unusual in that they are often not found in natural products: Fluoroalkyl groups (*2*, *3*) and strained ring systems that include small spirocycles and bicycles are examples (*4*). Interest in the latter area was fueled by an ongoing program at Pfizer (*5*), where difficulties in the synthesis of bicyclo[1.1.1]pentan-1-amine (**2**, Fig. 1A) led to the abandonment of a lead oncology clinical candidate (*6*). Developments in the synthesis of this strained motif date back to 1970 with Wiberg's classic synthesis of **2** from bicyclo[1.1.1]pentane in four steps via the intermediacy of bicyclo[1.1.1]pentan-1-carboxylic acid (see fig. S1) (*7*). Although this pioneering work allowed synthetic access to **2** and subsequent studies pointed to the counterintuitive stability of **A**, many improvements were carried out over the ensuing 46 years (*8*–*10*). All of these reports required ≥3 steps to form amine **2** because of the need for multiple functional group interconversions, rendering Pfizer's current in-house approach unsustainable (*10*). More globally, conventional preparations of substituted bicyclo[1.1.1]pentan-1-amine **1** have required the synthesis of the parent amine **2**, followed by amide formation (*11*) or substitution chemistry (*12*), limiting the retrosynthetic analysis of lead compounds such as **3** (*13*). The goal of this work was to solve both of these issues by (i) the invention of a process-friendly synthesis of amine **2**; and (ii) development of a route to **1** that does not even require the intermediacy of **2**, bypassing conventional retrosynthetic logic. Our strategy to address these challenges was to embrace the innate reactivity of the most strained C–C bond present in propellane **A** (~60 kcal/mol are stored in this bond) (*14*) by engaging it directly with an amine. This concept was then extended to other systems containing "spring-loaded" bonds (*15*, *16*) as a general tool to append small, cyclic bioisoteric motifs (**4** → **5**–**7**, Fig. 1B). We describe the preparation and use of convenient "strain-release reagents" (such as **A** to **C**) to expand chemical space for drug discovery: Specifically, the introduction of motifs such as bicyclo[1.1.1.]pentanes, azetidines, and cyclobutanes is delineated. The exquisite chemoselectivity of this approach has also been established, and initial applications to the areas of peptide labeling and bioconjugation are reported (see below). This work lays a foundation for the synthesis of new chemical entities, probe molecules, and clicklike

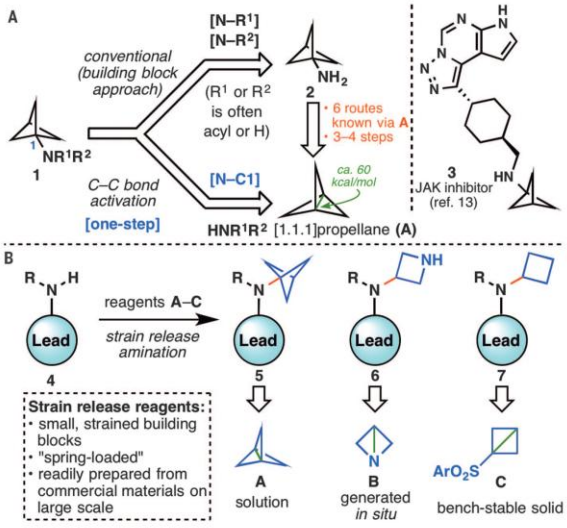


Fig. 1. Synthetic methods for incorporating small, strained ring systems. (**A**) Revisiting the retrosynthetic disconnection of an important scaffold in medicinal chemistry, bicyclo[1.1.1]pentan-1-amine. (**B**) Strain-release amination: "any-stage" functionalization of lead compounds in drug discovery.

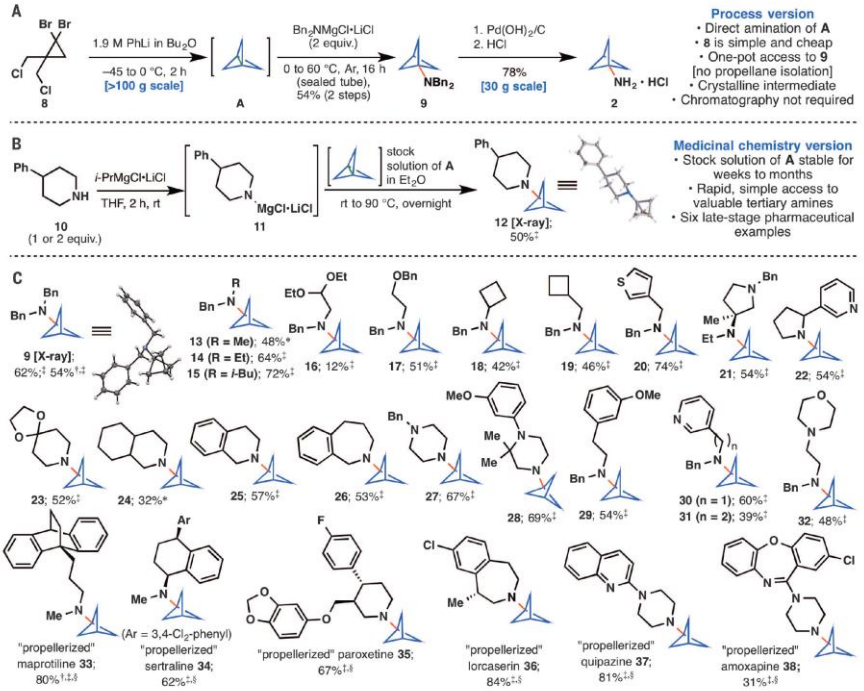
[1]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. [2]Chemical Research and Development, Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06340, USA. [3]Department of Chemistry, La Jolla Laboratories, Pfizer Inc., 10770 Science Center Drive, San Diego, CA 92121, USA.
*These authors contributed equally to this work.
†Corresponding author. E-mail: pbaran@scripps.edu

connections that rely on the native activation of strained C–C bonds.

Application of propellane strain-release amination

As mentioned above, efforts in this area were initiated on account of the practical difficulties encountered at Pfizer in procuring large quantities of bicyclo[1.1.1]pentan-1-amine **2** (Fig. 2A). The tendency of propellane **A** to react with strong nucleophiles such as *t*-BuLi and aryl Grignard reagents inspired our approach (*17*, *18*). Extensive exploration (see table S1) identified Davies-type amine nucleophiles (Bn_2N-Li) (*19*) as a good starting point, furnishing **9** in ~20% yield. The key breakthrough was the finding that the corresponding turboamide (*20*) (Bn_2NMgCl•LiCl) led to clean formation of **9** even on a >100 g scale. The use of PhLi leads to reproducible, scalable, and clean formation of propellane **A**. The dibenzyl group was then easily removed, and the HCl salt of **2** was precipitated (30 g scale). This protocol was successfully scaled up at an outsourcing vendor and can now be used in a process setting to deliver bicyclo[1.1.1]pentan-1-amine–containing clinical candidates economically on scale.

With a reliable route to stock solutions of propellane **A** (after codistillation with Et_2O, solution is stable for weeks to months at –20°C or –78°C, respectively), the scope of this direct "propellerization" was explored (Fig. 2B). Strain-release amination of **A** using a variety of in situ–derived turbo amides delivered a wide range of tertiary amines containing the valuable bicyclo[1.1.1]pentane bioisosteric motif. Figure 2 illustrates 29 different amines varying in complexity that can be easily accessed. In cases when the reaction did not go to completion, the starting amine could be recovered (e.g., **16**, **24**, **38**). The method tolerates a variety of functional groups, including acetals (**16**), benzyl ethers (**17**), ketals (**23**), and Lewis-basic groups (**21, 22, 27, 28, 30–32, 37, 38**).



Conditions: *Amine substrate (1 equiv.); †The HCl salt of the amine starting material was used; ‡Conditions: Amine substrate (2 equiv.); §The extra equivalent of the amine starting material was recovered in *ca.* 90% yield (See SM for details); ||rt = room temperature

Fig. 2. "Propellerization" of amine-containing substrates. Isolated yields are reported. (**A**) An improved synthesis of the known bicyclo[1.1.1]pentan-1-amine. (**B**) A general "propellerization" of amines enabled by strain-release reagents. (**C**) Substrate scope of amine-containing substrates.

Late-stage incorporation of this challenging bioisostere onto six different commercial drugs (Fig. 2C, **33**-**38**) obviated otherwise laborious multistep sequences to access these analogs. The use of turbo-amides is key to enabling the "any-stage" functionalization of both simple and complex amines with **A**. We anticipate that the path to these bioisosteres will find immediate and widespread use in medicinal chemistry. Indeed, this chemistry has already been field-tested at Pfizer (for example, compounds **14, 15, 17, 19, 21,** and **30** were prepared at Pfizer for use in ongoing programs).

Introduction of azetidine via strain release

The documented use of azetidines as a tactic to both rigidify amine backbones and serve as phenyl bioisosteres inspired the evaluation of a similar approach (*1*, *20*). Like the propellane systems, access to amino-azetidines is largely limited to a building-block approach that relies on the multistep synthesis of protected azetidinones (*21*). Strain-release amination of **B** was therefore evaluated as a means to simplify the preparation of such compounds. Isolated examples of the addition of nucleophiles to **B** are known but require superstoichiometric amounts of Lewis acids and only work with dibenzyl amine, anilines, and thiols (*22*). As depicted in Fig. 3, the addition of in situ–generated turbo-amides to a solution of in situ–generated **B** leads cleanly to azetidinylated products (**42**–**59**) that are subsequently trapped with a variety of acylating agents to simplify isolation and handling (free azetidines can be generated if desired). Using this protocol, azetidines were directly appended to 18 different amines varying in complexity, including three pharmaceutical agents.

Introduction of cyclobutane via strain release

Given the variety of medicinal contexts in which cyclobutane derivatives have been enlisted (*23*), we next explored a strain-release approach for this motif. The goal was to generate a stable reagent that would enable both rapid and mild "cyclobutylation" of amines but also permit further functionalization of intermediate adducts. Bicyclobutane and its substituted derivatives, since their first preparation in 1959 (*24*), have been the subject of many synthetic studies, most of which either engaged the strained system as a nucleophile or cleaved the center bond via a transition metal–mediated process (*25*, *26*). Rather than pursuing the parent bicyclobutane (a gas at room temperature) (*27*), we appended an arylsulfonyl group as a means to both activate the strained C–C bond and render the reagent bench stable. Encouragingly, a few examples have been reported wherein benzylamine, when employed as a solvent, could be added to phenylsulfonyl-substituted bicyclobutanes at 140°C (*28*, *29*). In seeking a reagent that would allow for more mild reaction conditions and the use of the amine as a limiting reagent, we synthesized a variety of substituted phenylsulfonylated bicyclobutanes (**C2** to **C7**, Fig. 4) and evaluated them in a strain-release amination with amine **39**. Not surprisingly, aryl sulfones containing electron-withdrawing substituents were the most reactive, and the addition of LiCl further accelerated the amination. Removal of the arylsulfonyl group could be easily achieved in the same pot under mild reductive conditions (Mg, MeOH). This protocol was applied to 16 diverse amines with the use of reagent **C7**, including four commercial drugs, to append the cyclobutyl group (Fig. 4B). The reaction of **C7** is chemoselective for amines in the presence of free hydroxyl groups; **71** could be prepared from 4-hydroxypiperidine in 43% yield over three steps (see supplementary materials for details). The arylsulfonyl group could also be used as a handle to generate other useful cyclobutane building blocks containing deuterium (**77**), alkyl (**78**), fluorine (**79**), and olefin (**80**) substituents. Strain-release amination is not limited to the three ring systems described here, as illustrated in Fig. 4D, wherein cyclopentane (*30*) could be easily appended to 1,2,3,4-tetrahydroisoquinoline (**81** → **83**) and *N*-benzylpiperazine (**84** → **85**). Given these collective findings, we anticipate that a wide range of strained C–C bonds

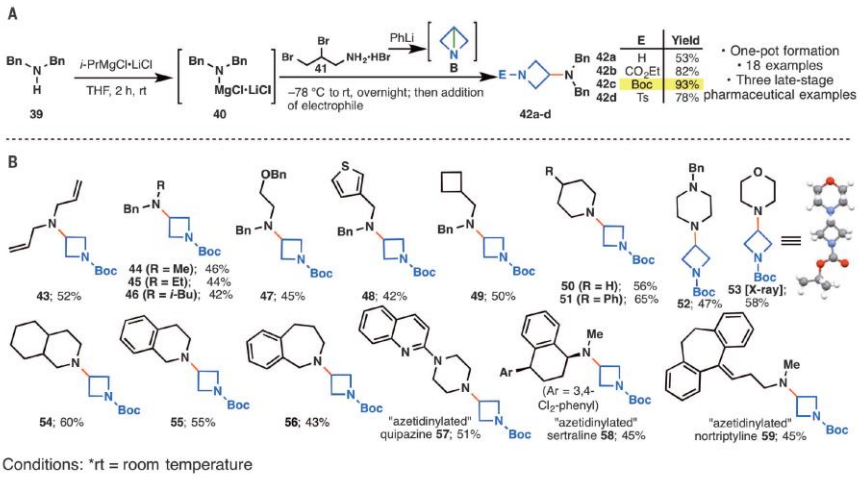
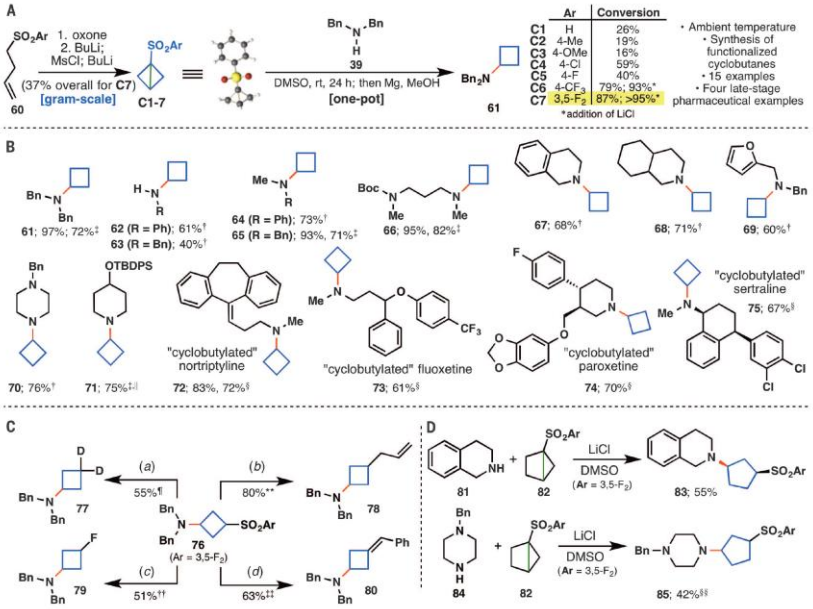


Fig. 3. "Azetidinylation" of amine-containing substrates. (**A**) A general "azetidinylation" of amines enabled by strain-release reagents. (**B**) Scope of amine-containing substrates.



*LiCl, DMSO, room temperature; †General procedure A with **C7**: one-pot, no purification of intermediates; ‡General procedure B with **C7**: intermediates isolated by column chromatography; §General procedure C with **C7**: one-pot, no purification of intermediates, reduction initiated by sonication; ‖This compound was also prepared from 4-hydroxypiperidine (43% over three steps, see SM for details); ¶(a) i) CD_3OD/CD_3ONa, ii) Na/Hg; **(b) i) LHMDS, allyl bromide, ii) Mg/MeOH; ††(c) i) LHMDS, NFSI, ii) Na/Hg; ‡‡(d) i) PhCHO, *t*-BuOK, ii) DMAP, Et_3N, Ac_2O, iii) Na/Hg; §§ Mixture of isomers (see SM for details); ‖‖rt = room temperature

Fig. 4. "Cyclobutylation" of amine-containing substrates. (**A**) A general "cyclobutylation" of amines with **C7** enabled by strain-release reagents. (**B**) Substrate scope of amine-containing substrates. (**C**) Diversification of intermediate cyclobutylsulfone **76**. (**D**) Installation of cyclopentane onto primary and secondary amines by strain-release amination.

will be amenable to amination and further functionalization.

Applications to peptide labeling

The "spring-loaded" electrophiles described herein exhibit a broad substrate scope for amination and inspired exploration of this platform in a more biologically relevant context. A model peptide (**86**, Fig. 5) was therefore prepared containing an assortment of proteinogenic nucleophilic functional groups and exposed to strain-release reagent **C7** in a mixed organic/aqueous solvent system. Remarkably, complete selectivity was observed for labeling of the cysteine thiol [91% isolated yield of **88** after 5 hours; see HPLC (high-performance liquid chromatography) trace in Fig. 5B]. In the presence of cysteine-free peptide **87**, no background reaction was observed (Fig. 5C) after 24 hours. In marked contrast, the commonly employed maleimide electrophile led to multiple adducts with **87** after only 1 hour of exposure. The complete chemoselectivity observed for cysteine shows promise for the use of strain-release functionalization in a variety of contexts, such as site-selective bioconjugation (*31*–*34*) and peptide stapling (*35*–*38*). The efficient tagging of other thiols, including glutathione and cysteine methyl ester, attests to the generality of the approach (see supplementary materials for details). Further, by modifying the electronic character of the aryl sulfone group, we could adjust the temporal parameters of the functionalization (Fig. 5D). This tunable click reaction may facilitate the strategic design of electrophilic covalent warheads for enzyme inhibition and activity-based protein profiling.

Outlook

The operational simplicity, mild reaction conditions, inexpensive preparation, and chemoselectivity exhibited by strain-release reagents **A** to **C** will facilitate their rapid adoption. More globally, an enormous variety of reagents based on this concept can be envisaged. For the task of procuring a specific target, this approach to bond formation will enable practitioners to refocus on the challenge of synthesizing a molecular scaffold rather than on the difficulty posed by small ring systems. We anticipate that this approach will also enable formation of distinct connections in the materials, polymer, and bioconjugation arenas.

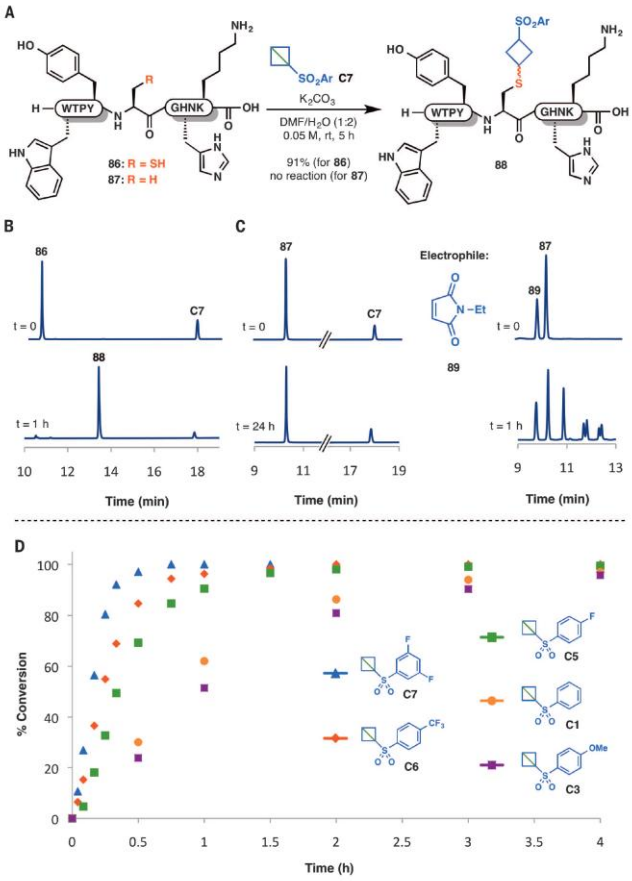


Fig. 5. Use of reagent C as a chemoselective cysteine tag for peptide and protein labeling. (**A**) Reaction of **C7** with functionalized peptides **86** and **87**. (**B**) HPLC chromatogram depicting rapid and clean conversion of **86** to cysteine-labeled product **88** after 1 hour. (**C**) Superior chemoselectivity of reagent **C7** relative to maleimide **89** in the presence of cysteine-free peptide **87**. (**D**) Reaction kinetics demonstrating the tunable functionalization of **86** with substituted arylsulfonyl bicyclobutane reagents.

REFERENCES AND NOTES

1. N. A. Meanwell, *J. Med. Chem.* **54**, 2529–2591 (2011).
2. C. Ni, M. Hu, J. Hu, *Chem. Rev.* **115**, 765–825 (2015).
3. Y. Fujiwara *et al.*, *Nature* **492**, 95–99 (2012).
4. M. V. Westphal, B. T. Wolfstädter, J. M. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem* **10**, 461–469 (2015).
5. Q. Michaudel, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **48**, 712–721 (2015).
6. A. F. Stepan *et al.*, *J. Med. Chem.* **55**, 3414–3424 (2012).
7. K. B. Wiberg, V. Z. Williams, *J. Org. Chem.* **35**, 369–373 (1970).
8. M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **100**, 169–234 (2000).
9. K. B. Wiberg, *Chem. Rev.* **89**, 975–983 (1989).
10. K. D. Bunker, N. W. Sach, Q. Huang, P. F. Richardson, *Org. Lett.* **13**, 4746–4748 (2011).
11. L. Zehnder *et al.*, *J. Med. Chem.* **54**, 3368–3385 (2011).
12. B. L. Bennett *et al.*, PCT Int. Appl. WO 2012145569 (2012).
13. K. Hayashi *et al.*, PCT Int. Appl. WO 2013024895 (2013).
14. K. B. Wiberg, F. H. Walker, *J. Am. Chem. Soc.* **104**, 5239–5240 (1982).
15. K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **25**, 312–322 (1986).
16. H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **40**, 2004–2021 (2001).
17. E. W. Della, D. K. Taylor, J. Tsanaktsidis, *Tetrahedron Lett.* **31**, 5219–5220 (1990).
18. M. Messner, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **2000**, 1137–1155 (2000).
19. S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron Asymmetry* **23**, 1111–1153 (2012).
20. C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed. Engl.* **47**, 1503–1507 (2008).
21. A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **108**, 3988–4035 (2008).
22. Y. Ikee *et al.*, *Chem. Pharm. Bull. (Tokyo)* **56**, 346–356 (2008).
23. M. L. Wrobleski *et al.*, *Bioorg. Med. Chem. Lett.* **16**, 3859–3863 (2006).
24. K. B. Wiberg, R. P. Ciula, *J. Am. Chem. Soc.* **81**, 5261–5262 (1959).
25. K. B. Wiberg, in *Advances in Alicyclic Chemistry* (Academic Press, New York, 1968), vol. 2, pp. 185–254.
26. M. A. A. Walczak, T. Krainz, P. Wipf, *Acc. Chem. Res.* **48**, 1149–1158 (2015).

27. G. M. Lampman, J. C. Aumiller, *Org. Synth.* **51**, 55–59 (1971).
28. Y. Gaoni, *Tetrahedron Lett.* **29**, 1591–1594 (1988).
29. Y. Gaoni, *Org. Prep. Proced. Int.* **27**, 185–212 (1995).
30. S. M. Jeffery, C. J. M. Stirling, *J. Chem. Soc., Perkin Trans.* **2**, 1617–1624 (1993).
31. O. Boutureira, G. J. L. Bernardes, *Chem. Rev.* **115**, 2174–2195 (2015).
32. C. S. McKay, M. G. Finn, *Chem. Biol.* **21**, 1075–1101 (2014).
33. N. Stephanopoulos, M. B. Francis, *Nat. Chem. Biol.* **7**, 876–884 (2011).
34. J. Kalia, R. T. Raines, *Curr. Org. Chem.* **14**, 138–147 (2010).
35. Y. H. Lau, P. de Andrade, Y. Wu, D. R. Spring, *Chem. Soc. Rev.* **44**, 91–102 (2015).
36. A. M. Spokoyny *et al.*, *J. Am. Chem. Soc.* **135**, 5946–5949 (2013).
37. Y. Wang, D. H.-C. Chou, *Angew. Chem. Int. Ed.* **54**, 10931–10934 (2015).
38. S. P. Brown, A. B. Smith 3rd, *J. Am. Chem. Soc.* **137**, 4034–4037 (2015).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/351/6270/241/suppl/DC1
Materials and Methods
Figs. S1 to S68
Tables S1 to S6
References (*39*–*68*)
NMR Spectra

21 October 2015; accepted 2 December 2015
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REPORTS

APPLIED OPTICS

Gain modulation by graphene plasmons in aperiodic lattice lasers

S. Chakraborty,[1]* O. P. Marshall,[1,2] T. G. Folland,[1] Y.-J. Kim,[2] A. N. Grigorenko,[2] K. S. Novoselov[2]*

Two-dimensional graphene plasmon-based technologies will enable the development of fast, compact, and inexpensive active photonic elements because, unlike plasmons in other materials, graphene plasmons can be tuned via the doping level. Such tuning is harnessed within terahertz quantum cascade lasers to reversibly alter their emission. This is achieved in two key steps: first, by exciting graphene plasmons within an aperiodic lattice laser and, second, by engineering photon lifetimes, linking graphene's Fermi energy with the round-trip gain. Modal gain and hence laser spectra are highly sensitive to the doping of an integrated, electrically controllable, graphene layer. Demonstration of the integrated graphene plasmon laser principle lays the foundation for a new generation of active, programmable plasmonic metamaterials with major implications across photonics, material sciences, and nanotechnology.

Among the many intriguing properties of graphene, its plasmonic characteristics are some of the most fascinating and potentially useful (*1*, *2*). Long-lived, tunable intrinsic graphene surface plasmons (SPs) have already been demonstrated in a number of experiments (*3*–*9*), including optical modulators (*10*, *11*), providing the potential for applications (*12*, *13*). In contrast to the noble metals that are usually used in SP devices (*13*, *14*), graphene's Fermi energy, E_F, and carrier concentration, n_s (and therefore its conductivity and SP mode properties), can be altered, for example, by electrical gating and surface doping (*3*, *15*, *16*). Consequently, the behavior of graphene SP-based structures can be modified in situ, without the need for structural device changes. In particular, graphene's optical and plasmonic properties are tunable in the terahertz (THz) spectral region (*3*, *17*), giving rise to the possibility of compact electrically controllable THz optical components (*18*). We incorporated graphene into a plasmonic THz laser microcavity to dynamically modulate round-trip modal gain values and therefore laser emission via E_F. In this way, gated graphene becomes a powerful tool with which to control the fundamental properties of a laser—a tool that is potentially extremely fast and all electrical in nature, with negligible electrical power requirements.

The interaction between light and matter can be altered by manipulating the electromagnetic density of states (DOS) using a microresonator (*19*, *20*). By incorporating a photonic lattice or plasmonic structure into a laser, one can control the frequency and amplification of resonant modes and hence manipulate the properties of lasing emission (*21*–*23*). Furthermore, by breaking the regularity of these structures it is possible to modulate the photon DOS and hence light-matter interaction at several frequencies simultaneously. This technique was used recently to develop an aperiodic distributed feedback (ADFB) cavity laser with a lattice that is in essence a computer-generated hologram (*24*, *25*). The hologram digitally encodes the Fourier transform of a desired optical filter function (multiple reflection resonances within the gain bandwidth of the laser), enabling photonic DOS manipulation at precise filter frequencies. In real space, a typical hologram lattice contains a multitude of phase shifts; the locations and sizes of scattering sites and defects are set such that via coherent backscattering the device enters a slow light regime. Transfer matrix method (TMM) calculations of the group delay transfer function (which is intrinsically linked to the photonic DOS) of an ADFB microcavity under the influence of gain reveal infinite-gain singularities [fig. S4; see (*26*) for further details]. These singularities represent the frequency and gain values at which self-oscillation occurs. The ADFB microcavity can produce coherent amplification of the cavity photons via stimulated emission processes because of the build-up of phase coherence at the singularities (*20*).

ADFB structures were realized in THz quantum cascade lasers (QCLs)—extremely long wavelength semiconductor lasers with active regions based on precisely engineered inter-subband transitions (*27*). Such ADFB THz QCLs provide an ideal proving ground for graphene-controlled gain modulation because they use SP-based waveguides (at a metal-semiconductor interface, Fig. 1A) (*28*). The first crucial step is to excite two-dimensional (2D) plasmons in an integrated, atomically thin graphene sheet to take full leverage of the computer-generated hologram principle. Hologram pixels are introduced to the QCL waveguide as plasmonic scattering sites along the longitudinal axis of the laser ridge (Fig. 1B). By depositing an electrically gateable graphene film onto these devices, our goal is to switch the THz SP at each pixel "on" or "off" by tuning n_s, thereby altering the photonic DOS and the degree to which the THz intersubband gain spectra follows the hologram response. For example, by modulating the hologram pixel scattering strength we approach the DOS singularities, resulting in a dramatic increase of light-matter interaction within the QCL gain media (*20*). Photon lifetimes (and hence modal gain values) are thereby enhanced, leading to selective enhancement of competing laser modes and a concomitant suppression of others.

A hologram with relatively weak feedback was chosen so that any subtle influence of graphene plasmons on laser emission was not hidden by

[1]School of Electrical and Electronic Engineering, University of Manchester, Manchester M13 9PL, UK. [2]School of Physics and Astronomy, University of Manchester, Manchester M13 9PL, UK.
*Corresponding author. E-mail: s.chakraborty@manchester.ac.uk (S.C.); kostya@manchester.ac.uk (K.S.N.)