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Organocatalytic Approaches to the Asymmetric Synthesis of *N*-Heterocycles:From Brønsted Acid Catalysis to Vinylogous Iminium Ion Activation

MEMORIA PRESENTADA POR-

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Abstract

The work compiled in this manuscript is focused on the use of diverse organocatalytic activation mechanisms for the asymmetric synthesis of interesting and valuable organic compounds. The use of chiral Brønsted acids as catalysts for the generation of *N*-acyl iminium ions and the employment of aminocatalysis for the activation of polyunsaturated carbonyl compounds has been studied.

The activation of dihydropyrrole derivatives as *N*-acyl iminium ions has been demonstrated, as well as the potential of *N*-monosubstituted hydrazones to act as C-nucleophiles in the enantioselective addition of hydrazones to dihydropyrroles under chiral BINOL-derived phosphoric acid catalysis. Moreover, the construction of enantioenriched proline derivatives has been performed after hydrazone moiety derivatization, showing the applicability of these compounds to behave as acyl anion equivalents.

On the other hand, the remote functionalization of $\alpha,\beta,\gamma,\delta$-unsaturated cyclic dienones has been performed under a chiral cinchona-derived primary amine catalyst. The reaction consisted in the vinylogous iminium ion activation of the polyunsaturated carbonyl compounds to undergo a 1,6-aza-Michael/1,4-Michael cascade reaction with complete regiocontrol employing 2-aminomalonates as double nucleophiles for the synthesis of relevant spirocyclic products.

Finally, and as part of a short stay carried out in the laboratories of Prof. V. K. Aggarwal in the University of Bristol, I participated in a project related to the use of the *in situ* lithiation-borylation methodology for the synthesis of enantioenriched hindered tertiary boronic esters, where the use of neopentyl boronic esters was proved essential to achieve high enantioselectivities with the most hindered substrates.

Resumen

El trabajo de investigación recogido en la presente memoria se centra en el uso de diferentes mecanismos de activación organocatalítica para la síntesis asimétrica de compuestos orgánicos de interés sintético. Se ha estudiado el empleo de catalizadores de ácido de Brønsted para la síntesis de iones *N*-acil iminio y también, el uso de aminocatalizadores para la activación de compuestos carbonílicos poliinsaturados.

Se ha demostrado por un lado la capacidad de activar derivados de dihidropirrol como iones de *N*-acil iminio, así como el potencial de las hidrazonas *N*-monosustituidas para actuar como C-nucleófilas, llevando a cabo la adición enantioselectiva de hidrazonas a dihidropirroles haciendo uso de la catálisis de ácidos fosfóricos derivados del BINOL. Además, se ha realizado la síntesis enantioselectiva de derivados de prolina mediante la derivatización del producto de hidrazona, demostrando la aplicabilidad de estos compuestos como equivalentes de aniones de acilo.

Por otro lado, se ha realizado la funcionalización remota de dienonas cíclicas α,β,γ,δ-insaturadas utilizando los catalizadores de amina primaria derivados de la cinchona. La reacción consiste en la activación ión iminio viníloga de compuestos carbonílicos poliinsaturados para llevar a cabo la reacción en cascada 1,6-aza-Michael/1,4-Michael con completo regiocontrol empleando 2-aminomalonatos como dobles nucleófilos para la síntesis de productos espirocíclicos relevantes.

Finalmente, y como parte de una breve estancia llevada a cabo en los laboratorios del Prof. V. K. Aggarwal en la Universidad de Brístol, tomé parte en la elaboración del proyecto relacionado con el uso de la metodología de litiación-borilación *in situ* para la síntesis de ésteres borónicos terciarios enantiopuros de gran impedimento estérico, donde se demostró que el uso de ésteres borónicos menos impedidos eran esenciales para conseguir alto grado de enantioselectividad con los sustratos estéricamente más impedidos.

Laburpena

Doktorego tesi hau aktibazio organokatalitikorako mekanismo desberdinen erabileran oinarritzen da interes sintetikoa duten konposatu organikoen sintesi asimetrikoa egiteko. *N*-azil iminio ioiak sortzeko, Brønsted azido katalizatzaileen erabilera ikertu da, halaber, konposatu karboniliko asegabetuen aktibaziorako aminokatalizatzaileen erabilera ere aztertu da.

Alde batetik, dihidropirrol deribatuak *N*-azil iminio ioi bezala aktibatzeko gaitasuna frogatu da, eta beste alde batetik hidrazona *N*-monoordezkatuak C-nukleofilo moduan jarduteko potentziala ere erakutsi da. Horretarako, hidrazonen eta dihidropirrolen adizio enantioselektiboa burutu da BINOL egitura duten azido fosforiko katalizatzaileak erabiliz. Gainera, prolina deribatuen sintesi enantioselektiboa gauzatu da, hidrazonen deribatizazioa burutuz, konposatu hauek azil anioi bezala duten aplikagarritasuna frogatuz.

Bestaldetik, dienona zikliko α,β,γ,δ-asegabetuen β,γ-funtzionalizazioa burutu da, *cinchona*tik lortutako amina primarioak katalizatzaile bezala erabiliz. Erreakzioa asegabetasun ugariko konposatu karbonilikoen aktibazioan oinarritzen da, iminio ioi binilogoa eratuz, 1,6-aza-Michael/1,4-Michael kaskada erreakzioa burutzeko erregioselektibitate osoa lortuz, 2-aminomalonatoak erabiliz nukleofilo bikoitz moduan jarduteko eta produktu espirozikliko interesgarriak sintetizatzeko.

Bukatzeko, Bristoleko Unibertsitatean egindako epe laburreko egonaldian, Dr. V. K. Aggarwal irakaslearenpean, *in situ*-zko litiazio-borilazio metodologian oinarritzen den proiektu batean parte hartu nuen, eragozpen handiko ester boroniko tertziario enantiopuruak sintetizatzeko, non neopentil ester boronikoen erabilera ezinbestekoa dela frogatu den.

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1

Introduction

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2. Organocatalytic Activation Mechanisms

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   2.2. Non-Covalent Catalysis: Brønsted acid Catalysis

3. Precedents of the Group

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1. ASYMMETRIC ORGANOCATALYSIS

One of the challenges for synthetic organic chemists is the enantioselective synthesis of chiral molecules due to the importance that these compounds have received in the pharmaceutical and agrochemical industries. Nowadays, asymmetric catalysis remains as the best option to access enantioenriched structures, because of both cost and environmental reasons. Even though metal catalysis[1] and enzymatic methods[2] have dominated this field for many years, asymmetric organocatalysis has emerged as a valuable alternative to catalyze chemical transformations in a stereoselective way.[3]

The term "organocatalysis" was firstly used by MacMillan in 2000, opening a new field of research within asymmetric catalysis.[4] However, the pioneering work employing small chiral organic molecules in catalytic amounts can be attributed to Bredig and Fiske in 1912. They described the first organocatalytic enantioselective C-C bond formation reaction for the synthesis of mandelonitrile by addition of HCN to benzaldehyde in the presence of quinine or quinidine observing some degree of enantioinduction (Scheme 1.1).[5]
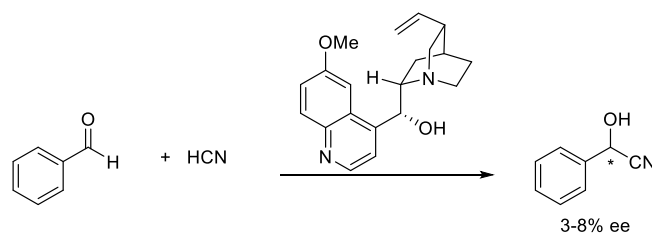
Scheme 1.1

1 Metal catalysis: a) Temkin, O. N. *Homogeneous Catalysis with Metal Complexes*; Temkin, O. N., Ed.; Wiley: Chichester, 2012; b) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, 2nd ed.; c) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; 2nd ed.

2 Enzymatic catalysis: a) *Enzyme Catalysis in Organic Chemistry*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2012; 3rd ed.; b) Muhammad, M.; Noriho, K.; Masahiro, G. *Org. Biomol. Chem.* **2010**, *8*, 2887; c) Junhua, T.; Zhao, L.; Ran, N. *Org. Process Res. Dev.* **2007**, *11*, 259; d) *Enzymes in Synthetic Organic Chemistry*; Wong, C. H., Whitesides, G. M., Eds.; Elsevier: Oxford, 1994; Vol. 12, 1st ed.

3 For selected reviews on organocatalysis, see: a) *Stereoselective Organocatalysis. Bond Formation and Activation Modes*; Rios Torres, R., Ed.; Wiley: New Jersey, 2013; b) Marson, C. M. *Chem. Rev.* **2012**, *41*, 7712; c) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618; d) *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; Vicario, J. L., Badía, D., Carrillo, L., Reyes, E., Eds.; RSC Publishing: Cambridge, 2010; e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; f) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413; g) *Enantioslective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; h) Yang, J. W.; List, B. *Science* **2006**, 1584; i) *Asymmetric Organocatalysis, From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A.; Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005.

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

5 Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7.

After this work, other relevant organocatalytic asymmetric reactions were reported in the following years obtaining higher enantioselectivities. This is the case of the enantioselective addition of methanol to methyl phenyl ketene catalyzed by a quinine derivative, described by Pracejus[6] in 1960 or the Hajos-Parrish-Eder-Sauer-Wiechert reaction that made use of L-proline as catalyst in an intramolecular aldol reaction.[7] Later on, between 1980 and the late 1990s, further breakthroughs were reported such as those reactions employing quaternary ammonium salts as catalysts based on phase transfer catalysis concept,[8] or the use of chiral thioureas by Inoue[9] or Jacobsen[10] in the hydrocyanation of aldehydes and imines.

Nevertheless, the renaissance of this field was officially set in 2000 when List, Lerner, and Barbas III published the L-proline-catalyzed enantioselective intermolecular aldol reaction providing evidence of the participation of enamine intermediates (Scheme 1.2a)[11], together with the publication of the first highly enantioselective organocatalytic Diels-Alder reaction catalyzed by a chiral imidazolidinone salt proceeding under iminium ion activation reported by MacMillan (Scheme 1.2b).[4]
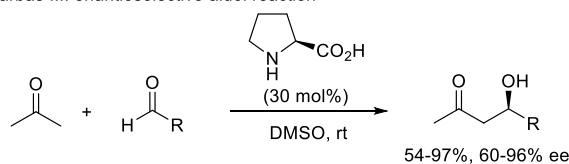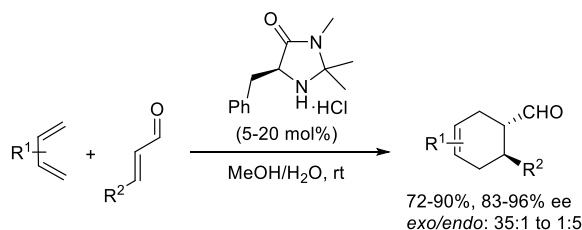
Scheme 1.2. Development of organocatalysis by List, Lerner, Barbas III and MacMillan.

[6] Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
[7] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; b) Hajos, Z. G.; Parrish, D. R. *German Patent* DE 2102623, **1971**; c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496; d) Eder, U.; Sauer, G.; Wiechert, R. *German Patent* DE 2014757, **1971**.
[8] a) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710. b) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
[9] Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229.
[10] a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. b) Sigman, M. N.; Pederson, R. L.; Wang, Y. F.; Wong, C. H. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
[11] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

After these two remarkable works, subsequent publications have been reported in the field of aminocatalysis and the development and evolution of other activation mechanisms applied to multiple organic reactions happened at a fast rate. Today, asymmetric organocatalysis is considered, together with metal and enzymatic catalysis, one of the most important strategies for the enantioselective synthesis of chiral compounds at least on an academic level.[12] The advantages over transition metal catalysis or biocatalysis relays on the fact that the catalysts are usually more stable, less toxic, relatively inexpensive and easier to prepare and to handle. Organocatalytic reactions require milder reaction conditions, taking into account that the reactions can be typically carried out in the presence of oxygen and atmospheric moisture. In addition, this methodology does not leave metal traces on the final purified product, becoming a very attractive tool for the preparation of compounds for which metal contamination is strictly forbidden, such as active pharmaceutical ingredients.

However, there are some disadvantages associated to asymmetric organocatalysis that are still unsolved. Normally, long reaction times are needed and the amount of catalyst necessary to run the reaction is often much higher to that employed in metal catalysis, increasing the costs and consequently limiting the applications in industrial production.[13] Another important issue is the lack of a universal catalyst. Usually, the catalyst is chosen considering the functionalities present in the substrates and the required reaction conditions. Thus it is necessary to test every catalyst or to create new ones to obtain good results for applying the reaction to substrates of different nature. Designing a catalyst that could be useful for a wide range of reactions would be of interest for natural product synthesis or in medicinal chemistry, in order to develop its usefulness for the pharmaceutical industry. Organocatalysis applied to heterogeneous catalysis and flow-chemistry is gathering huge importance within industry, the application of these concepts being still in its infancy.[14]

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[12] For selected reviews on asymmetric organocatalysis activation modes: a) *Asymmetric Organocatalysis 1;* List, B., Ed.; Thieme Verlagsgruppe: Stuttgart, 2012; b) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406; c) Buckley, B. R.; Farah, M. M. *Annu. Rep. Prog. Chem.* **2011**, *107*, 102; d) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.

[13] a) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825; b) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH:Weinheim, 2004.

[14] Shaikh, I. R. *J. Catal.* **2014**, 402860.

2. ORGANOCATALYTIC ACTIVATION MECHANISMS

The classification of asymmetric organocatalysts is often made according to the type of interaction between the catalyst and the substrate in the transition state. In this sense, organocatalytic activation manifolds are classified as either, **covalent catalysis**, or **non-covalent catalysis** depending on the formation of covalent or other weaker bonds (hydrogen-bonding, ion pair, etc.) between the catalyst and the substrate. The most studied activation mode among covalent organocatalysis is *aminocatalysis*,[15] which consists in the use of primary or secondary amines as catalysts that interact with the substrate (aldehyde or ketone) through the formation of an azomethine intermediate. *N-heterocyclic carbenes* (NHCs) constitute another important class of catalysts in this group that interact with aldehydes to form a nucleophilic enaminol intermediate (Breslow intermediate) after condensation.[16] For non-covalent catalysis, weaker interactions are established between the catalyst and the substrate and the most relevant activation within this category is the one that activates the substrate by *hydrogen bonding* interactions.[17] In this group we can find the use of ureas and thioureas,[18] squaramides,[19] guanidines[20] or phosphoric acids.[21] As efficient promoters of reactions in which the activation of an electrophilic substrate is achieved through interaction with those molecules forming a network of H-bonds. In addition, different methodologies that activate the substrate through non-covalent interactions are *ion pair catalysis*[22], being *phase*

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[15] For some recent reviews on aminocatalysis: a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632; b) Bernal, P.; Monge, D. *All Res. J. Chem.* **2010**, *1*, 4; c) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.; d) Marigo, M.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138; e) List, B. *Chem. Commun.* **2006**, 819.

[16] For some reviews on *N*-heterocyclic carbene catalysis, see: a) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686; b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511; c) Grossman, A.; Enders, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 2; d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

[17] For recent reviews on hydrogen-bonding catalysis, see: a) Bernardi, L.; Fochi, M.; Franchini, M. C.; Ricci, A. *Org. Biomol. Chem.* **2012**, *10*, 2911; b) Siau, W. Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298; c) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009; d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520; f) Pihko, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062.

[18] Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

[19] Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

[20] Selig, P. *Synthesis* **2013**, *45*, 703.

[21] For references on this topic see Chapter 2.

[22] a) Shirakawa, S.; Maruoka, K.; *Angew. Chem., Int. Ed.* **2013**, *52*, 4312; b) Jew. S.; Park, H. *Chem. Commun.* **2009**, 7090; c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

transfer catalysis (PTC)[23] the most studied case. Chiral *Brønsted base catalysis*[24] activating pro-nucleophiles by deprotonation is also another highly active field.

Figure 1.1 shows some representative examples of organic catalysts employed under different activation mechanisms.

A) Covalent catalysis

Aminocatalysis: enamine, iminium, dienamine, trienamine, SOMO

N-Heterocyclic carbene catalysis

Others: tertiary amines, phosphines, ylides, etc.

B) Non-covalent catalysis

Hydrogen bond catalysis

Phase transfer catalysis

Chiral Brønsted Base catalysis
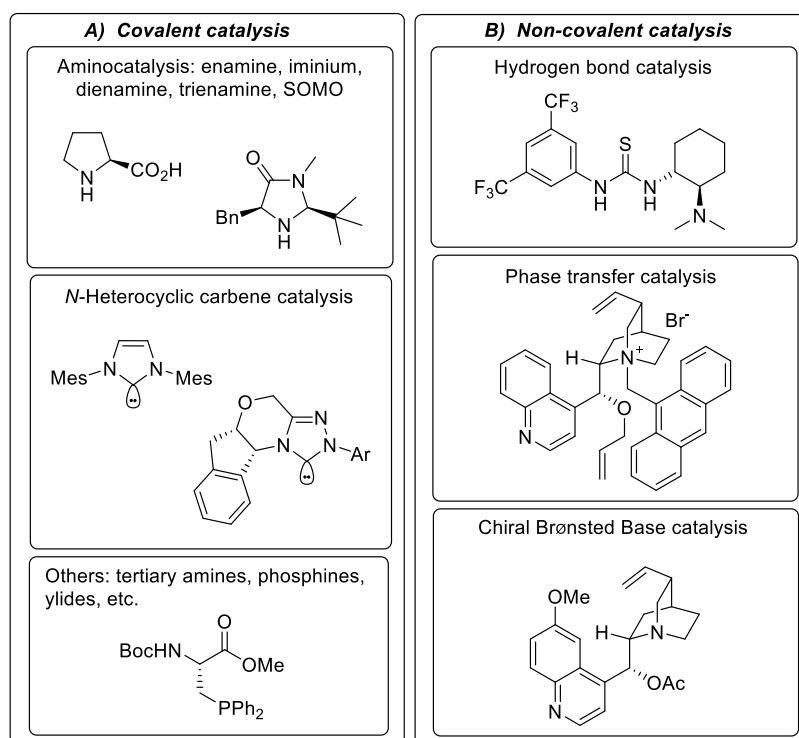
Figure 1.1

2.1. Covalent Catalysis: Aminocatalysis

As mentioned before, since 2000 continuous effort has been directed towards asymmetric organocatalytic reactions. The majority of these transformations are chiral amine-based reactions, named aminocatalysis. This activation mode uses chiral secondary or primary amines for the formation of different azomethine intermediates through condensation with

[23] For some 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. S.; Park, H-G. *Chem. Commun.* **2009**, 7090; d) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679; e) *Asymmetric Phase Transfer Catalysis*; Maruoka, K., Ed.; Wiley-VCH: Weinheim, 2008; f) Hasimoto. T.; Maruoka, K. *Chem. Rev.* **2007,** *107*, 5656.

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

carbonyl compounds. The condensation of primary or secondary amines with enolizable carbonyl compounds leads to enamine intermediates able to interact with electrophiles at α-position (Scheme 1.3-left), while the condensation with α,β-unsaturated carbonyl compounds renders iminium ion intermediates capable of reacting with nucleophiles at β-position (Scheme 1.3-right).
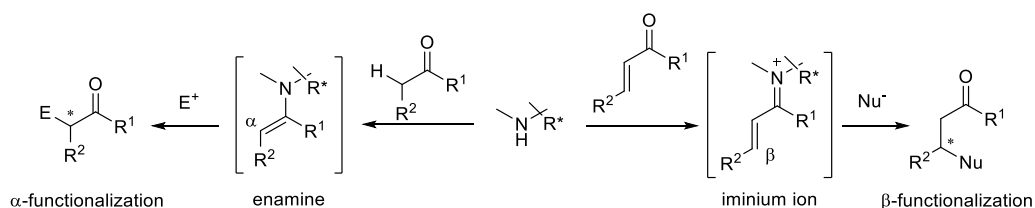
Scheme 1.3

These two strategies were applied successfully and simultaneously by List, Lerner and Barbas III in the already mentioned enantioselective intermolecular aldol reaction catalyzed by L-proline based on enamine activation,[11] and by MacMillan in the organocatalytic Diels-Alder reaction catalyzed by chiral imidazolidinone salts based on iminium ion activation.[4] After these two discoveries, a plethora of organocatalytic transformations have been developed using these strategies, that have become powerful methodologies for the generation of enantioenriched organic compounds.

In this context, enamine catalysis[25] encompasses multiple organic reactions for the α-functionalization of carbonyl compounds. These transformations are believed to follow a common mechanistic pathway (Scheme 1.4). Firstly, an iminium ion is formed activating the carbonyl compound by lowering the LUMO energy and thus increasing the acidity of the proton at the α-position. The tautomerization of these species leads to an enamine intermediate, with a higher HOMO energy than the corresponding aldehyde or ketone,

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[25] For some reviews in enamine catalysis, see: a) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491; b) Kano, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 907; c) Mukherjee, S. Enamine Catalysis of α-Functionalizations and Alkylations. In *Asymmetric Organocatalysis I: Lewis Base and Acid Catalysts*; List, B., Ed.; Thieme Verlagsgruppe: Stuttgart, 2012; p. 217-270; d) Ríos, R.; Moyano, A. Enamines in Catalytic Enantioselective Conjugate Additions. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, 2010; p. 191-218; e) Pikho, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem.* **2010**, *291*, 29; f) Sulzer,-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3132; g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

facilitating the reaction with an electrophile *via* nucleophilic substitution or nucleophilic addition. Finally, after a hydrolysis step of the resulting iminium ion, the α-functionalized product is released and the catalyst is regenerated to restart another catalytic cycle.
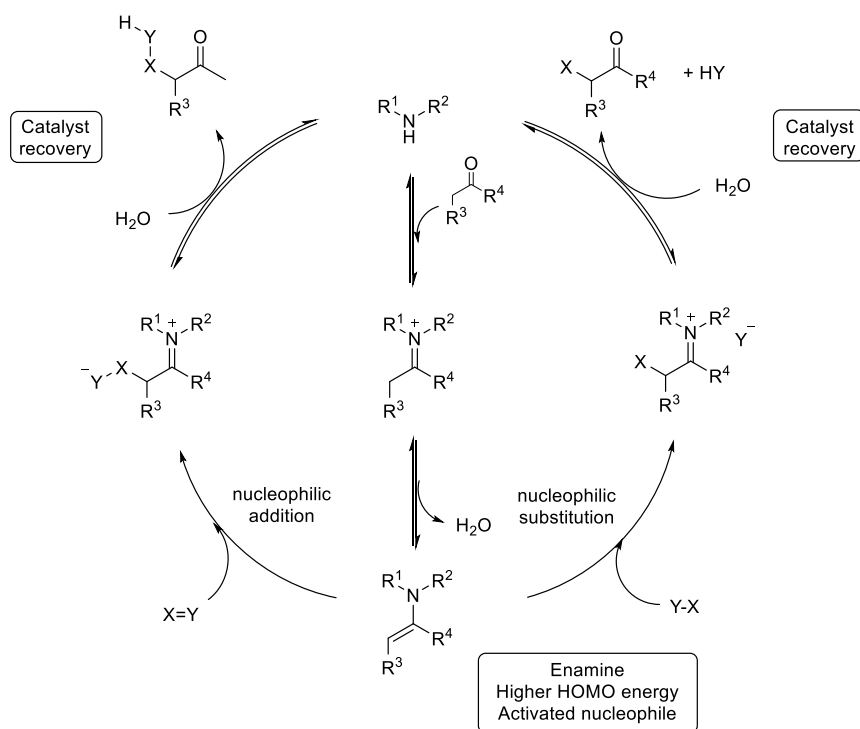
Scheme 1.4

In the case of iminium ion catalysis,[26] the numerous innovative examples involving this strategy are based on the LUMO lowering effect associated to the formation of an iminium ion between a α,β-unsaturated carbonyl compound and the amine catalyst, thus making it more electrophilic than the previous enal or enone towards the nucleophilic attack at the β-position. Hydrolysis of the β-functionalized enamine intermediate will release the desired product and

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[26] For some reviews in iminium catalysis, see: a) MacMillan, D. W. C.; Watson, A. J. B. Iminium Catalysis. In *Science of Synthesis Reference Library: Asymmetric Organocatalysis*; List, B., Ed.; Thieme Verlagsgruppe: Stuttgart, 2012; p. 309-401; b) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. Iminium Activation. In *Handbook of Catalytic Asymmetric Conjugate Reactions: Michael Reactions, Organocatalysis and more;* Córdova, A., Ed.; Wiley-VCH, Weinheim, 2010; p. 219-294; c) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759; d) Erkkilae, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416; e) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

the catalyst ready to restart another catalytic cycle. Normally, a Brønsted acid is also incorporated as a co-catalyst to accelerate the formation of the iminium ion salt (Scheme 1.5).
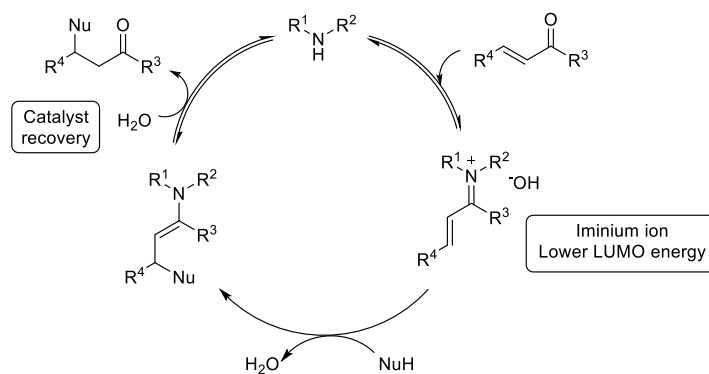
Scheme 1.5

The origin of stereoinduction in these two methods is based on the chiral information present on the amine catalyst.[25f,27] Typically, a sterically bulky substituent is used to differentiate the two stereogenic faces of the enamine, hindering the approach of the external reagent by one of the two faces. In addition, this substituent has to control the geometry of the enamine intermediate (*E* or *Z* stereoisomers and anti or syn conformers) and of the iminium ion intermediate (*Z,E* stereoisomer or *E,E* stereoisomer) to favour one of the two isomers. In enamine catalysis, the *E* enamine will be favoured due to steric interaction between the α-substituents with the catalyst in the *Z* isomer, and in the case of iminium ion catalysis, the *E,E* isomer will form preferentially, because of the destabilizing interactions between the catalyst and the α-substituent happening in the *Z,E* conformation (Scheme 1.6).
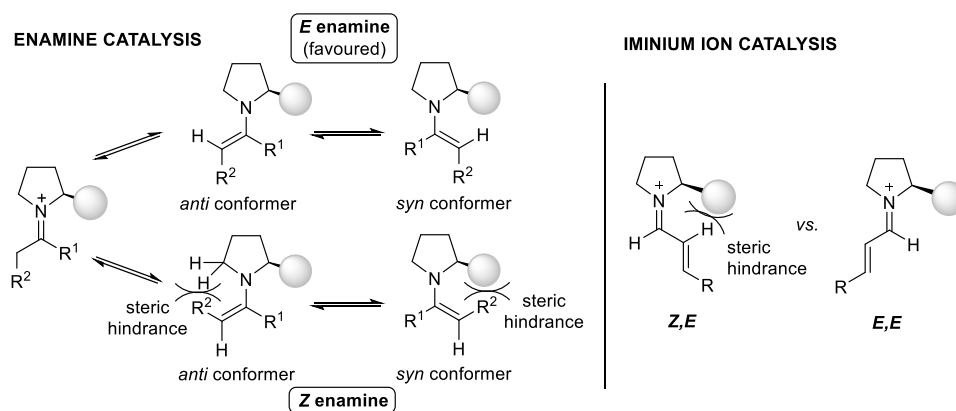
Scheme 1.6

In a simultaneous manner, the approach of the electrophile/nucleophile has to be efficiently controlled from one side in order to obtain enantioenriched compounds. As mentioned, this discrimination could be directed through steric shielding, promoting the addition from the less hindered face, or in the case of a bifunctional catalyst, by a sterodirecting group that will direct the electrophile/nucleophile trajectory by secondary interactions from the face where this element is placed (Scheme 1.7).
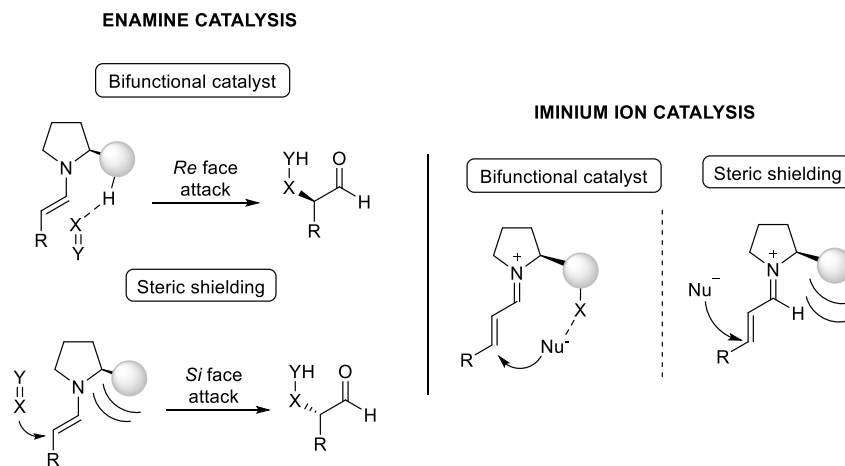
Scheme 1.7

Additionally, these strategies have been combined with the concept of vinylogy, introducing new aminocatalytic strategies for the functionalization of carbonyl compounds at more remote positions. In the case of enamine catalysis, this strategy consists in the implementation of the HOMO-raising effect associated to enamine catalysis to α,β-unsaturated

carbonyl compounds (dienaminocatalysis) and to polyconjugated carbonyl compounds (trienaminocatalysis and tetraenaminocatalysis), allowing the functionalization of carbonyl compounds at γ, ε and ζ positions in enantioenriched form. In iminium ion catalysis, the δ-functionalization of polyunsaturated aldehydes and ketones in a stereoselective manner has been possible to achieve by applying the LUMO-lowering effect through the conjugated system, giving rise to the vinylogous iminium ion activation concept. These strategies will be explained more deeply in Chapter 3.

2.2. Non-Covalent Catalysis: Brønsted acid Catalysis

Brønsted acid catalysis has emerged as a powerful strategy for the development of new activation mechanisms for catalytic asymmetric reactions.[28] One of the most explored activation methods within Brønsted acid catalysis is the one that activates the substrate by forming hydrogen-bonds. These catalysts have the ability to remove electron density from the substrate, lowering the energy of the LUMO of the electrophile *via* protonation, which activates the substrate towards the reaction with nucleophiles.[17] It is of vital importance to generate an efficient conformationally rigid and well defined catalyst-substrate complex that would permit effective stereocontrol.

The first enantioselective reaction catalyzed by a chiral Brønsted acid based on hydrogen-bonding interactions was developed by Jacobsen *et al*. This involved the use of a chiral urea shown in Scheme 1.8 as catalyst, activating an imine substrate towards the strecker reaction affording the corresponding amino nitrile products in high yields and enantioselectivities (Scheme 1.8).[29]

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[28] a) *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*; Maruoka, K., Ed.; Georg Thieme Verlag: Stuttgart, 2012; b) Knowles, R. R.; Jacobsen, E. N. *PNAS*, **2010**, *107*, 20678; c) Akiyama, T. Acid Catalysis. In *Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008; p. 62-107; d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

[29] a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
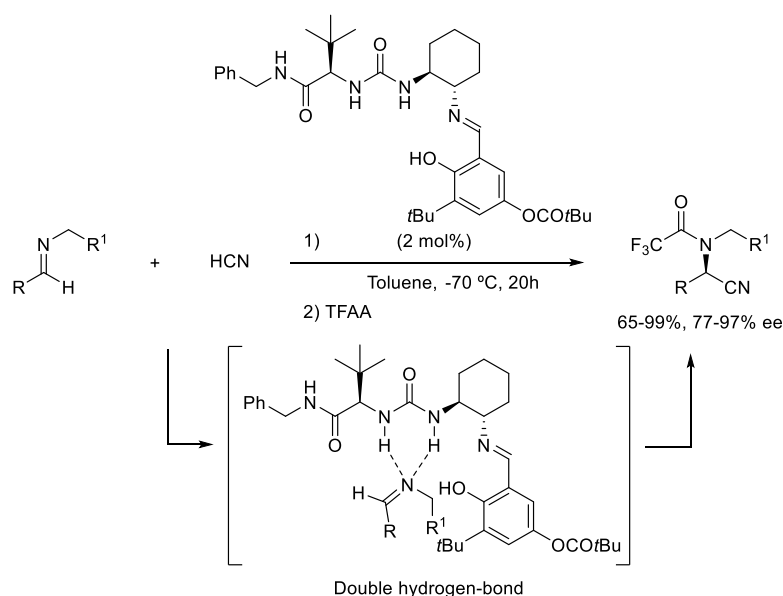
Scheme 1.8

In the mechanistic analysis carried out for the reaction, based on NMR, kinetic and computational data indicated that the imine was being activated by the catalyst through a dual hydrogen-bond interaction involving the two protons of the urea moiety and the nitrogen on the imine scaffold.[30]

This type of catalysts have become very efficient and broadly used in several asymmetric transformations.[12d,17] After this initial breakthrough, numerous catalysts with different structural and functional frameworks have been discovered to promote different organic reactions enantioselectively. In this context, the development of bifunctional catalysts containing additional coordination sites that are therefore able to activate simultaneously the electrophile and the nucleophile of the reaction arose as a powerful tool among hydrogen-bonding catalysts.

A good example of this concept is shown in Scheme 1.9. In 2003, Takemoto and co-workers developed a chiral bifunctional thiourea catalyst that also incorporates a tertiary amine as additional element in the chiral scaffold as highly efficient catalyst for the enantioselective Michael reaction between malonates and nitroalkenes. Key aspect for the

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[30] Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

success of the reaction was the bifunctional character of the catalyst, that made use of the thiourea scaffold for activating the nitroolefin by hydrogen-bonding and the tertiary amine as Brønsted base for the activation of the nucleophile (Scheme 1.9).[31] Due to the sulphur atom, the NH acidity of thioureas is higher than the parent ureas and exhibit a poorer hydrogen-bond acceptor ability avoiding self-association of the catalyst. Thus, the use of thioureas as catalysts has shown a more efficient outcome to perform asymmetric reactions. The modularity of most thiourea catalysts is based on the same principle. The substitution of one of the nitrogen atoms modulates the acidity of the NH hydrogens, usually employing electron-withdrawing groups at the aromatic ring. On the other hand, a chiral substituent is placed in the other nitrogen atom for asymmetric induction, and frequently an sterodirecting element is introduced at the chiral scaffold, such as a tertiary amine to activate the nucleophile and directing the stereochemical outcome of the reaction (Scheme 1.9).
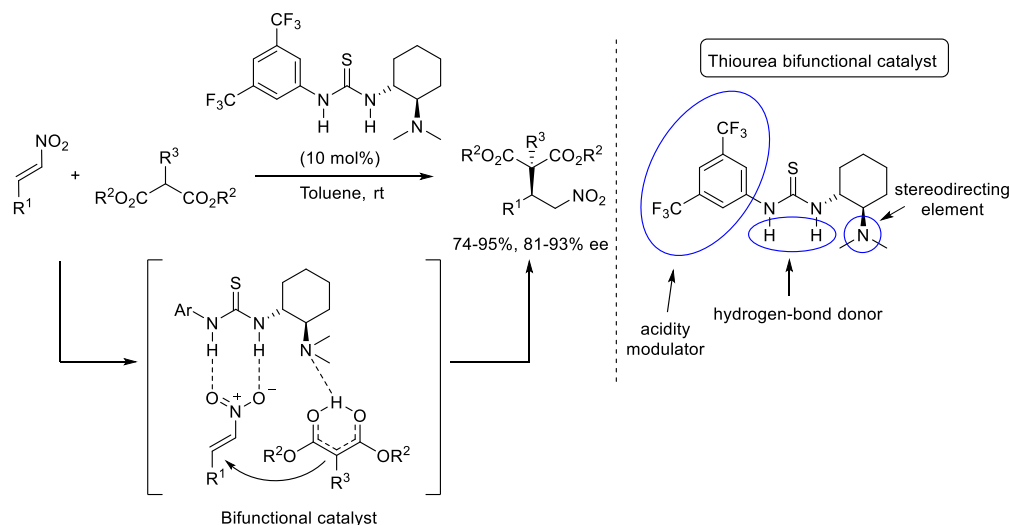
Scheme 1.9

Rawal and colleagues introduced a new type of highly efficient bifunctional catalyst that incorporates the squaramide moiety as the hydrogen-bond donor element and that has proved to catalyze a wide number of asymmetric transformations with success.[32] The reaction between diphenylphosphite and nitroalkenes is a representative example on the use of this type

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[31] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 15672.

[32] Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

of catalysts for the activation of electrophiles and nucleophiles simultaneously (Scheme 1.10).[33] Chiral squaramides have shown their ability to efficiently activate the electrophile by dual hydrogen-bonding, due to the larger distance between the two acidic protons of the squaramide scaffold compare to the thioureas catalysts (Scheme 1.10).
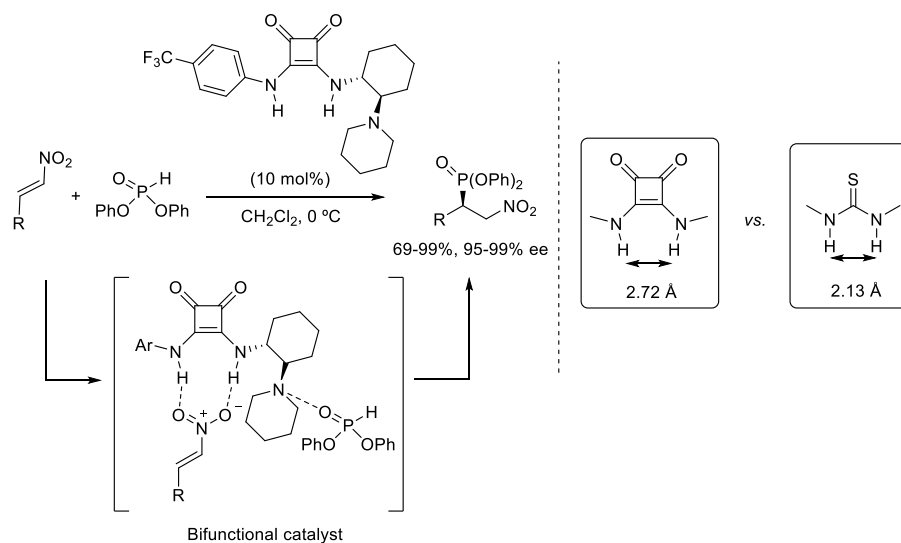
Scheme 1.10

Alternatively, Brønsted acids that can engage through single H-bonding interaction with the substrate have also been identified as outstanding catalysts for a variety of reactions. An interesting example reported by Rawal and colleagues is shown in Scheme 1.11, in which the enantioselective hetero-Diels-Alder reaction between benzaldehydes and dienes catalyzed by TADDOL afforded the corresponding heterocyclic adducts in very good yields and enantioselectivities (Scheme 1.11).[34] In this case, the diol catalyst was proposed to interact with the aldehyde through the formation of a single hydrogen-bond, being the second OH moiety involved in intramolecular H-bonding with the other OH group that contributes to the formation of a conformationally rigid intermediate.

[33] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153.
[34] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature*, **2003**, *424*, 146.
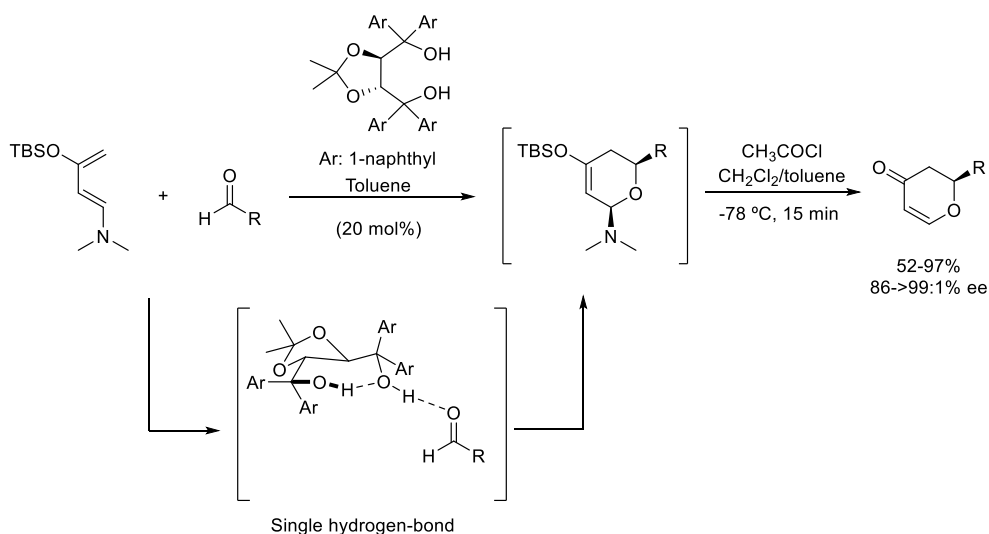
Scheme 1.11

However, the use of diols as hydrogen-bond donor catalysts entails a very limited number of transformations in which these compounds can be applied to promote the corresponding reaction because of their relatively low acidity. This means that the activation of more unreactive systems required the use of more acidic molecules as catalysts with enhanced performance. In this sense, pioneering reports that opened the field to the activation of unreactive systems with the help of chiral phosphoric acids were reported in 2004 simultaneously by the groups of Akiyama and Terada, developing the first generation of BINOL-derived phosphoric acids as Brønsted acid catalysts to activate imines and carbonyl compounds. Akiyama and co-workers reported the enantioselective Mannich-type reaction between aldimines and ketene silyl acetals, employing a 3,3'-disubstituted (*R*)-BINOL phosphoric acid as catalyst for the construction of β-aminoesters in very good yields and enantioselectivities (Scheme 1.13).[35] Simultaneously, the group of Terada published the enantioselective Mannich reaction between *N*-Boc-protected arylimines and acetyl acetone using a related BINOL-based phosphoric acid as catalyst, affording enantioenriched β-aminoketones in high yields (Scheme 1.13).[36] In both cases the chiral phosphoric acid

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[35] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
[36] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

catalyst was able to protonate the electrophilic substrate, and thus activate the imine towards the attack of the nucleophile.
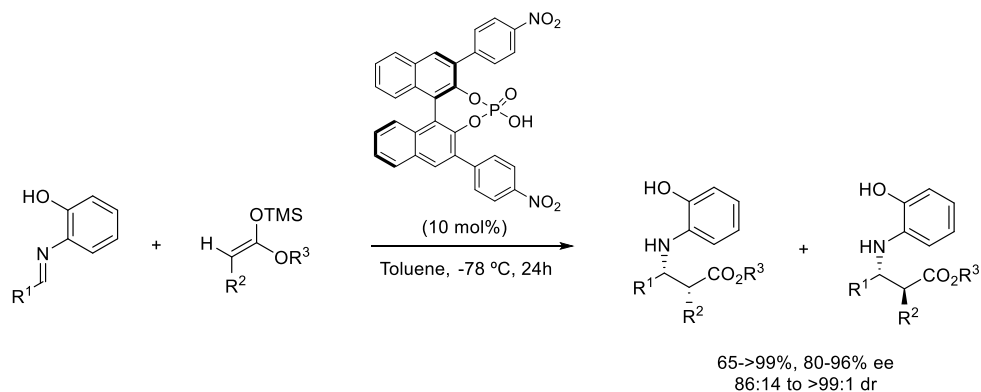
Scheme 1.12
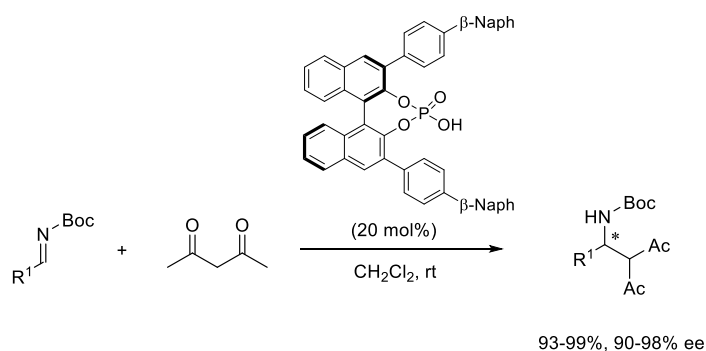
Scheme 1.13

The number of catalysts associated to these activation mechanisms is rapidly growing, as well as the transformations that they are able to perform, having become, undoubtedly, a powerful field for the development of new asymmetric organocatalytic reactions. The chemistry related with the use of chiral BINOL-based Brønsted acids will be covered in more detail in Chapter 2.

3. PRECEDENTS OF THE GROUP

From the beginning, our research group has been devoted to the development of new methodologies for asymmetric synthesis. Initially, the group was focused on the use of chiral auxiliaries for the construction of chiral building blocks or natural products. More precisely, the use of β-aminoalcohol (*S,S*)-(+)-pseudoephedrine as chiral auxiliary was exploited in enolate chemistry[37] and conjugate addition reactions.[38]

More recently, the group focused its interest towards asymmetric organocatalysis. More specifically, a great part of the research work corresponded to aminocatalysis. The first work in this field was directed to the use of enamine activation in the Michael reaction between aldehydes and β-nitroacrolein dimethyl acetal.[39] The Michael reaction led to α,β-disubstituted enantioenriched aldehydes, that could be transformed into the corresponding highly functionalized pyrrolidines by simple procedures (Scheme 1.14).[40]
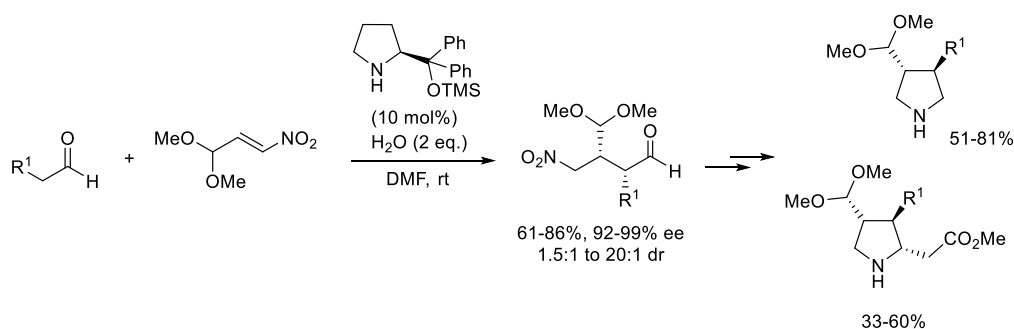
Scheme 1.14

Afterwards, the group focused on the activation of α,β-unsaturated carbonyl compounds under iminium ion catalysis employing chiral primary amines and more frequently chiral secondary amines. There have been reported numerous publications for the functionalization

[37] Selected examples: a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem*. **2011**, *76*, 460; b) Iza, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *RCS Adv*. **2013**, *3*, 25800; c) Iza, A.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2006**, 4065; d) Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2003**, *14*, 347; e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett*. **2006**, *8*, 2535.

[38] Conjugate addition reactions: a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem*. **2009**, *74*, 4404; b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem*. **2006**, *71*, 7763; aza-Michael reactions: c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem*. **2005**, *70*, 8790; d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2004**, *69*, 2588; application to natural product synthesis: e) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron* **2007**, *63*, 11421.

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

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

of these electrophiles at β-position stereoselectively (Scheme 1.15). The first examples were focused on the use of substituted tetrazol frameworks as nucleophiles for the enantioselective aza-Michael reaction of α,β-unsaturated aldehydes (Scheme 1.15a-b).[41] The group has also exploited the conjugated addition of acyl anion equivalents in umpolung transformations, by employing *N*-nitromethylphthalimide and ethyl glyoxylate hydrazones as masked acyl anion equivalents. In this context, a highly efficient protocol was developed for the organocatalytic enantioselective β-hydroxymoylation of α,β-unsaturated aldehydes with *N*-nitromethylphthalimide as the hydroxymetanimidoyl anion equivalent.[42] The obtained oximes could be transformed into the corresponding enantioenriched α-substituted monoprotected 1,4-dialdehydes through simple reaction procedure (Scheme 1.15c). Hydrazones were also proved to behave as efficient umpolung reagents in the enantioselective conjugate addition reaction of α,β-unsaturated aldehydes that after oxidation afforded γ-hydrazono carboxylic acids stereoselectively using a α,α-diarylprolinol derivative as catalyst. These compounds could be transformed as well into highly enantioenriched 1,4-dicarbonyl compounds after simple reaction procedures (Scheme 1.15d).[43] The iminium ion activation has also been extended to cascade processes, where bis-nucleophile reagents were employed. The conjugate addition reaction over the Michael acceptor is followed by hemiaminalization where the nucleophilic part of the molecule reacted with the formyl/acyl group present in the conjugated product generating a stable cyclic adduct (Scheme 1.15e-g). These examples included the reaction of enals with *N,N'*-disubstituted hydrazides to form polysubstituted enantioenriched pirazolidine type heterocycles,[44] the reaction with α-aminoacetones to generate γ-lactams after oxidation[45] and the reaction of enones with diethyl aminomalonate for the construction of optically active proline derivatives using a cinchona alkaloid derived primary aminocatalyst.[46]

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

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

[43] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 114872. It has been found that ethyl glyoxylate *N*-tosylhydrazones can be used as sulfonyl group donors, reacting with Michael acceptors in sulfa-Michael type reactions, by using Brønsted base catalysis, though the steroselective version is still unprecedented. Fernández, M.; Uria, U., Orbe, L.; Vicario, J. L.; Reyes, E.; Carrillo, L.: *J. Org. Chem.* **2014**, *79*, 441.

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

[45] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.*, **2013**, *355,* 653.

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

Scheme 1.15
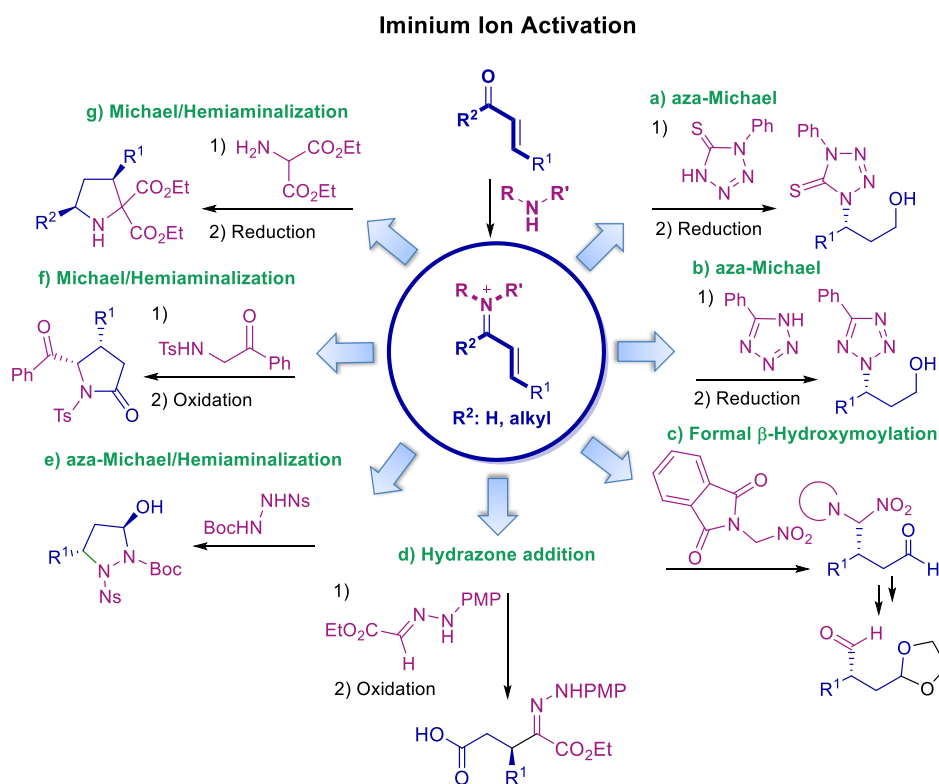
This activation mechanism was further exploited in the first example of a formal (3+2) cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides as 1,3-dipoles, providing access to densely functionalized pyrrolidine scaffolds in high yields and excellent stereocontrol (Scheme 1.16a).[47] This reaction has been widely explored regarding the substitution of the substrates, giving the opportunity to expand the reaction scope to different dipoles and dipolarophiles,[48] and giving access to several heterocyclic structures (Scheme 1.16b).[49] Additionally, mechanistic studies were carried out in collaboration with the group of Prof. Fernando Cossío, where the computational calculations revealed that the

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

[48] a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307; b) Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313; c) Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* **2013**, 2669.

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

reaction consisted on a stepwise mechanism through a Michael/Mannich cascade reaction.[50] Firstly, the iminium ion of the α,β-unsaturated aldehyde is formed to react with the 1,3-dipole in a Michael type reaction, generating the enamine intermediate that is able to react with the electrophilic unit present in the azomethine ylide. A similar reaction have been developed using nitrones as 1,3-dipoles, affording highly substituted enantioenriched *N*-hydroxypyrrolidines (Scheme 1.16c).[51] In addition, the group has developed diverse cascade reactions taking advantage of this combination of iminium/enamine activation manifolds, having developed different procedures such as, oxa-Michael/aldol reaction/hemiaminalization,[52] Aza-Michael/aldol reaction/dehydration,[53] Michael/Michael[54], Michael/α-alkylation[55] and oxa-Michael/Michael (Scheme 1.16d-h).[56]

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

[51] Prieto, L.; Juste-Navarro, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764.

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

[53] Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L, Badía, D. *Chem. Commun.* **2012**, *48*, 2092.

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

[55] a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701; b) Martínez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240.

[56] Orue, A.; Uria, U.; Roca-López, D.; Delso, I.; Reyes, E.; Carrillo, L.; Merino, P.; Vicario, L. J. *Chem. Sci.* **2017**, *8*, 2904.

Scheme 1.16
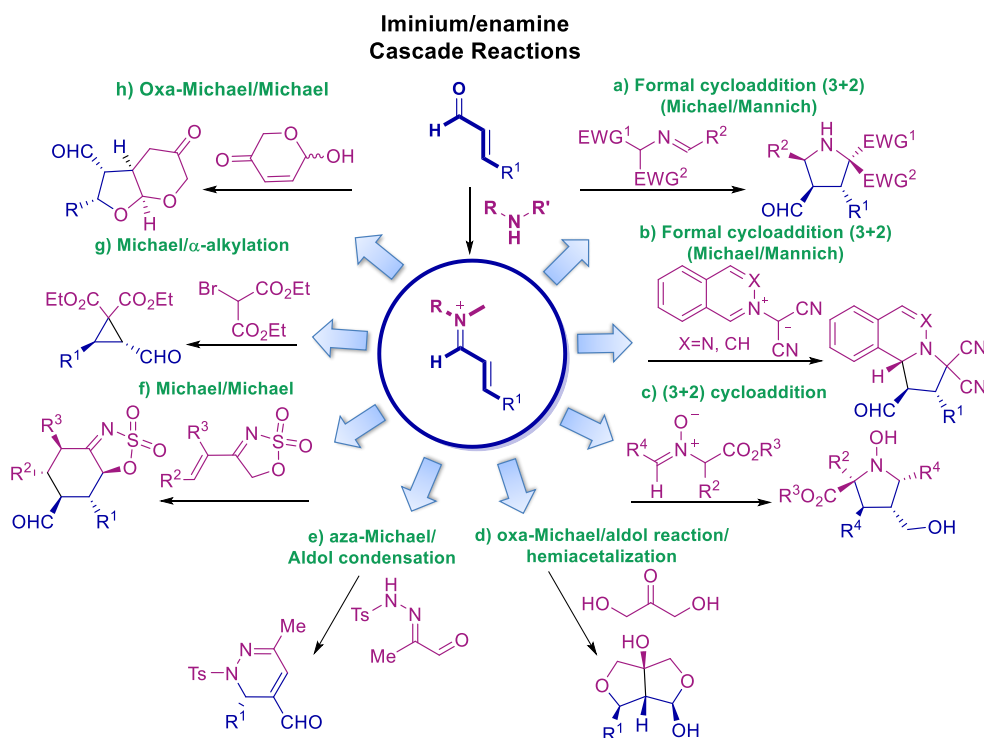
On the other hand, by combination of the enamine and iminium ion strategies with the principle of vinylogy, the stereoselective remote functionalization of different unsaturated carbonyl compounds has been demonstrated through several contributions from our research group. In this context, using dienamine catalysis, the group has developed $(2+2)$[57] and $(5+2)$[58] cycloaddition reactions in a stereoselective manner (Scheme 1.17). These reactions, have also to be considered as formal cycloadditions rather than pericyclic reactions. In this context, computational studies of the $(5+2)$ cycloaddition reaction were carried out in collaboration with Prof. Pedro Merino and Prof. Karl Anker Jørgensen, showing that the reaction worked through a stepwise mechanism.[59] Dienamine catalysis has also been used for the formation of enantioenriched tetrahydro-1*H*-isochromanes in a Diels-Alder reaction/β-elimination process, starting from enolizable α,β-unsaturated aldehydes and racemic 5-acyloxydihydropyranones.[60]

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

[58] Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3043.

[59] Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L.; Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.* **2016**, *18*, 884.

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

In an extension of the methodology, trienamine catalysis has also been studied using unconjugated 2,5-dienals as suitable substrates, being a key feature for the efficient condensation with the catalyst and promoting the construction of six member carbocyles through a Diels-Alder cycloaddition reaction with nitroalkanes.[61]
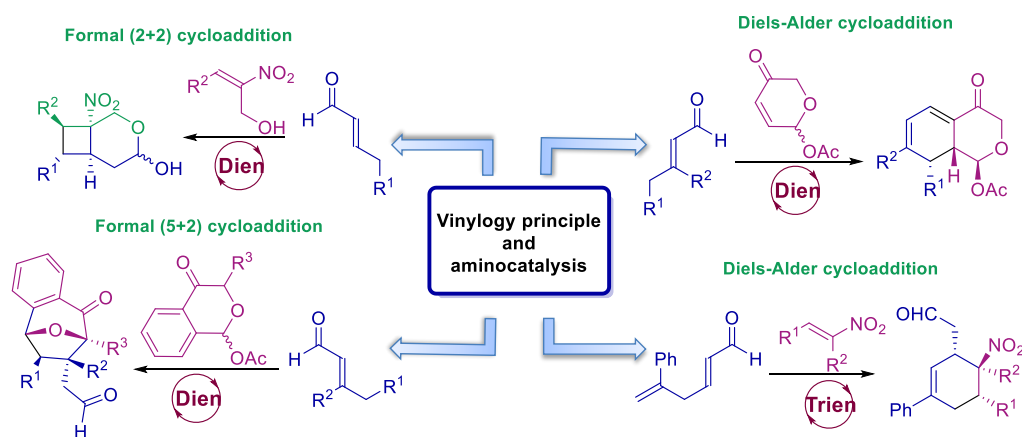
Scheme 1.17

More recently, cyclopropylacetaldehydes have been employed as precursors of polyfunctionalized intermediates, after cyclopropane ring opening. These aldehydes are able to condense with a secondary amine catalyst, generating an enamine intermediate, thus converting the substrate into a donor-acceptor cyclopropane. This intermediate is prone to undergo ring opening, forming a new α,β-unsaturated iminium ion intermediate, ready for the reaction with a nucleophile. The different functionalities present in the intermediates have been exploited, developing a straightforward access to enantioenriched pyrroloquinoline derivatives through a one-pot reaction consisted of cyclopropane ring opening/aza-Michael/aldol condensation cascade reaction, followed by *in situ* lactamization (Scheme 1.18).[62]

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

[62] Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.
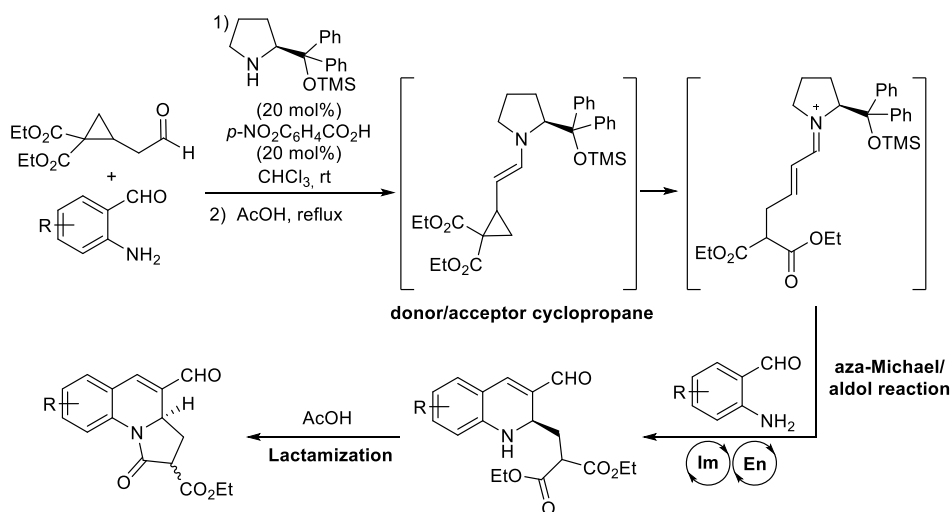
Scheme 1.18

Finally, the group has also shown interest in other different activation mechanisms within organocatalysis (Scheme 1.19). Specifically, NHC catalysis and hydrogen-bonding catalysis have been explored. *N*-heterocyclic carbene catalysis was applied successfully to an enantioselective benzoin reaction using ynones as electrophiles (Scheme 1.19-left).[63] Furthermore, bifunctional squaramide/tertiary amine catalysts were employed for the construction of highly functionalized carbocycles with high stereocontrol in a Michael/Henry cascade sequence (Scheme 1.19-right).[64]
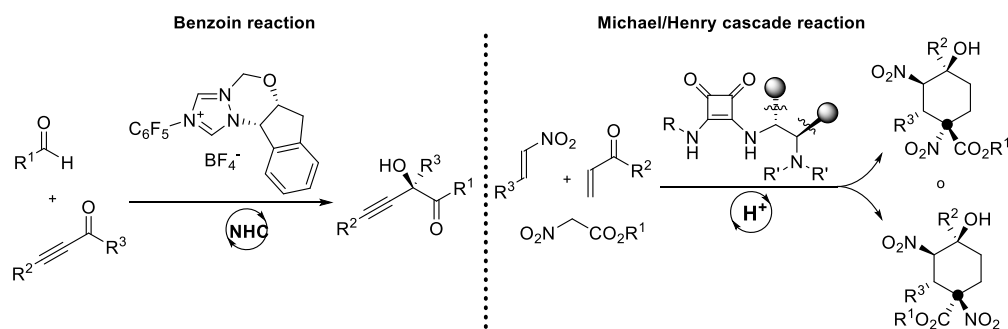
Scheme 1.19

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

[64] 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. *Beils. J. Org. Chem.* **2015**, *11*, 2577.

In conlusion, our research group has focused on the development of new methodologies for promoting the catalytic and asymmetric versions of a variety of synthetically relevant reactions taking advantage of diverse organocatalytic activation mechanisms, such as aminocatalysis, Brønsted acid catalysis and NHC catalysis. The reactions developed in the group under different aminocatalytic activation manifolds have been able to functionalize aldehydes in different positions by exploiting the different activation mechanisms. Furthermore, more sophisticated reaction procedures have been developed, such as cascades and cycloaddition reactions for the construction of more elaborated structures. Moreover, the use of other types of catalysts, such as Brønsted acid catalysts as hydrogen-bond donors and NHC catalysts have also been successfully employed for the enantioselective synthesis of polyfunctionalized carbocycles and tertiary alkynyl carbinols, respectively. The research reported within this manuscript comprises the efforts of our research group to cover organocatalytic activation manifolds that have not been previously used in our group, such as BINOL-based phosphoric acids as catalysts in the addition of hydrazones to enamides. On the other hand, it is also focused on the use of the vinylogous iminium ion activation approach to develop cascade reactions. The next pages further elaborate the objectives of the research work covered in this manuscript.

4. GENERAL OBJECTIVES OF THE PRESENT WORK

The work presented in this thesis is directly linked with the recent research activity of the group. In this sense, it is based on the development of new asymmetric transformations for the construction of highly functionalized enantioenriched heterocycles, employing asymmetric organocatalysis as the main tool. Specifically, two different strategies will be used for the synthesis of chiral adducts.

The **first general objective** will be to develop a new methodology for the addition of acyl anion equivalents to cyclic enamides under chiral phosphoric acid catalysis based on previous research by our group.[43] Hydrazones will be employed as umpoled C nucleophiles to react through a 1,2-addition with *N*-acyl iminium ions generated *in situ* from dihydropyrroles in the presence of a chiral Brønsted acid catalyst. In this sense, it is expected that the protonation of the cyclic enamide would form an ion pair that would promote the reaction with the hydrazone in an appropriate chiral environment to generate the enantioenriched pyrrolidine based hydrazones (Scheme 1.20).
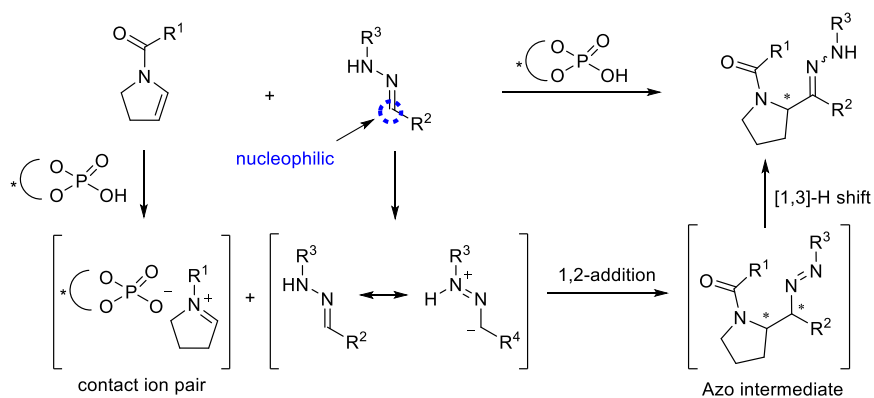
Scheme 1.20

The **second general objective** will focused on the development of a new reaction between α,β,γ,δ-unsaturated enones and aminomalonates, the latter acting as bisnucleophilic reagents, that are expected to undergo double 1,6-1,4-addition reaction to the polyunsaturated system. This reaction will be carried out by a chiral primary amine catalyst able to condense with the cyclic dienone to form the vinylogous iminium ion intermediate that would react with the 2-aminomalonate in an 1,6-aza-Michael reaction, that would render a dienamine

intermediate in equilibrium with the iminium ion. This iminium ion would undergo the second 1,4-Michael reaction with the nucleophilic part of the 2-aminomalonate, affording the spirocyclic adduct (Scheme 1.21).
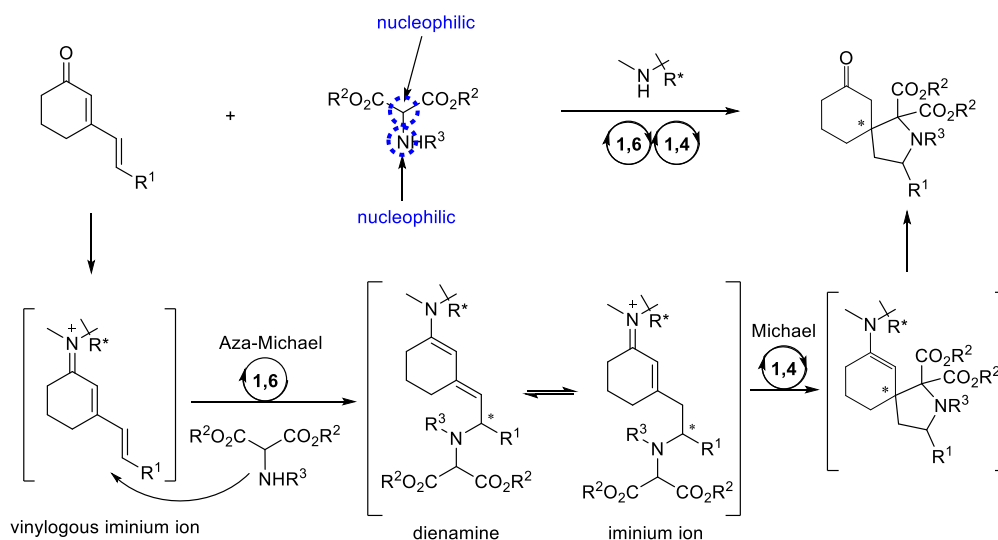
Scheme 1.21

Finally, a short chapter on the work developed in the group of Prof. V. K. Aggarwal as a result of a short (3 month) stay carried out between May and August of 2015 is included. This research project consisted in the enantioenriched synthesis of hindered tertiary boronic esters using the *in situ* lithiation-borylation methodology under mild conditions (Scheme 1.22).
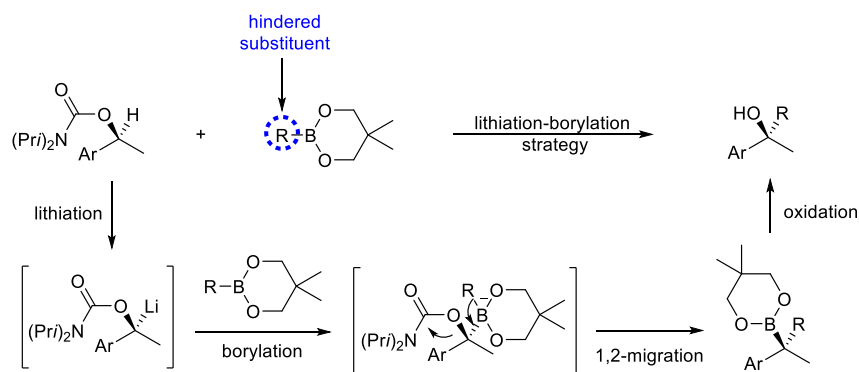
Scheme 1.22

2

2

Hydrazones as Acyl Anion Equivalents in the Chiral Phosphoric Acid-Catalyzed Enantioselective Addition to Dihydropyrroles

1. Introduction

    1.1. Chiral BINOL-derived Brønsted acids

    1.2. Hydrazones as reagents in organocatalytic reactions under Brønsted acid catalysis

2. Specific Objectives and Work Plan

3. Results and Discussion

    3.1. Proof of concept

    3.2. Optimization of the reaction conditions

    3.3. Scope and limitations

    3.4. Transformation of the adducts

    3.5. Mechanistic proposal

4. Conclusions

1. INTRODUCTION

In chapter 1, it was already illustrated that chiral phosphoric acids constitute prominent examples of efficient Brønsted acids catalysts. More precisely, BINOL-derived phosphoric acids are the principal catalyst architecture within this group of catalysts.[1] As shown earlier, the first report showing the ability of BINOL-derived phosphoric acids as chiral Brønsted acid catalysts was developed in 2004 by two groups independently. Akiyama[2] and Terada[3] simultaneously introduced the use of chiral BINOL-phosphoric acids as suitable catalysts for the Mannich reaction between aldimines and ketene silyl acetals or acetyl acetone providing the corresponding enantioenriched β-aminoesters and β-aminoketones (See Scheme 1.12 and 1.13 in Chapter 1).

After these two seminal works, numerous publications have been reported in different enantioselective transformations using these catalysts for the activation of imines and other types of electrophiles.[4] This reactivity has been thoroughly investigated, however, other less reactive substrates, such as carbonyl compounds or less basic substrates have remained elusive until a few years ago. As a result, and trying to expand the activation of (pro)electrophiles other than imines, different families of catalysts have been developed depending on the nature of the Brønsted acidic site.

The acidity of these catalysts is an essential factor to be taken into account when using these catalysts for asymmetric synthesis. Some insights into the variation of pK_a values of phosphoric acid catalysis have been studied[5]. As a representative example, in 2013 Rueping

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[1] For some reviews on asymmetric chiral BINOL-derived phosphoric acid catalysis, see: a) *Asymmetric Brønsted Acid Catalysis*; Rueping, M., Parmar, D., Sugiono, E., Eds.; Wiley-VCH: Weinheim, 2016; b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047; c) Akiyama, T. Phosphoric Acid Catalyzed Reactions of Imines. In *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*; Maruoka, K., Ed.; Georg Thieme Verlag,:Sttutgart, 2012; p.169-218; d) Terada, M.; Momiyama, N. Phosphoric Acid Catalysis of Reactions Not Involving Imines. In *Asymmetric Organocatalysis 2: Brønsted Base and Acid Catalysts, and Additional Topics*; Maruoka, K., Ed.; Georg Thieme Verlag,:Sttutgart, 2012; p. 219-278; e) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706; f) Cheon, C. H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043; g) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539; h) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227; i) Terada, M. *Chem. Commun.* **2008**, *2008*, 4097.

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

[3] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

[4] For some reviews involving transformations using chiral phosphoric acids, see: a) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262; b) Terada, M. *Synthesis* **2010**, *12*, 1929; c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

[5] For studies on the pK_a of different phosphoric acids, see: a) Yang, C.; Xue, X.-S.; Jin, J.-L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 7076; b) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudoerfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524.

and co-workers conducted pK$_a$ measurements of commonly used BINOL-derived phosphoric acids in acetonitrile by using UV/vis spectrometric methods.[6] The authors described a correlation between the acidity of the catalyst and the reactivity. They showed a general tendency that when more acidic catalysts were used, higher rate constants were achieved for a model reaction. However, the stereochemical outcome of the reaction is dependent on other factors and not exclusively by the acidity of the catalyst.
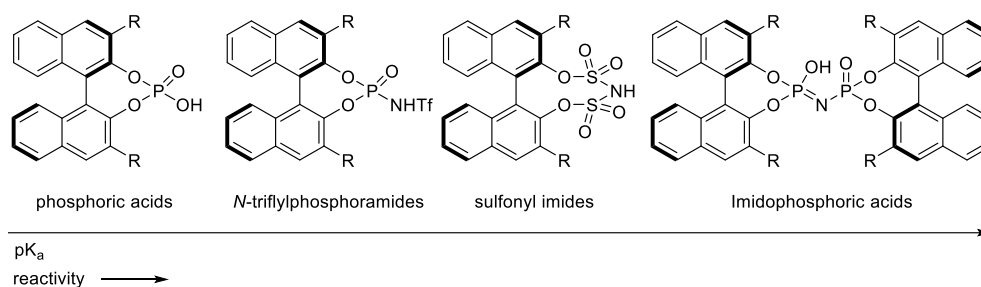
Figure 2.1

The efficient control of the stereochemical outcome of the reaction is another relevant feature to take into account. In this aspect, several factors have important influence in the stereoselectivity of the process in which this type of compounds are used as catalysts. The core structure is a BINOL-based conformationally rigid entity with axial chirality. The 3,3'-positions of this framework are usually modified electronically or sterically. These substitutions have been proved to be essential for the stereoinduction, because they create a specific substrate recognition site and a proper chiral environment. Additionally, the bifunctional character of the catalyst plays an important role in the stereocontrol of the reaction, because as well as acting as a Brønsted acid, the P=O moiety can act as a Lewis basic site, thus, having an additional point of interaction with the pronucleophile (Figure 2.2).

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6   Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569.
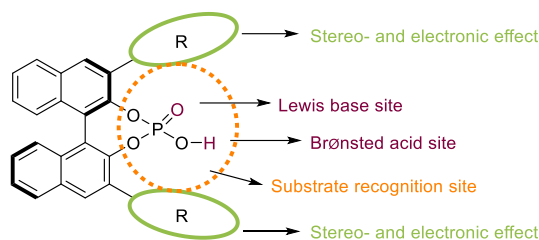
Figure 2.2

As a consequence, the modulation of all these factors has proved to be essential when using these catalysts in asymmetric reactions. Indeed, it has been impossible to find a universal chiral BINOL-derived phosphoric acid catalyst to efficiently promote the broad number of enantioselective transformations known until date, thus, the search for the appropriate catalyst in every reaction need to be checked.

1.1. Chiral BINOL-derived Brønsted acids

Phosphoric acids and related derivatives activate substrates in a similar way to Lewis acids. As described in chapter 1 for Brønsted acid catalysis, these architectures activate the electrophile by lowering the LUMO-energy *via* protonation or H-bonding. The manner to activate the electrophile can be performed in four different ways, depending on the interaction between the catalyst and the substrate: i) mono activation; ii) dual activation; iii) bifunctional activation; iv) counterion catalysis. Mono activation corresponds to the simplest activation mode where the electrophile is activated by a single hydrogen-bond contact with the catalyst. In dual activation, the catalyst establishes two contacts with the electrophilic substrate to perform the reaction with stereocontrol, and in the bifunctional activation manifold the catalyst activates both the electrophile and the nucleophile by hydrogen-bonding. Finally, in counterion catalysis, the catalyst protonates the substrate to generate the phosphate anion, that would form an ion pair with the cationic electrophilic species (Figure 2.3).

Activation modes

| Mono activation | Dual activation | Bifunctional activation | Counterion catalysis |
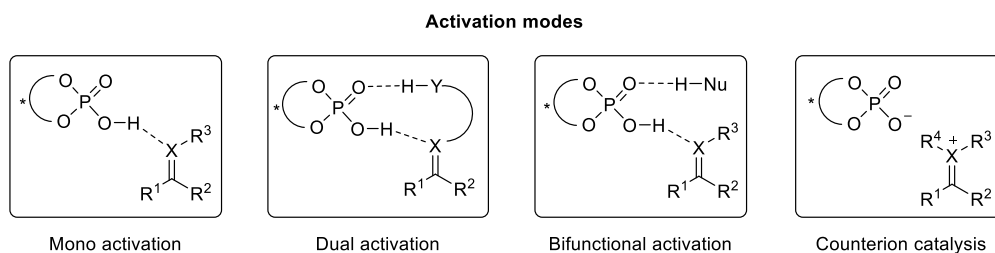
Figure 2.3

The mono activation manifold is the simplest activation scheme, based on a single contact activation of the electrophile *via* hydrogen-bond or ion-pair, through interaction between the Brønsted acidic site of the catalyst and the substrate. One of the first representative examples on the use of this strategy was developed by the group of Terada in 2004 in the enantioselective aza-Friedel-Craft reaction between a broad substrate scope of *N*-Boc aldimines and methoxyfuran. The reaction was carried out in dichloroethane at -35 ºC in the presence of 2 mol% of chiral BINOL-derived phosphoric acid catalyst, activating the imine trough a single contact hydrogen-bond interaction affording the final chiral amines in excellent yields and enantioselectivities (Scheme 2.1).[7]

R: 2,4,6-(CH$_3$)$_3$C$_6$H$_2$
(2 mol%)

DCE, -35 ºC, 24 h

80-96%, 86-97% ee

mono activation of iminium ion
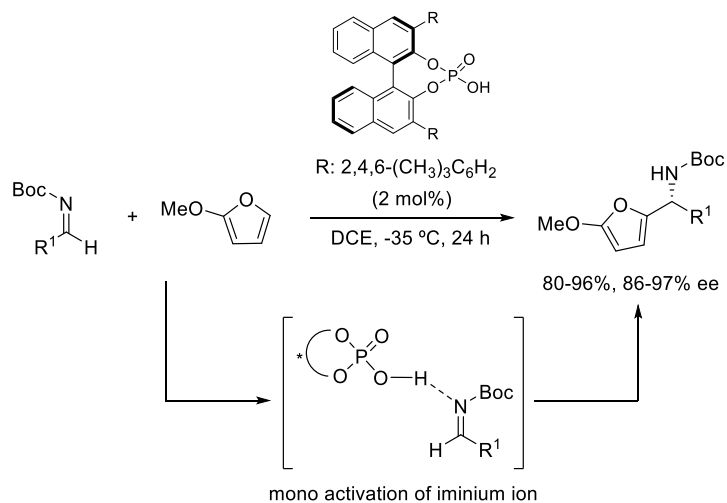
Scheme 2.1

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

In this sense, the exact nature of the catalyst-substrate interaction is still a matter of intense debate. The Brønsted acid can interact with the electrophilic substrate by establishing a hydrogen-bond. But the possibility for Brønsted acids to completely protonate the substrate, with the phosphate anion remaining in close contact with the cationic protonated substrate can also be considered as a reliable possibility. In 2011, Rueping and Gschwind tried to elucidate the exact nature of the catalyst/imine interaction in reactions involving the activation of imines by phosphoric acid catalysts. Based on NMR studies, they revealed that electron-rich imines were more likely to interact *via* protonation/ion-pairing interaction with the catalyst, while electron-deficient imines tended to interact through hydrogen-bonding. However, other elements such as the acidity of the catalyst, the temperature and the solvents had also important influence on the nature of this interaction (Figure 2.4).[8]
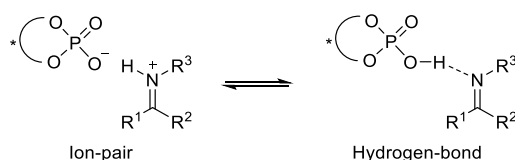
Figure 2.4

However, the activation of carbonyl compounds under this organocatalytic mechanism requires of more acidic Brønsted acid catalysts due to the lower lewis basicity of carbonyl group compared to the parent imines. In these cases, more acidic *N*-triflyl phosphoramide catalysts are normally used, as it is shown in the Diels-Alder reaction between silyloxydienes and ethyl vinyl ketone described by Yamamoto in 2006. In this work the formation of an oxonium ion by protonation with the chiral phosphoric acid catalyst is proposed, this undergoing [4+2]-cycloaddition with silyloxydienes to afford polyfunctionalized cyclohexenes in very good yields and enantioselectivities (Scheme 2.2).[9]

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

[9] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

Mono activation of oxonium ion
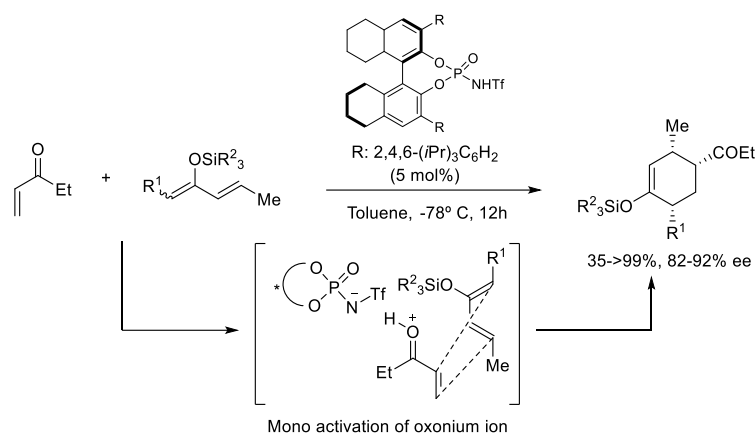
Scheme 2.2

In a different approach, the dual activation implies two contacts between the catalyst and the electrophilic substrate of the reaction. These interactions can happen in two ways: i) the substrate is doubly activated by the acidic proton and the P=O Lewis basic site of the catalyst. Substrates with an acidic proton next to the active site are prone to behave through this mechanism; ii) the substrate is doubly activated by the acidic proton of the catalyst, interacting simultaneously with two points of the molecule, which normally occurs when a Lewis basic group is close to the reacting point (Figure 2.5).
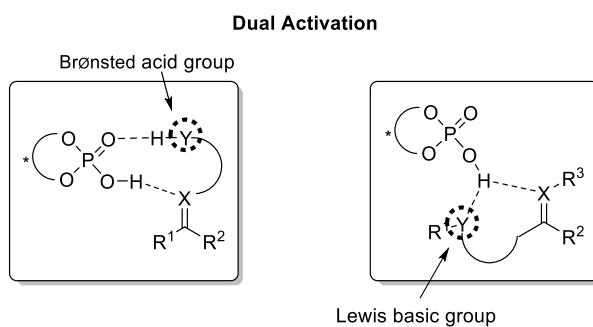
Dual Activation

Figure 2.5

The examples using this method are more limited compared to the other activation modes, however, several transformations have been reported with very good results in terms of reactivity and stereocontrol. The first example in which the electrophile is doubly activated through the acidic proton and the phosphoryl oxygen of the catalyst was the Mannich reaction reported by Akiyama in 2004. In this reaction the nitrogen atom of the aldimine electrophile

interacts with the acidic proton of the catalyst through hydrogen bond, and at the same time, the O-H group in the *N*-aryl substituent of the aldimine is able to form an additional hydrogen bond with the P=O site of the catalyst, activating the electrophile towards the attack of the ketene silyl acetal, affording the desired β-aminoesters in very good yields and enantioselectivities (Scheme 2.3). The use of these aldimines has been explored by the group of Akiyama through this type of dual activation strategy in diverse asymmetric transformations, such as vinylogous Michael type reaction,[10] aza-Diels-Alder reaction,[11] and inverse electron demand aza-Diels-Alder reaction.[12]
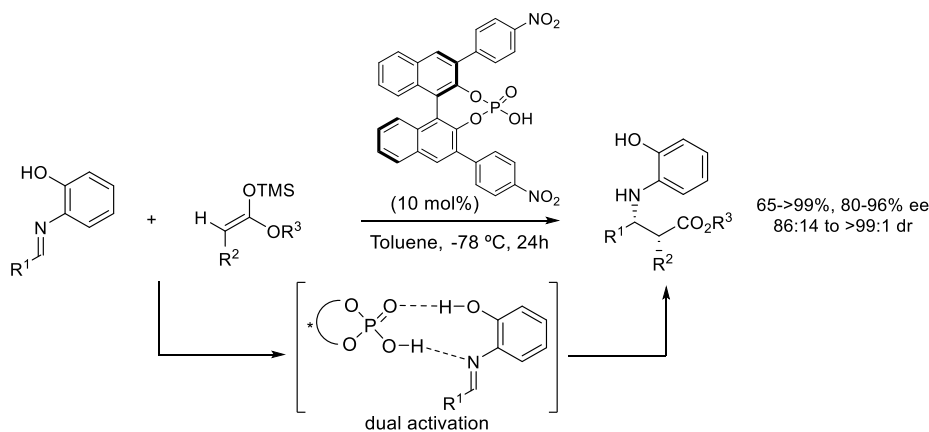
Scheme 2.3

A good example of dual activation, proceeding by two simultaneous contacts with the acidic proton of the catalyst is the Nazarov cyclization developed by the group of Rueping shown in Scheme 2.4. The α-alkoxy group of the α-alkoxy ketone was found to be essential for the activation of the carbonyl group by activating the substrate in a bidentate coordination. Under optimal conditions the corresponding cyclopentanes were obtained in good yields and excellent enantioselectivities (Scheme 2.4).[13] Other Nazarov cyclizations based on this initial example have been developed afterwards with success employing this activation scheme.[14]

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[10] Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.

[11] a) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796; b) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.

[12] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.

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

[14] a) Raja, S.; Ieawsuwan, W.; Korotkov, V.; Rueping, M. *Chem. Asian J.* **2012**, *7*, 2361; b) Kerr, D. J.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1740; c) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450.
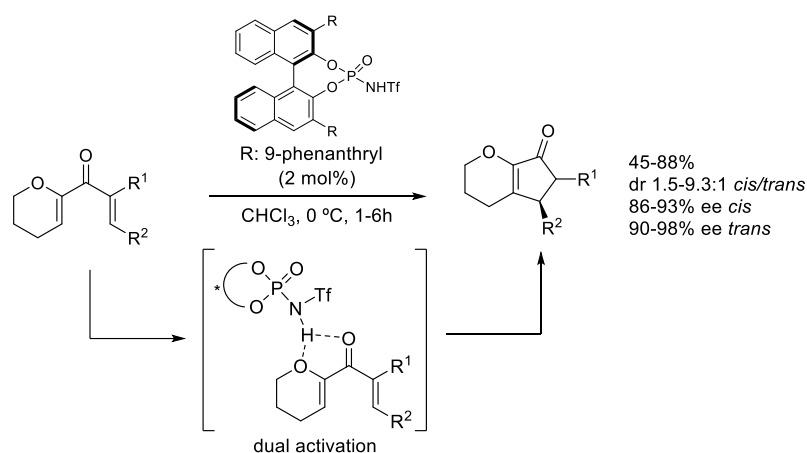
Scheme 2.4

On the other hand, bifunctional activation is the approach that covers most of the reactions catalyzed by chiral BINOL-derived phosphoric acids. In the most widely accepted model that explains the mechanistic pathways for reactions proceeding under this scheme, the catalyst activates the electrophile through hydrogen-bonding interactions with the P-OH moiety, while the phosphoryl oxygen acts as a Lewis base interacting with the pronucleophile. Moreover, diverse publications have been reported to present a valuable explanation for the stereochemistry observed in different reactions,[15] for which the model proposed by Goodman and co-workers is the most accepted one. They focused on reactions between different nucleophiles and imines, thus the chiral phosphoric acid would be establishing interactions with both substrates. The substituents at the 3,3'-position of the BINOL moiety also control the stereochemical outcome of the reaction, promoting the approach of the nucleophile by the less hindered face of the catalyst and by creating an appropriate chiral pocket to hold both substrates.

The aza-ene type reaction disclosed by Terada in 2006 is a good example of this behaviour (Scheme 2.5). As it is indicated, this transformation involves the addition of enecarbamates to *N*-benzoyl imines under only 0.1 mol% of phosphoric acid catalyst, leading

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[15] a) Reid, J. R.; Goodman, J. M. *J. Am. Chem. Soc.* **2016**, *138*, 7910; b) Reid, J. P.; Simón, L.; Goodman, J. M. *Acc. Chem. Res.* **2016**, *49*, 1029; c) Greindl, J.; Hioe, J.; Sorgenfrei, N.; Morana, F.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 15965; d) Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

to β-amino-imine derivatives in good yields and very good enantioselectivities.[16] According to the Goodman model, the reaction through the *E* diastereoisomer of the imine will be preferred where the *N*-benzyloxy substituent, being more sterically demanding, is placed in such a way to avoid destabilizing interactions with the 3,3'-substituent in the catalyst affording the final compounds in enantioenriched form, approaching the enecarbamate from the more unshielded *Re* face.

R: 9-anthracenyl
(0.1 mol%)
Toluene, rt, 5h

53-97%, 92-98% ee
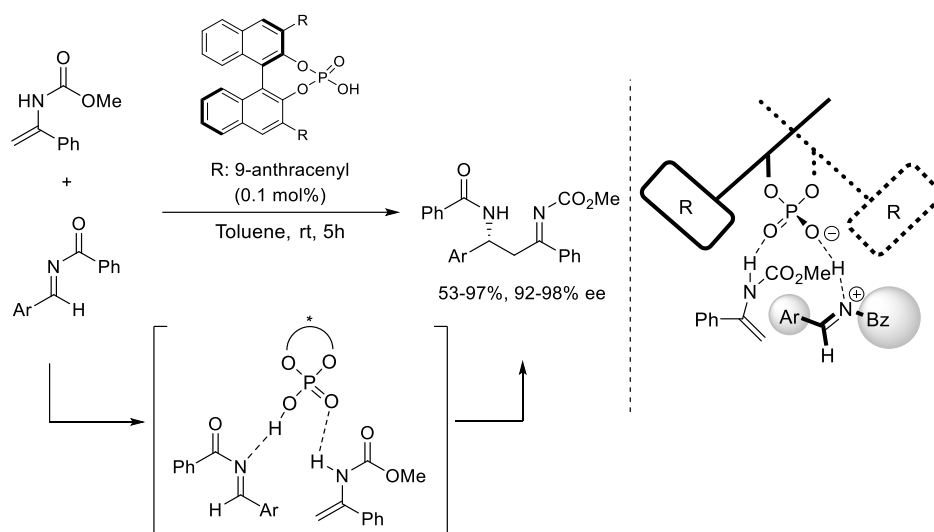
Scheme 2.5

The catalytic architecture is also highly flexible that allows to accommodate electrophiles with varying structures within the chiral pocket but still being able to provide geometrically designed transition-states for a highly stereocontrolled reaction to occur. A good example is found on the Friedel-Crafts reaction between indoles and imines shown in Scheme 2.6 and reported independently by two different groups.[17] As it can be seen in the scheme, the reaction provided products with the opposite chirality but using the same enantiomers of the BINOL-based phosphoric acid catalyst. This different stereochemical outcome can also be explained making use of the Goodman models. For both cases, the indole interacts with the phosphoryl oxygen moiety through the NH unit and it is located in the transition-state at the left-hand side

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[16] a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254; For another similar example: b) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546.

[17] a) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565; b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.

of the catalyst to avoid the steric interaction with the 3,3'-substituents. In the reaction involving *N*-acyl imines, the more bulky substituent of the imine is located at the empty right quadrant to minimize the steric repulsion between subsitutents of the catalyst and the imine, positioning the less steric demanding group (Ac) at the left-hand side for an *endo* approach, and delivering the *S*-configured products. However, when *N*-tosyl imines are used, the larger substituent at the imine is the tosyl group, which is placed at the less sterically demanding right-hand side of the catalyst to avoid destabilizing interactions with the 3,3'-substituents. Thus, the reaction will occur in an *exo* approach, obtaining the opposite *R*-configuration.
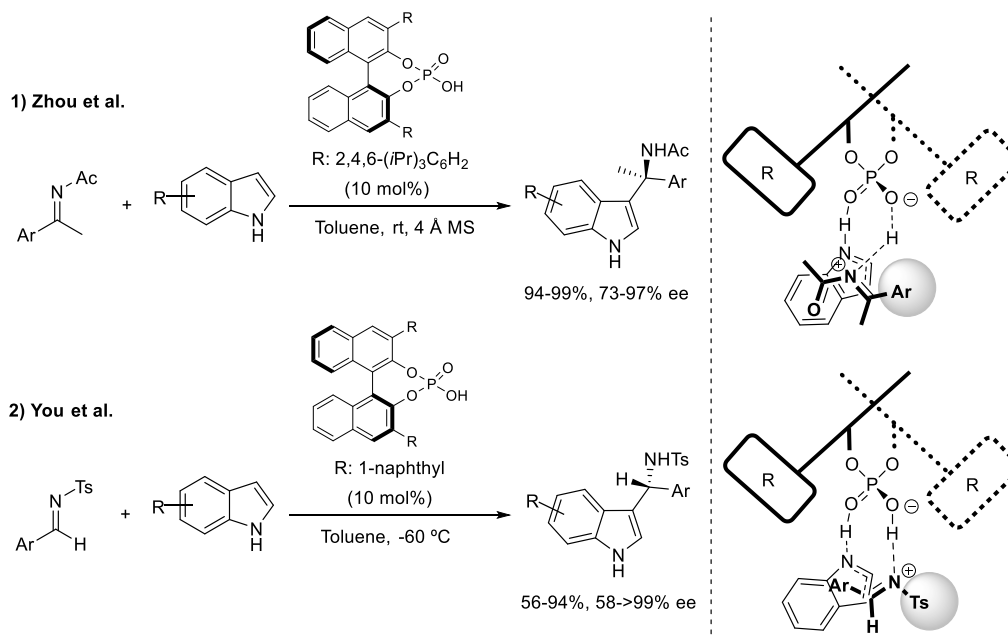
Scheme 2.6

This chemistry is not just limited to the use of imines as electrophiles undergoing activation by the Brønsted acid catalyst, and diverse transformations involving the addition of nucleophiles to carbonyl compounds have also been possible. The well-known Baeyer-Villiger reaction reported by Ding in 2008 is an interesting application on the use of chiral phosphoric acid catalysts for the activation of carbonyl compounds. In this case, the reaction between 3-substituted cyclobutanones and hydrogen peroxide in the presence of a chiral phosphoric acid,

led to the corresponfing γ-lactones in excellent yields and up to 93% of enantiomeric excess.[18] The mechanism of the reaction was studied in detail two years later.[19] Experimental data and theoretical studies confirmed that the catalyst was acting in a bifunctional mode activating both substrates in a synergistic manner through partial proton transfer in a two-step concerted mechanism (Scheme 2.7).
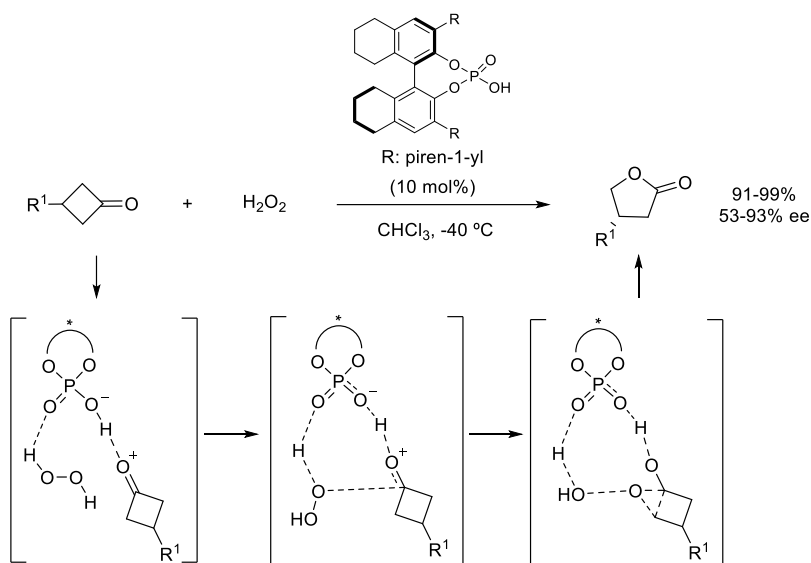
Scheme 2.7

Finally, counterion catalysis is the fourth possibility for a Brønsted acid to activate an electrophile which can take place through the formation of an ion pair by protonation of the electrophile and generation of the phosphate anion, the latter remaining tightly bounded to the protonated electrophile cation.

A good example of this activation manifold is the first asymmetric allylic alkylation reported by Rueping and co-workers in 2011 shown in Scheme 2.8.[20] In this reaction the catalyst was able to protonate the allylic alcohol moiety which subsequently dehydrated to form a carbocation that underwent reaction with the phenol unit leading to the formation of enantioenriched 2H-chromenes in an overall intramolecular allylic alkylation process in high yields (Scheme 2.8). The mechanism of the reaction showed that a carbocation was effectively

[18] Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840.
[19] Xu, S.; Wang, Z.; Li, Y.; Zhang, X.; Wang, H.; Ding, K. *Chem. Eur. J.* **2010**, *16*, 3021.
[20] Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.

formed, because when running the reaction with enantioenriched starting materials and in the presence of an achiral phosphoric acid, the stereochemical information was lost during the process. This confirms the formation of a tightly bounded contact ion pair between the allylic carbocation and the phosphoramide anion, the latter being able to transfer its stereochemical information to the final reaction product.
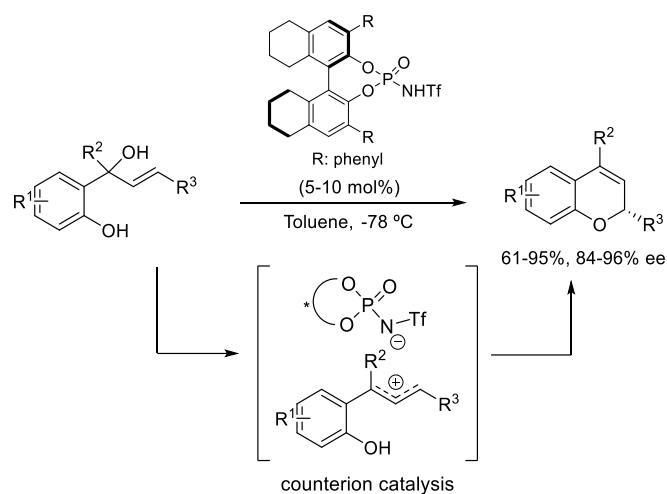
Scheme 2.8

The generation of cationic species and phosphate/phosphoramide anions has been widely studied in several other asymmetric transformations. For example, the formation of *N*-acyl iminium ions as intermediates for the addition of nucleophiles has been investigated using hemiaminals as precursors. For instance, in 2010 Rueping and collaborators developed a Friedel-Crafts reaction between hydroxylactams and indoles in which the *N*-acyliminium ion electrophile was generated by loss of a molecule of water from the hydroxylactam tarting material promoted by the chiral phosphoric acid, and generating a chiral contact ion pair with the phosphate anion. Then, this intermediate was able to react in a chiral environment with indole to yield γ,γ'-disubstituted γ-lactams in moderate yields and good enantioselectivities (Scheme 2.9).[21]

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[21] Rueping, M.; Nachtsheim, B. J. *Synlett* **2010**, 119.
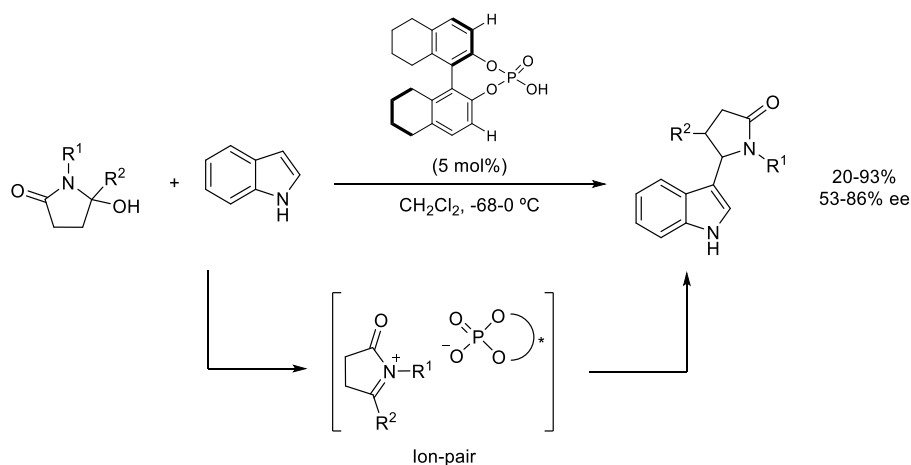
Scheme 2.9

A related strategy was used to perform more elaborated reactions. In 2009, Dixon and co-workers reported a cascade hemiaminal formation/dehydration/intramolecular *N*-aciliminium cyclization catalyzed by a chiral BINOL-derived phosphoric acid. In this reaction enol lactones and tryptamines were used as starting materials for the formation of an amide intermediate that underwent intramolecular 1,2-addition forming the required hemiaminal intermediate that next cyclized *via* chiral phosphoric acid-catalyzed dehydrative condensation, generating the key *N*-acyliminium ion intermediate closely associated to the chiral phosphate anion. Under this contact ion pair, the *N*-acyliminium ion suffered the intramolecular nucleophilic attack of the indol moiety in a chiral environment, affording the final polycyclic structures in high yields, with complete diastereoselectivity and very good enantioselectivities (Scheme 2.10).[22]

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[22] Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796.
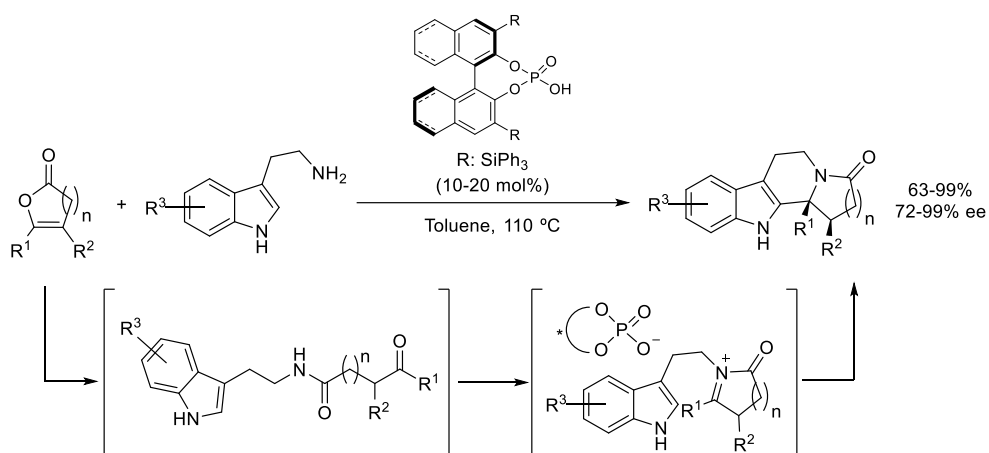
Scheme 2.10

On the other hand, the formation of more challenging oxonium ions has also been possible, although controlling the stereoinduction of the process had been a difficult task for many years. In this context, List reported the organocatalytic intramolecular transacetalization reaction on hydroxyl acetals to deliver enantioenriched acetals under phosphoric acid catalysis (Scheme 2.11). [23] It is proposed that by protonation of the acetal moiety at the substrate by the chiral phosphoric acid catalyst, is followed by eliminination of ethanol forming an oxonium/phosphate ion pair facilitating the intramolecular cyclization in a stereocontrolled way. The bifunctional character of the catalyst was found to be essential in the activation of the substrate, forming double hydrogen bonds.

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[23] Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536.
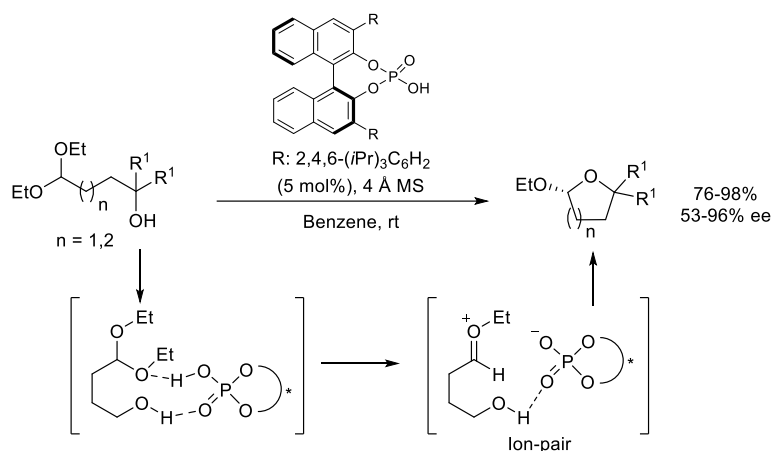
Scheme 2.11

In addition, several different reactions have been published taking advantage of this strategy to form oxonium ions from carbonyl and acetal precursors, carrying out kinetic resolutions of racemic alcohols,[24] desymmetrizations,[25] acetalizations[26] and spiroacetalizations,[27] addition of cyanides[28] and hydrogenations.[29] In addition, the asymmetric ring opening of aziridines[30] and the *in situ* generation of carbocations[31] with chiral phosphoric acids has also been possible in an intramolecular manner or by addition of different nucleophiles.

The asymmetric counteranion-directed catalysis (ACDC) introduced by List in 2006 can also be gathered as a specific case of reactions in which the formation of a close contact ion pair is key for stereocontrol.[32] An interesting example was reported by this author in 2008 carrying out the epoxidation of enals. The catalyst consisted of chiral BINOL-derived

[24] Ćorić, I.; Mueller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.

[25] Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13593.

[26] Kim, J. H.; Ćorić, I.; Vellalath, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 4474.

[27] Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074.

[28] Lu, C.; Su, X.; Floreancig, P. E. *J. Org. Chem.* **2013**, *78*, 9366.

[29] a) Terada, M.; Yamanaka, T.; Toda, Y. *Chem. Eur. J.* **2013**, *19*, 13658; b) Hsiao, C.-C.; Liao, H.-H.; Sugiono, E.; Atodiresei, I.; Rueping, M. *Chem. Eur. J.* **2013**, *19*, 9775.

[30] a) Nakamura, S.; Ohara, M.; Koyari, M.; Hayashi, M.; Hyodo, K.; Nabisaheb, N. R.; Funahashi, Y. *Org. Lett.* **2014**, *16*, 4452; b) Senatore, M.; Lattanzi, A.; Santoro, S.; Santi, C.; Della, S. G. *Org. Biomol. Chem.* **2011**, *9*, 6205; for mechanistic studies, see: c) Della, S. G. *Tetrahedron* **2013**, *69*, 50; e) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186; f) Della, S. G.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330; e) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084.

[31] a) Wang, P.-S.; Zhou, X.-L.; Gong, L.-Z. *Org. Lett.* **2014**, *16*, 976; b) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.

[32] Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.

phosphate amine salt used to activate the aldehyde during the formation of the iminium ion through condensation with the amine and leaving the chiral phosphate anion ready to control the stereoselectivity of the reaction. The corresponding epoxide adducts were furnished in very good yields and high diastereo- and enantioselectivities (Scheme 2.12).[33]
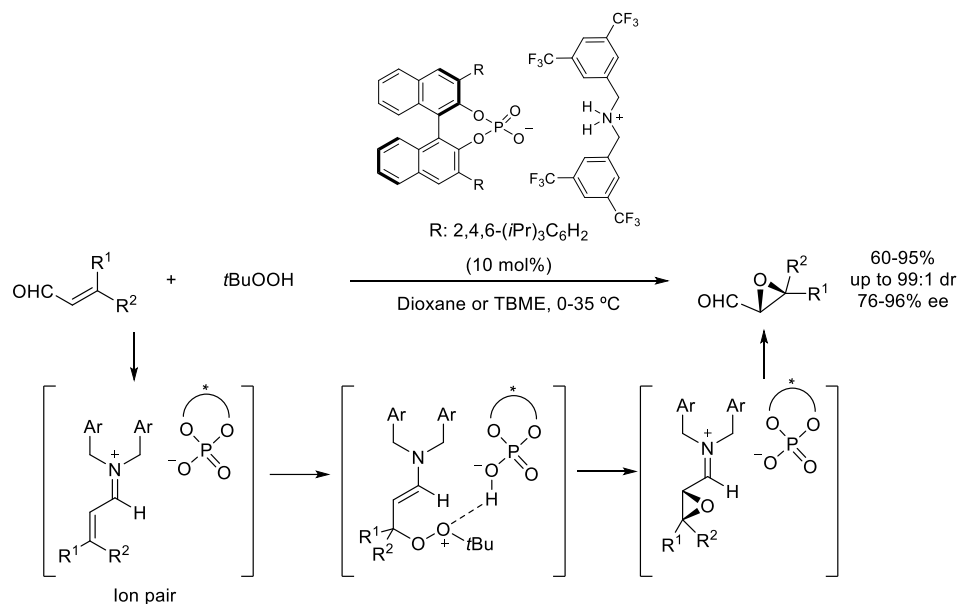
Scheme 2.12

1.2. Hydrazones as Reagents in Organocatalytic Reactions under Brønsted acid Catalysis

Hydrazones and their derivatives constitute a versatile class of compounds due to their easy access, stability and multiple active sites present in their structure. They have shown an important ability in asymmetric synthesis, acting as chiral ligands in metal complexes,[34] or as chiral auxiliaries,[35] demonstrating their potential for the construction of heterocyclic structures. On the other hand, hydrazones have played an important role as reagents in

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

[34] Some examples: a) Denmark, S. E.; Chang, W.-T. T.; Houk, K. N.; Liu, P. *J. Org. Chem.* **2015**, *80*, 313; b) Álvarez-Casao, Y.; Monge, D.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2015**, *17*, 5104; c) Egger, L.; Tortoreto, C.; Achard, T.; Monge, D.; Ros, A.; Fernández, R.; Lassaletta, J. M.; Lacour, J. *Adv. Synth. Catal.* **2015**, *357*, 3325; d) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798; e) Arai, T.; Endo, Y.; Yanagisawa, A. *Tetrahedron: Asymmetry* **2007**, *18*, 165; f) Mino, T.; Shirae, Y.; Yajima, T.; Sakamoto, M.; Fujita, T. *Heterocycles* **2006**, *68*, 1233; g) Lassaletta, J. M.; Alcarazo, M.; Fernández, R. *Chem. Commun.* **2004**, 298; h) Mino, T.; Ogawa, T.; Yamashita, M. *J. Organomet. Chem.* **2003**, *665*, 122.

[35] Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

asymmetric organocatalysis, taking advantage of their ambiphilic properties, making them suitable reagents for numerous asymmetric transformations. Depending on the substituents present in their structure, hydrazones can act with different reactivity patterns as both nitrogen atoms of the hydrazone are nucleophilic, while the azomethine carbon is able to act as C-nucleophile as well as a C-electrophile, by modulating the structure of the hydrazone (Figure 2.6).
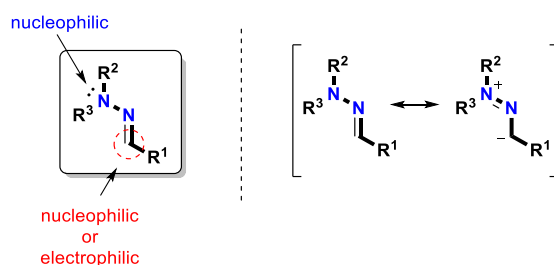
Figure 2.6

These properties of hydrazones have been essential for the application of these compounds as efficient reagents in several organocatalytic asymmetric transformations.[36] In this sense, the activation of these compounds by Brønsted acids has been explored and some examples correspond to the use of chiral BINOL-derived phosphoric acids.

Hydrazones are typically employed as C-electrophiles when activated by a chiral phosphoric acid. In this context, the group of Tsogoeva exploited the usefulness of *N*-acylhydrazones as substrates able to react with TMSCN through a Strecker reaction[37] or to undergo [3+2]-cycloaddition reactions[38] with cyclopentadienes in each of the reactions affording the final adducts in moderate to good yields and very good enantioselectivities (Scheme 2.13). The mechanism of these both reactions is uncertain, proposing both a mono activation or dual activation manifold. In the Strecker reaction, according to the authors, one of the proposed possibilities relied on the initial silylation of the hydrazone followed by two point of interaction between the catalyst and the electrophile (dual activation). However, another proposed possibility consisted on single hydrogen-bond interaction (mono activation),

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[36] For a review on the use of hydrazones in asymmetric organocatalysis, see: Retamosa, M. G.; Matador, E.; Monge, D.; Lassaletta, J. M.; Fernández, R. *Chem. Eur. J.* **2016**, *22*, 13430.

[37] Zamfir, A.; Tsogoeva, S. B. *Org. Lett.* **2010**, *12*, 188.

[38] a) Serdyuk, O. V.; Zamfir, A.; Hampel, F.; Tsogoeva, S. B. *Adv. Synth. Catal.* **2012**, *354*, 3115; b) Zamfir, A.; Tsogoeva, S. B. *Synthesis* **2011**, 1988.

where *tert*-butanol was the responsible for removing the silicon group from TMSCN and allowed the attack of the nucleophile (Scheme 2.13).
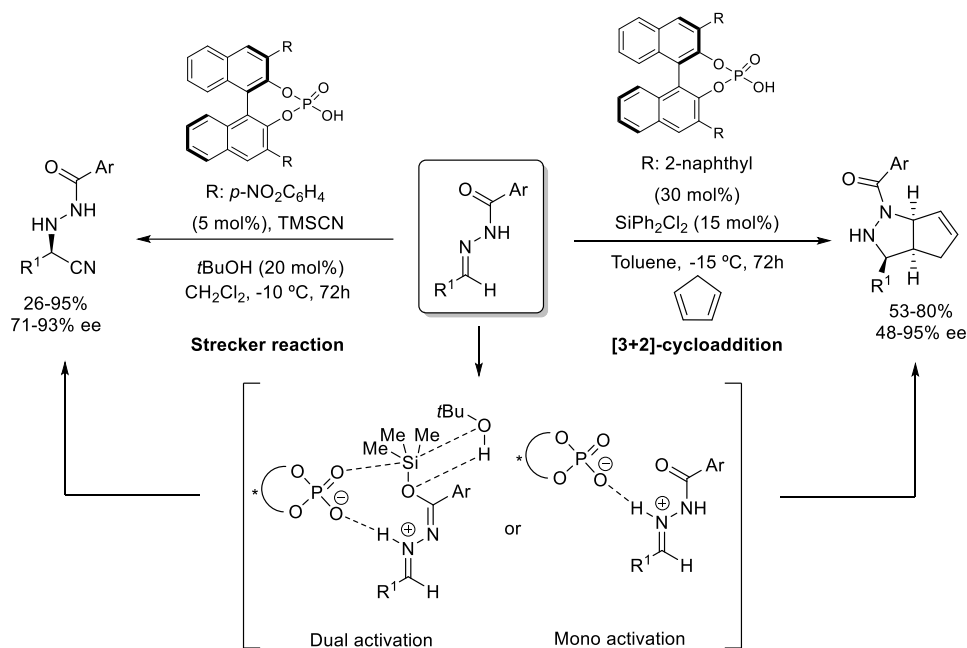
Scheme 2.13

That same year, Rueping and co-workers demonstrated that the use of a more acidic *N*-triflyl phosphoramide catalyst was able to promote the [3+2]-cycloaddition reaction without the addition of any silicon reagent, obtaining the desired bicyclic adducts in high yields and enantioselectivities and using only 2.5 mol% of catalyst. The higher acidity of the catalyst was found to be crucial for reactivity, allowing the employment of styrenes and further extending further the scope of the reaction. In this case, the authors proposed a mono activation model to explain the observed stereochemistry (Scheme 2.14).[39] Later, the same group was able to expand the scope of this activation strategy to vinyl ethers in a (3+2)-cycloaddition reaction.[40]

[39] Rueping, M.; Maji, M. S.; Küçük, H. B.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 12864.

[40] Hong, X.; KüÇük, H. B.; Maji, M. S.; Yang, Y. –F.; Rueping, M.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 13769.
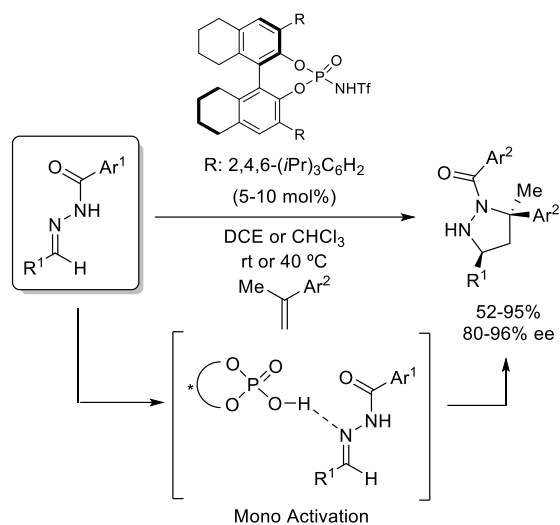
Scheme 2.14

As another interesting example on the use of hydrazones as electrophiles activated by a chiral Brønsted acid is the enantioselective Fischer type reaction for the enantioselective synthesis of indoles through desymmetrization of hydrazones carried out by List and co-workers. In this work, a chiral spirocyclic phosphoric acid was used as catalyst, obtaining the final adducts in good yields and high selectivities (Scheme 2.15).[41] A dynamic kinetic resolution pathway involving the formation of a chiral hydrogen-bond-assisted ion pair for under dual activation of the hydrazone was proposed to justify the outcome of the reaction. From the two possible diastereomeric transition states, only one undergoes the [3,3]-sigmatropic rearrangement obtaining high enantioselectivities. Later computational studies analysing the mechanism of this reaction revealed that together with these as well as these hydrogen-bonding contacts, CH/π interactions between the catalyst and the substrate were also responsible for the enantiocontrol of the process.[42]

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[41] a) Kötzner, L.; Webber, M. J.; Martínez, A.; De Fusco, C.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5202; b) Martínez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9486; c) Mueller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534; b) Martínez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9486.

[42] For some insights in the mechanism of asymmetric Fischer indolizations, see: a) Wheeler, S. E.; Seguin, T. J.; Guan, Y.; Doney, A. C. *Acc. Chem. Res.* **2016**, *49*, 1061; b) Seguin, T. J.; Lu, T.; Wheeler, S. E. *Org. Lett.* **2015**, 17, 3066; c) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752−5755.
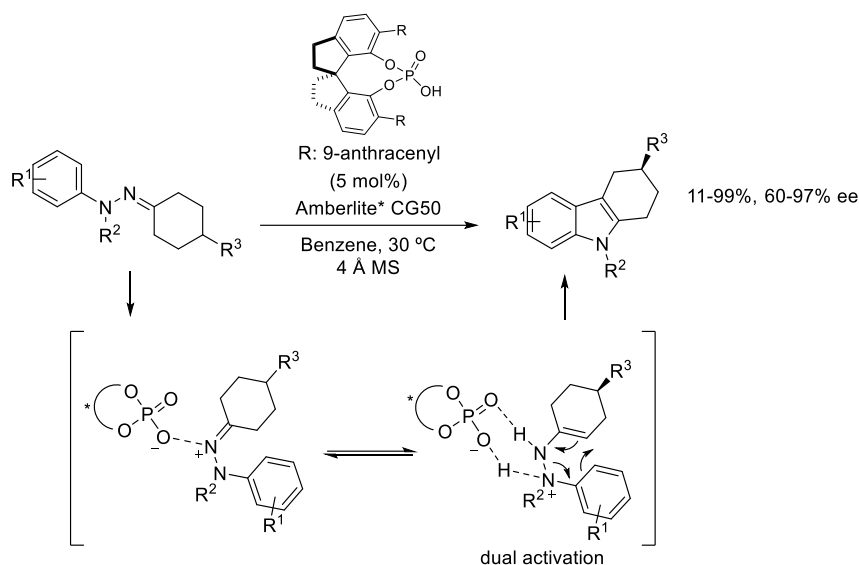
Scheme 2.15

Finally, a Brønsted acid catalyzed 6π-electrocyclization of α,β-unsaturated *N*-imino-hydrazonium salts has also been reported by List and co-workers. In this example, hydrazones in combination with enals were employed to generate the key intermediates capable of undergoing the asymmetric 6π-electrocyclization reactions after activation by the phosphoric acid catalyst providing enantioenriched 1,4-dihydropyridazines in good yields (Scheme 2.16).[43]
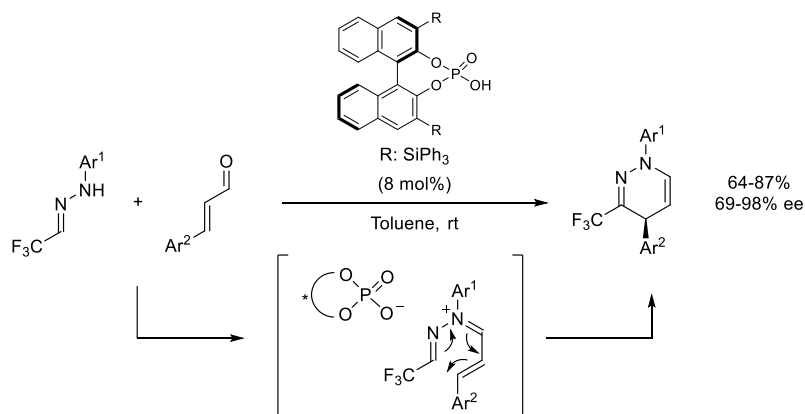
Scheme 2.16

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[43] Das, A.; Volla, C. M. R.; Atodiresei, I.; Bettray, W.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 8008.

The first example using hydrazones as C-nucleophiles in asymmetric organocatalysis employing chiral BINOL-derived phosphoric acids as catalysts was reported by Rueping in 2007. This reaction consisted in the reaction between hydrazones and *N*-Boc imines in the presence of a chiral phosphoric acid. In this reaction, the hydrazones acted as nucleophiles at the azomethine carbon, to react with activated iminines in an aza-enamine reaction. The corresponding aminohydrazones were obtained in good yields and good enantioselectivities (Scheme 2.17).[44] The author proposed the participation of the catalyst through the mono activation manifold, in which a single hydrogen-bonding interaction was proposed to be established between the N-acyl iminium cation and the catalyst, with the hydrazone undergoing addition externally, without any additional interaction with the catalyst.
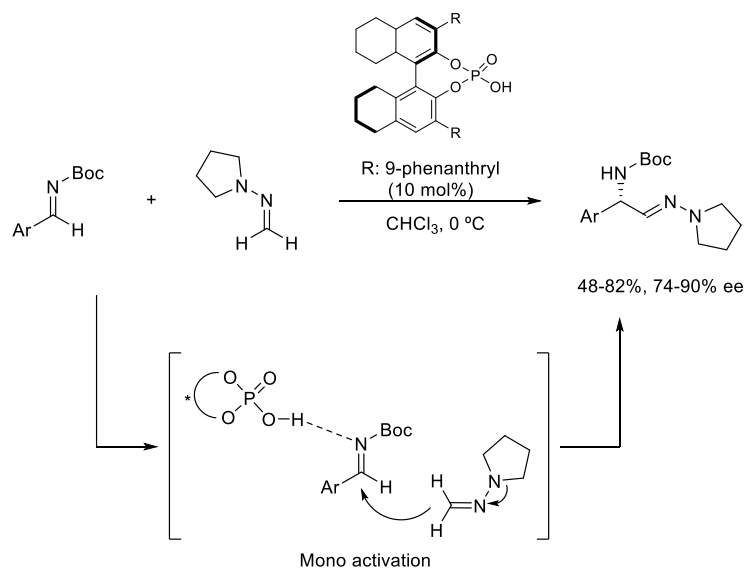
Scheme 2.17

Very recently, another example on the use of hydrazones as C-nucleophiles emerged by the group of Zhu. In this case they employed *N*-monosubstituted hydrazones as α-azo carbanion equivalents for the addition to imines. More precisely, the reaction consisted in an enantioselective imino aza-enamine reaction between *N-tert*butylhydrazones and *N*-Boc imines, generating β-amino diazenylalkanes with two contiguous stereocentres in high yields,

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[44] Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Koeckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065.

diastereo- and enantioselectivities. The proposed mechanistic model is based on bifunctional activation, where the catalyst in this case is able to activate both the electrophile and the nucleophile by hydrogen-bonding (Scheme 2.18).
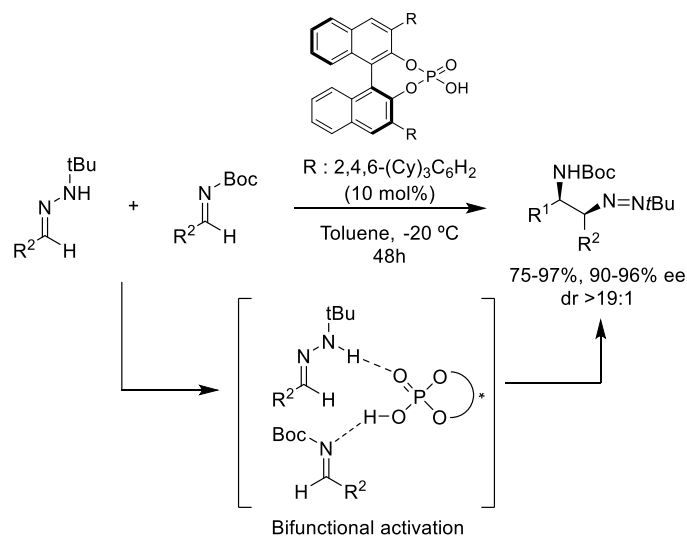
Scheme 2.18

To sum up, the field of chiral BINOL-derived phosphoric acid catalysis has appeared as a distinguished discipline for the development of asymmetric transformations through their capability to activate a wide range of functional groups. This type of catalysts have received a great deal of attention from numerous research groups around the world. Moreover, new synthetic utilities are arising, such as counterion catalysis or the combination with metal catalysis, providing unique catalytic properties to carry out highly stereoselective transformations. However, the application of these catalysts is still limited to a rather narrow scope of reactions in which these can be applied to. For this reason, still further research is needed in order to find new reactions and transformations in which these catalysts can provide improved performance.

2. SPECIFIC OBJECTIVES AND WORK PLAN

Our group has demonstrated the use of *N-p* -methoxyphenylhydrazones derived from glyoxylates as C nucleophiles and acyl anion equivalents in the enantioselective conjugate addition of to α,β-unsaturated aldehydes under iminium ion activation, affording 1,4-dicarbonyl compounds in high yields and enantioselectivities. Firstly, the conjugate addition of hydrazones to unsaturated aldehydes in the presence of an α,α-diarylprolinol catalyst led to γ-azoaldehydes in good yields. These intermediates could be transformed into α-hydrazono carboxylic acids in high yields and enantioselectivities and more interestingly they could be converted into enantioenriched 1,4-dicarbonyl compounds after oxidation and ethanolysis/hydrolysis sequence (Scheme 2.19).[45]
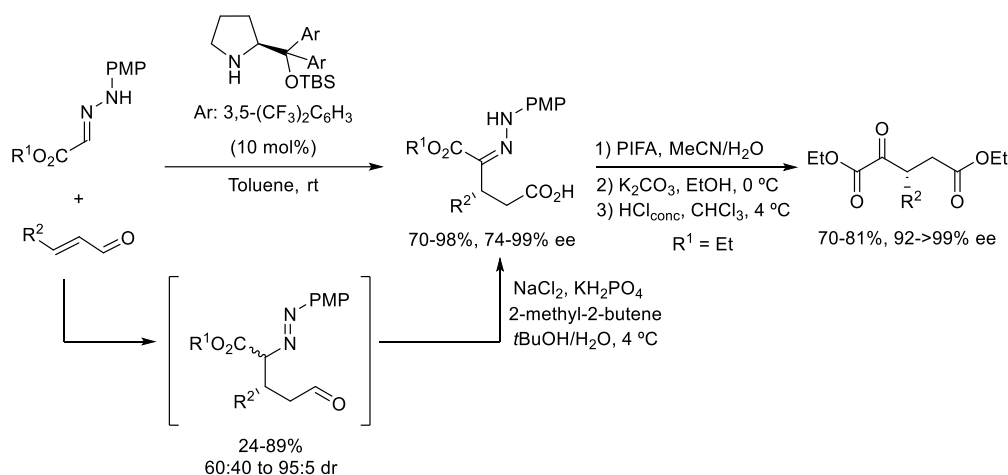
Scheme 2.19

In connection with this previous research, we decided to employ the ability of this type of hydrazones as potential C-nucleophiles able to undergo **1,2-addition reaction of hydrazones to dihydropyrroles under Brønsted acid catalysis.** Our proposal is based on the interesting feature of using simple reagents as starting materials, that would generate a cyclic *N*-acyl iminium ion under chiral phosphoric acid catalysis by protonation, forming an ion pair with the phosphate anion, and creating an appropriate chiral environment for the 1,2-addition of the nucleophilic hydrazones (Scheme 2.20).

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[45] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872.
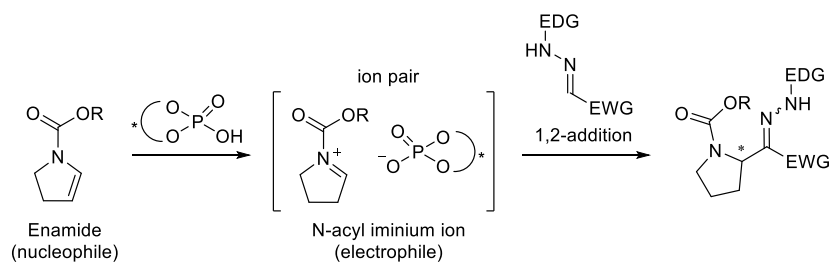
Scheme 2.20

In order to achieve the stated objective, the following work plan was designed:

1. *Proof of concept*: The projected reaction between hydrazones and cyclic enecarbamates will be surveyed using *N*-Boc-2,3-dihydro-1*H*-pyrroles and *p*-methoxyphenylhydrazone derived from ethyl glyoxylate as model substrates. The ability of phosphoric acids and derivatives as catalysts to promote this reaction will be surveyed (Scheme 2.21).
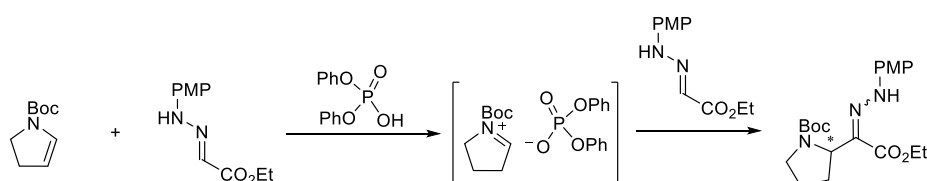
Scheme 2.21

2. *Optimization of the reaction*: Once the viability of the reaction has been verified, a screening of several chiral phosphoric acid catalysts and other experimental parameters such as solvent, additives and temperature will be studied with the aim to obtain the final adduct in high chemical yield and optimal stereocontrol (Scheme 2.22).
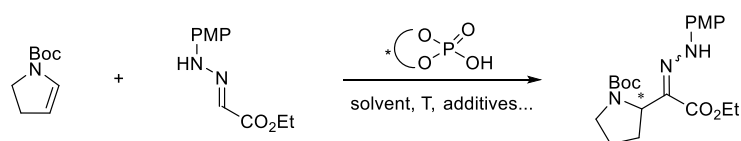
Scheme 2.22

3. *Scope of the reaction*: Once the best reaction conditions have been established, the application of the methodology to different substrates will be evaluated. On the one hand, several cyclic enecarbamates incorporating different substituents at the nitrogen atom and within the cyclic structure will be surveyed. On the other hand, the tolerance of the

reaction towards hydrazones, with different substituents at the nitrogen atom and at the azomethine position will also be studied (Scheme 2.23).
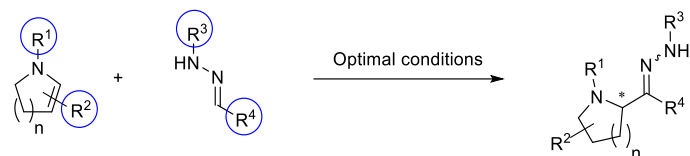
Scheme 2.23

4. *Transformation of the adducts:* Trying to establish the potential of hydrazones as acyl anion equivalents, the cleavage of the synthesized α-hydrazono substituted pyrrolidines to unmask the carbonyl functionality will be surveyed (Scheme 2.24).
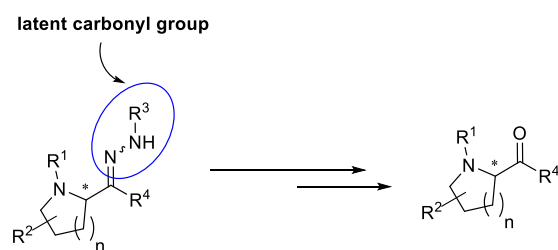
Scheme 2.24

3. RESULTS AND DISCUSSION

Once the methodologies and literature examples on this topic have been reviewed, and after establishing the specific objectives and work plan, the most relevant results obtained on this part of the research work will be presented and discussed.

3.1. Proof of concept

We decided to evaluate the viability of the projected reaction employing commercially available *N*-Boc-2,3-dihydro-1*H*-pyrrole **1a** and *p*-methoxyphenylhydrazone **2a** as model system. Toluene was incorporated as solvent and the reaction was carried out with two different achiral catalysts (diphenyl phosphate and diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate) in order to evaluate the influence of their acidity on the reaction results (Scheme 2.25). In both cases the hydrazone **3a** was obtained in good yield and as single diastereoisomer, probably due to the fast 1,3-[H] shift occurred in the azo-compound. These initial trials showed that both catalysts were able to form the corresponding *N*-acyliminium ion regardless their pk$_a$ and that the hydrazone behaved as expected, as C-nucleophile. Although the configuration of the C=N bond of the product could not be undoubtedly assigned by NOESY NMR experiment, it should be pointed out that the N-H group in adduct **3a** appeared at remarkable low fields (12 ppm) which could be an indication of an intramolecular hydrogen-bond between the N-H group of the hydrazone and the carbonyl group of the carboxylate.
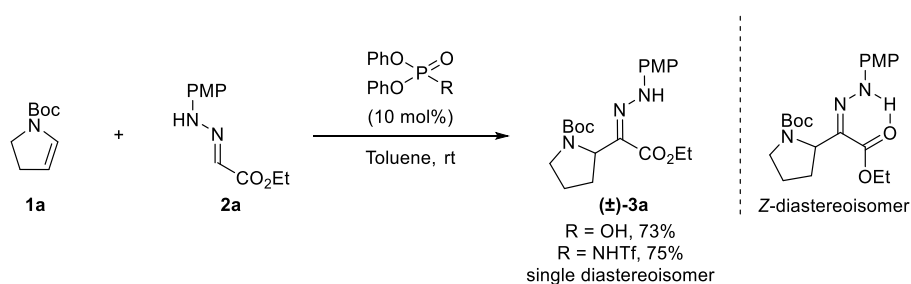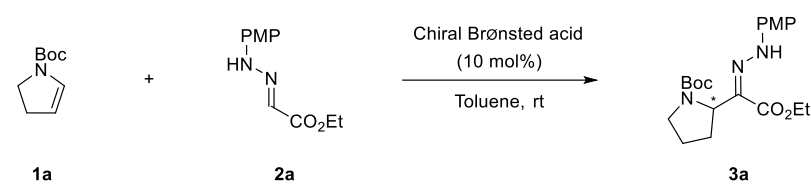
Scheme 2.25

3.2. Optimization of the reaction conditions

Once the possibility of carrying out the reaction in the presence of a Brønsted acid catalyst was verified, we next proceeded to evaluate the effect of different BINOL-based chiral Brønsted acids on the reaction.

Table 2.1: Chiral BINOL-derived Brønsted acid catalyst survey.[a]

Entry	Catalyst	Yield 3a (%)[b]	ee 3a (%)[c]
1	**4a**	53	25
2	**4b**	52	23
3	**4c**	54	68
4	**4d**	53	15
5	**4e**	61	8
6	**4f**	74	0
7[d]	**4f**	48	-2

[a] The reaction was performed in 0.26 mL of toluene and 0.13 mmol scale of **1a**, using 1.2 eq. of **2a** at rt.[b] Isolated product yield of **3a** after flash column chromatography.[c] Determined by HPLC analysis of the pure product.[d] Reaction carried out at -78 ºC.

As shown in Table 2.1, when the chiral phosphoric acid possessed a bulky substituent at the 3,3'-position (**4a-c**), adduct **3a** was achieved in moderate yield and enantiocontrol, being the case of *(R)*-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (TRIP) **4c** the most promising one with 68% of enantiomeric excess (Entries 1-3). A most acidic phosphoric acid **4d** could not improve the results previously obtained, which suggested us that more acidic catalysts could not be appropriate in this reaction. Nevertheless, and in order to verify our hypothesis, two different BINOL-derived *N*-triflyl phosphoramides (**4f-g**) were tested which are known to be 5-6 pk$_a$ (in CH$_3$CN) units more acidic than their corresponding phosphoric acids.[6] In both cases the reaction was faster and the yield of the

desired product was improved, although the catalyst could not control the enantioselectivity of the process even at lower temperatures (Entries 5-7).

Encouraged by the promising results, we next decided to evaluate different solvents employing catalyst **4c** in order to achieve the highest possible yield and stereoselectivity (Table 2.2).

Table 2.2: Evaluation of different solvents in the reaction.[a]

Entry	Solvent	Yield 3a (%)[b]	ee 3a (%)[c]
1	toluene	54	68
2	benzene	53	65
3	*o*-xylene	43	67
4	CH₂Cl₂	52	49
5	CHCl₃	27	26
6	EtOAc	83	57

[a] The reaction was performed in 0.26 mL of solvent and 0.13 mmol scale of **1a**, using 1.2 eq. of **2a** for 14h. [b] Isolated product yield of **3a** after flash column chromatography. [c] Determined by HPLC analysis of the pure product.

Initially, non-polar solvents were examined, such as benzene and *o*-xylene trying to maintain a close chiral contact ion pair, however, they did not afford better results than those obtained with toluene (Entries 2-3 *vs* Entry 1). Next, we moved on to test polar solvents, which could stabilize ions in the medium (Entries 4-6), but these showed no ability to control the enantioselectivity of the process.

With toluene as the best performing solvent, we proceeded to study the effect of other parameters on the reaction, such as temperature and drying agents (Table 2.3).

Table 2.3: Influence of temperature and drying agents in the reaction.[a]

Entry	T (ºC)	Additive	Yield 3a (%)[b]	ee 3a (%)[c]
1	rt	-	54	68
2	-5	-	43	74
3	-15	-	30	71
4	-20	-	-	-
5[d]	-5	MgSO$_4$	45	76
6[d]	-5	4 Å MS	40	82
7[d,e]	-5	4 Å MS	42	86

[a] The reaction was performed in 0.26 mL of toluene and 0.13 mmol scale of **1a**, using 1.2 eq. of **2a** for 14h. [b] Isolated product yield of **3a** after flash column chromatography. [c] Determined by HPLC analysis of the pure product. [d] 27 mg of additive was added. [e] Reaction carried out with dry toluene.

When lowering the reaction temperature to -5 ºC the enantioselectivity of the product was slightly increased (Entry 2), though compromising the yield of the process. However, at lower temperature, we could not observe any improvement, affording the product in low yield and even halting the reaction at -20 ºC (Entries 3-4). The use of MgSO$_4$ showed no significant improvement (Entry 5), however, when using 4 Å molecular sieves, the product was obtained with 82% of enantioselectivity, albeit in similar yield (Entry 6). Additionally, when running the reaction with dry toluene, the enantioselectivity was even increased to 86%, though the yield was still an issue to bear in mind (Entry 7).

Depending on the reaction conditions, the generated azo intermediate was not able to reach the final product through [1,3]-hydride shift process at the same rates. Therefore, quenching and purifying the products at longer times, we could improve the enantioselectivity of the process. We carried out different experiments, trying to promote the [1,3]-H shift more rapidly, such as, the addition of acidic additives, however, in all cases the enantioselectivity decreased. We also tested leaving the reaction for longer time, and this was found to be the most optimal choice, without observation of the azo intermediate (Scheme 2.26).
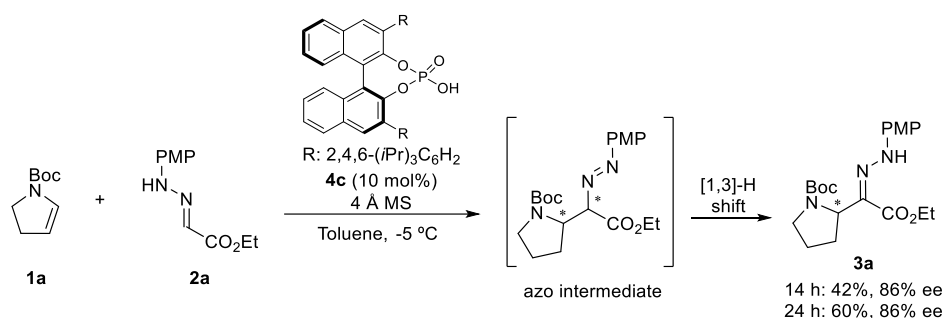
Scheme 2.26

After intensive screening of different concentrations, additives, equivalents, etc. we were unable to improve neither the yield nor the enantioselectivity of the process. So, we decided to optimize the structure of hydrazone and dihydropyrrole reagents (Table 2.4).

Table 2.4: Study of the effect of the structure of the hydrazone and dihydropyrrole.[a]

Entry	R^1	R^2	Prod. 3	Yield 3 (%)[b]	ee 3 (%)[c]
1	Boc (**1a**)	4-OMeC$_6$H$_4$ (**2a**)	**3a**	60	86
2	Boc (**1a**)	4-SMeC$_6$H$_4$ (**2b**)	**3b**	53	92
3	Boc (**1a**)	Ph (**2c**)	**3c**	63	88
4	Boc (**1a**)	4-NO$_2$C$_6$H$_4$ (**2d**)	**3d**	n.r.[d]	n.r.
5	Boc (**1a**)	*t*Bu (**2e**)	**3e**	87	72
6[e]	Boc (**1a**)	Ph (**2c**)	**3c**	96	93
7[f]	Fmoc (**1b**)	Ph (**2c**)	**3f**	93	92
8	Ph (**1c**)	Ph (**2c**)	**3g**	n.r.[d]	n.r.
9[g]	CSNHBn (**1d**)	Ph (**2c**)	**3h**	95	92
10[h]	CSNHAr (**1e**)	Ph (**2c**)	**3i**	98	>99

[a] The reaction was performed in 0.26 mL of dry toluene and 0.13 mmol scale of **1a**, using 1.2 eq. of **2** and 27 mg of MS for 24h. [b] Isolated product yield of **3** after flash column chromatography. [c] Enantioselectivity determined by HPLC analysis of the pure product. [d] No reaction. [e] Reaction carried out with 1.5 eq. of **1a** added in six portions every 1h 30 min and 1.0 eq. of **2c**. [f] Reaction carried out at 10 ºC. [g] dr = 5.8:1. [h] Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$, dr = 5:1.

We checked the behaviour of the reaction when introducing substituents of different nature at the nitrogen position in the hydrazone moiety. With a more electron-donor substituent at the nitrogen atom of the hydrazone, the reaction worked with lower yield, though reaching 92% of enantioselectivity (Entry 2). If we introduced a phenyl ring, the reaction worked with slightly better yield and very good enantioselectivity (Entry 3). However, when using an electron-withdrawing group, the reaction could not take place (Entry 4). If we introduced a *tert*-butyl substituent, the desired adduct was obtained in high yield, albeit with lower enantioselectivity (Entry 5). At this point, however, the yield of the reaction was still an issue to solve and we proceeded to study the effect of other parameters on the reaction like the stoichiometric ratio between different reagents, observing that very good yield and enantioselectivity could be obtained when using hydrazone **2c** as limitant substrate and *N*-Boc-2,3-dihydro-1*H*-pyrrole added in portions (Entry 6). Next, we decided to examine the outcome of the reaction with diverse dihydropyrroles and using hydrazone **2c**. As outlined in Table 2.4, cyclic enecarbamates were able to promote the reaction in excellent yields and enantioselectivities even at 10 ºC for *N*-Fmoc-2,3-dihydro-1*H*-pyrrole **1b** (Entries 6-7). However, when using a phenyl enamine the reaction could not take place (Entry 8). Finally, when employing the cyclic enethiourea **1d**, having an N-H group in the structure for an additional point of interaction with the catalyst, the reaction worked very well, affording the final compound in 98% yield and 92% of enantioselectivity as two diastereoisomers (Entry 9). We realized that the N-H group on the cyclic enethiourea scaffold was responsible for the better results obtained. We considered that the N-H group of the thiourea moiety would form an additional hydrogen-bond with the phosphoryl oxygen of the catalyst, generating a more strongly bound ion pair intermediate to promote higher asymmetric induction. In fact, to our pleasure, we could afford excellent yield in 2 hours and perfect enantioselectivity, though as a mixture of diastereoisomers (Scheme 2.27). However, this was not an issue, because the cleavage of the hydrazone moiety to afford the carbonyl compound is one of the objectives to confirm their usefulness as acyl anion equivalents. Furthermore, when using the more acidic cyclic enethiourea **1e**, the results were improved obtaining the final product with complete enantioselectivity although with 5:1 dr (Entry 10).
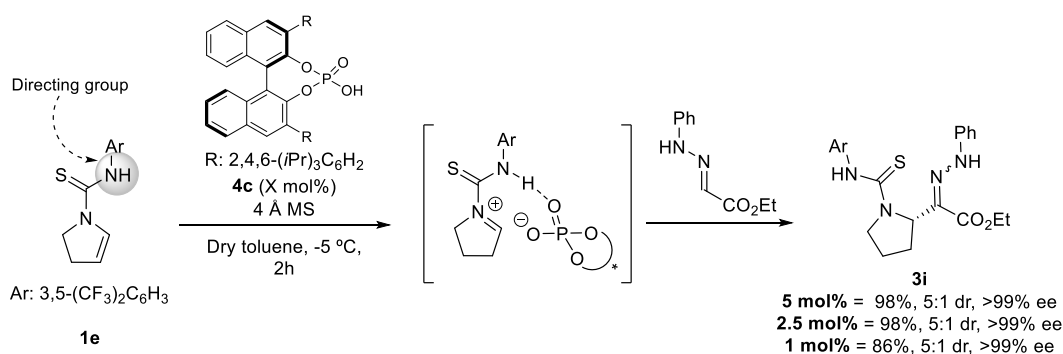
Scheme 2.27

In addition, the reaction could be performed with 5.0 and 2.5 mol% of catalyst without erosion of yield or enantioselectivity, and the amount of catalyst could be reduced to 1 mol% affording the product in 86% yield and >99% ee. Therefore, the optimal conditions were established to be 5 mol% of catalyst **4c**, in dry toluene, at -5 ºC and in the presence of 4 Å MS.

3.3. Scope and limitations

At this point, and having established the optimal protocol for the 1,2-addition reaction of hydrazones to cyclic enethioureas, we decided to extend the methodology to differently substituted reagents.

Table 2.5: Scope of the reaction with hydrazones substituted at nitrogen atom.[a]

Entry	R[1]	Prod. 3	Yield 3 (%)[b]	dr 3 (Z/E)[c]	ee 3 (%)[d]
1	Ph (**2c**)	**3i**	98	5:1	>99
2	4-OMeC$_6$H$_4$ (**2a**)	**3j**	85	6.7:1	98
3	*t*Bu (**2e**)	**3k**	80	>20:1	91

[a] The reaction was performed in 0.18 mL of dry toluene and 0.09 mmol scale of **2**, using 1.5 eq. of **1e** and 18 mg of MS. [b] Isolated product yield of **3** after flash column chromatography. [c] Determined by ^{1}H NMR analysis of the pure product. [d] Enantioselectivity determined by HPLC analysis of the pure product.

Aromatic or alkyl substituents with electron-donating character in the nitrogen position of the hydrazone were well tolerated achieving the desired product in very good yield and excellent enantioselectivity (Entries 2-3).

Next, we evaluated different hydrazones, but in this case with substituents of different nature at the azomethine position as shown in Table 2.6.

Table 2.6: Scope of the reaction using cyclic enethiourea **1e** and different hydrazones.[a]
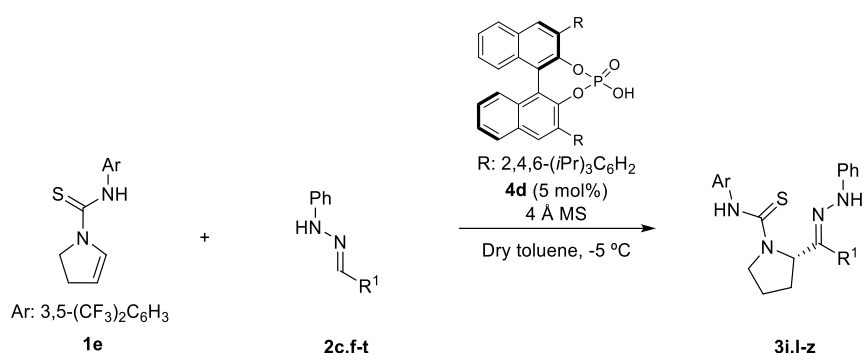
Entry	R^1	Prod. 3	Yield 3 (%)[b]	dr 3 (Z/E)[c]	ee 3 (%)[d]
1	CO_2Et (**2c**)	**3i**	98	5:1	>99
2	CO_2iPr (**2f**)	**3l**	87	7.8:1	99
3	COMe (**2g**)	**3m**	87	1:10	98
4	CF_3 (**2h**)	**3n**	73	16:1	99
5	C_6F_5 (**2i**)	**3o**	n.r.[f]	n.r.	n.r.
6[e]	C_6F_5 (**2i**)	**3o**	78	>20:1	97
7[e]	$4\text{-}CNC_6H_4$ (**2j**)	**3p**	90	1.4:1	88
8[e]	$4\text{-}CF_3C_6H_4$ (**2k**)	**3q**	60	2:1	86
9[e]	$4\text{-}CO_2MeC_6H_4$ (**2l**)	**3r**	65	2:1	83
10[e]	$4\text{-}BrC_6H_4$ (**2m**)	**3s**	79	3.2:1	92
11[e]	$4\text{-}ClC_6H_4$ (**2n**)	**3t**	82	3.4:1	90
12[e]	$4\text{-}FC_6H_4$ (**2o**)	**3u**	95	4:1	94
13[e]	$3\text{-}FC_6H_4$ (**2p**)	**3v**	80	3:1	84
14[e]	$2\text{-}FC_6H_4$ (**2q**)	**3w**	94	8.4:1	82
15[e]	Ph (**2r**)	**3x**	94	4.5:1	90
16[e]	$4\text{-}MeC_6H_4$ (**2s**)	**3y**	83	5.5:1	91
17[e]	$4\text{-}OMeC_6H_4$ (**2t**)	**3z**	60	6.2:1	83

[a] The reaction was performed in 0.18 mL of dry toluene and 0.09 mmol scale of **2**, using 1.5 eq. of **1e** and 18 mg of MS.[b] Isolated product yield of **3** after flash column chromatography.[c] Determined by ^1H NMR analysis of the pure product.[d] Enantioselectivity determined by HPLC analysis of the pure product.[f] No reaction.

As it was expected, electron-withdrawing groups at the azomethine position of the hydrazone worked perfectly, being feasible to introduce a bulkier substituent (Entry 2), even different functional groups such as a ketone (Entry 3) or a trifluoromethyl group (Entry 4). Moreover, electron-withdrawing aromatic substituents are tolerated as well, although this time 10 mol% of catalyst was necessary to use in order to obtain the desired product (Entry 5 *vs* Entry 6). Regardless the electronic nature (Entries 6-12) or the substitution pattern (Entries 13-14) in the aromatic ring of the hydrazone at the azomethine position, in all the cases the desired products **3** were obtained with excellent results. Gratifyingly, even more challenging substrates worked well, being possible to introduce phenyl (Entry 15) or electron-donating groups (Entries 16-17) achieving the final products with excellent results.

Next, we turned our attention to the use of different cyclic enethioureas, as it is shown in a The reaction was performed in 0.18 mL of dry toluene and 0.09 mmol scale of **2b**, using 1.5 eq. of **1** and 18 mg of MS. Isolated product yield of **3** after flash column chromatography, dr determined by ^{1}H NMR analysis of the pure product and ee determined by HPLC analysis of the pure product.[b] Reaction carried out with the same reaction conditions but with 10 mol% of catalyst **4c**.[c] dr (**3ab:3ab'**) = 3.2:1.[c] dr (**3ac:3ac'**) = 2.5:1.[d] No reaction.[e] Reaction carried out at rt for 7 days with single addition of **1j**.[f] Reaction carried out at rt by addition of **1k** during 2 days.

Scheme 2.*28*. The cyclic enethiourea with two methyl groups in C4-position (**1f**) showed excellent yield and stereoinduction. Remarkably, when an alkyl substituent was introduced in C3-position of the ring (**1g** and **1h**), a second stereogenic centre is formed achieving the desired products in good yields and very good enantioselectivities, albeit as a mixture of diastereoisomers regarding the new C3-stereogenic centre formed. However, the reaction showed a limitation when modifying the ring size of the electrophile, and with a bigger six member ring, it was impossible to obtain the product, regardless the substitution of the nitrogen atom (enethiourea **1i** or Boc **1j**). Even when seven member ring *N*-Boc-2,3,4,5-tetrahydro-1*H*-azepine **1k**, in the optimized reaction conditions was used the starting material was recovered. After screening of different experimental parameters, the product **3ae** could be obtained in low yield and low enantioselectivity performing the reaction at room temperature. Similarly, cyclic enecarbamate **1k** was able to react with hydrazone **2b**, affording the desired hydrazone **3ag** in 76% yield, but 51% of enantioselectivity. These results could not be improved in any case, showing the limitation of the reaction regarding different ring sizes.

R: 2,4,6-(iPr)$_3$C$_6$H$_2$

4c (5 mol%)
4 Å MS

Dry toluene, -5 ºC

1e-i   **2b-c**   **3i,aa-af**

Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$

3i[a]
98%, >99% ee
5:1 dr

3aa[a]
89%, >99% ee
3:1 dr

3ab[b]
60%, 94/97% ee
1.1:1 dr[c]

3ac[b]
89%, 84/>99% ee
1:1 dr[c]

3ad[b]
n.r.[d]

3ae[b]
-5 ºC = n.r.[d]
25 ºC = 31%, 35% ee[e]

3af[b]
-5 ºC = n.r.[d]
25 ºC = 76%, 51% ee[f]

[a] The reaction was performed in 0.18 mL of dry toluene and 0.09 mmol scale of **2b**, using 1.5 eq. of **1** and 18 mg of MS. Isolated product yield of **3** after flash column chromatography, dr determined by ^{1}H NMR analysis of the pure product and ee determined by HPLC analysis of the pure product. [b] Reaction carried out with the same reaction conditions but with 10 mol% of catalyst **4c**. [c] dr (**3ab:3ab'**) = 3.2:1. [c] dr (**3ac:3ac'**) = 2.5:1. [d] No reaction. [e] Reaction carried out at rt for 7 days with single addition of **1j**. [f] Reaction carried out at rt by addition of **1k** during 2 days.

Scheme 2.28

In addition, it should be mentioned that the reaction could be performed in a bigger scale without erosion in yield or enantioselectivity (Scheme 2.29-top), and moreover, it was possible to carry out the reaction in a sequential manner in high yield and enantioselectivity by synthesizing the hydrazone *in situ.* (Scheme 2.29-bottom).
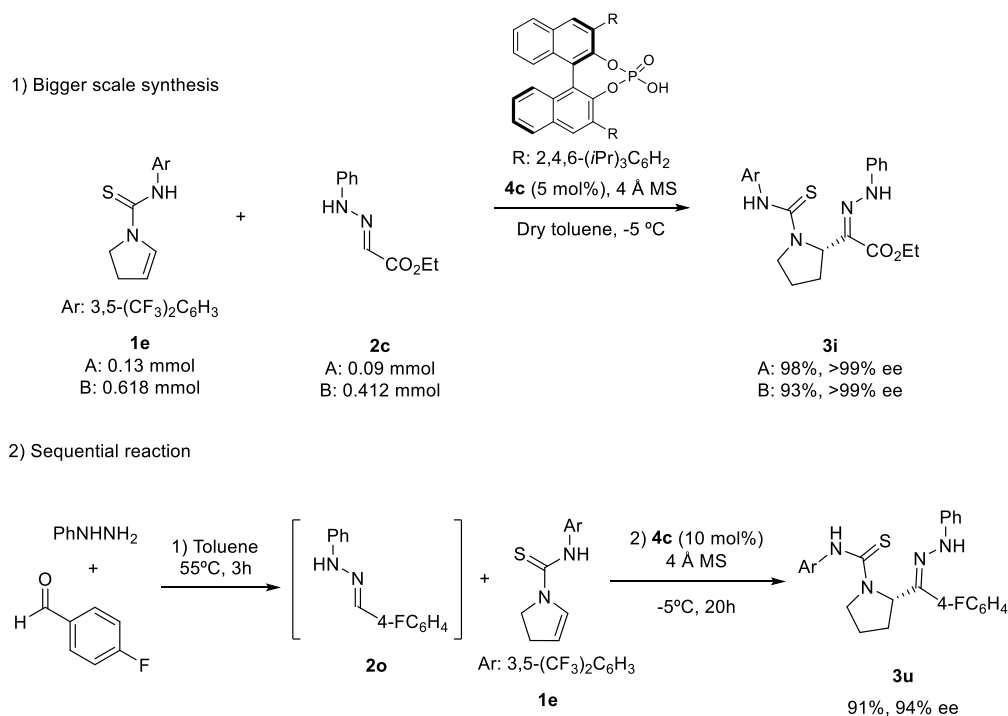
Scheme 2.29

All the products of this reaction were isolated as solids, and the hydrazone **3m** could be recrystallized, determining the absolute configuration by single crystal X-ray analysis. The absolute stereochemical outcome showed a (*S*) configuration of the minor diastereisomer. The absolute configuration of all adducts **3h-ac** obtained by this method were tentatively assigned by analogy (Figure 2.7).
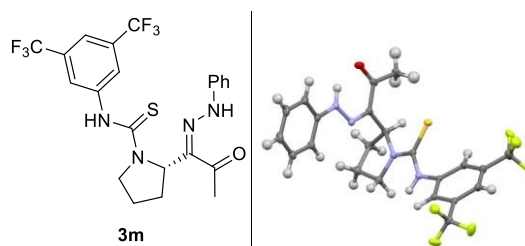
Figure 2.7

In the case of products **3ab-ac**, where a new stereogenic centre was formed at C3, a NOESY experiment was performed to confirm the relative configuration of these adducts. The

presence of n.O.e signal between the protons in C2- and C3-positions of the cyclic ene-thiourea indicated a (2*S*,3*R*) configuration of the major diastereoisomer (Figure 2.8).[46]

R = Me (**3ab**)
R = Et (**3ac**)
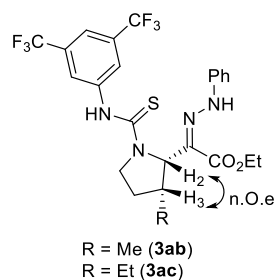
Figure 2.8

3.4. Transformation of the adducts

Having developed a successful protocol for the enantioselective 1,2-addition reaction of hydrazones to cyclic enethioureas, we proceeded to address our final goal of derivatizing the adducts to afford different structural products and prove the ability of hydrazones to act as acyl anion equivalents. For this purpose, we started to evaluate the oxidative and hydrolytic cleavage of hydrazones extensively used for the generation of carbonyl compounds. Several acidic and basic hydrolysis protocols were surveyed, but whereas less acidic reagents resulted in the recovery of unreacted starting material, harder conditions or more acidic ones, unmasked hydrazone in low yield and at the expense of the stereogenic centre. However, the use of oxalic acid resulted in the cleavage of hydrazone **3k**, though obtaining the adduct **5a** in low yield and as a racemic mixture, possibly due to keto-enol tautomerization (Scheme 2.30).

Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$
3k

(HCO$_2$)$_2$ ·H$_2$O
(5 eq.)
THF, reflux

5a
47%, 0% ee
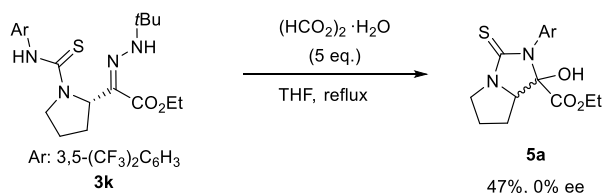
Scheme 2.30

Numerous oxidative reagents were tested as well, including hypervalent iodine reagents, ozonolysis, *m*CPBA, peracetic acids, etc. Ozonolysis, widely apply for the cleavage of *N,N'*-

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[46] See experimental section.

dialkylhydrazones was ineffective with our hydrazones, achieving most of the times decomposition of the starting material. With the most oxidants, however, the cyclization of the adduct was observed due to the increase electrophility of the hydrazone azomethine carbon when the hypervalent iodine reagent links to the hydrazone framework. The best results were obtained using bis(trifluoroacetoxy)iodobenzene (PIFA) as the oxidant, obtaining the bicyclic products in good yield, as a single diastereoisomer and maintaining the high enantioselectivity (Scheme 2.31). Moreover, this new formed adduct (**6a**) could be derivatize even further obtaining the product **7a** in high yield and with complete enantiocontrol after decarboxylation promoted by a base.

Ar: 3,5-(CF$_3$)$_2$C$_6$H$_3$

3i,x

6a-b
R^1 = CO$_2$Et, 73%, >99% ee, > 20:1 dr
R^1 = Ph, 90%, 90% ee, dr > 20:1

7a
R^1 = CO$_2$Et
88%, >99% ee, dr >20:1
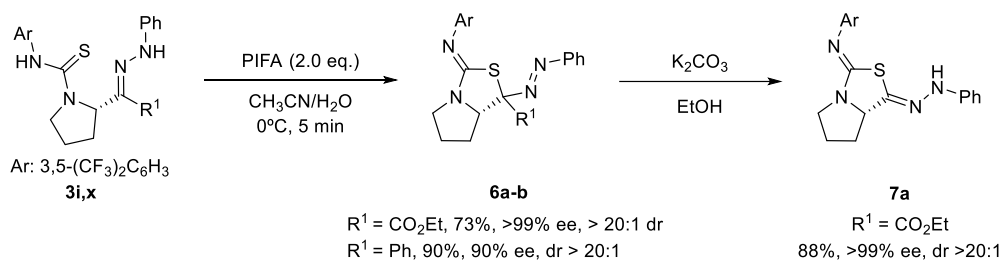
Scheme 2.31

At this point and having seen that the hydrazone was susceptible of cyclization, we decided to protect the N-H group of the thiourea moiety by addition of methyl iodide. As depicted in Scheme 2.32, S-H group of the thiourea was protected in high yield and enantioselectively, avoiding the previous cyclization in the next step. When using TMSOK as reagent **9a** was afforded in good yield but with loss of enantioselectivity. When employing *N*-bromosuccinimide as oxidative reagent, however, product **10a** was achieved in moderate yield, but without erosion of enantioselectivity (Scheme 2.32).
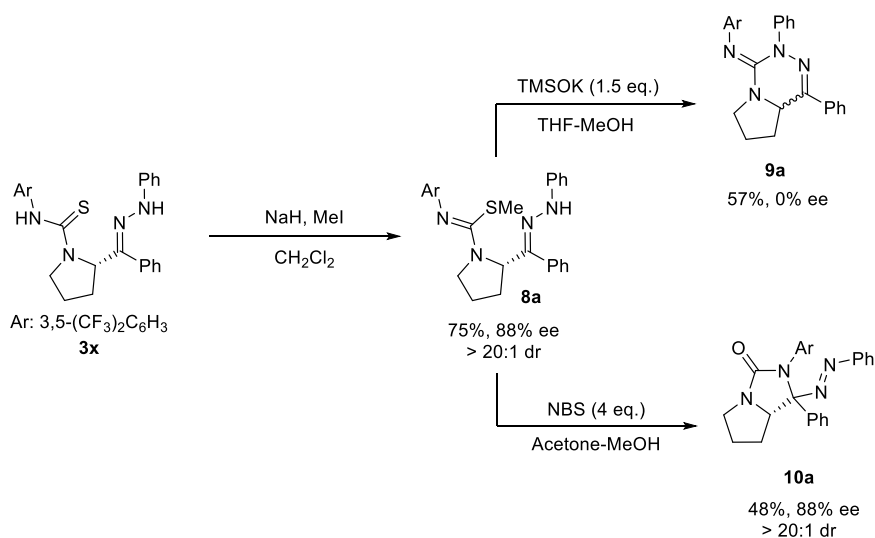
Scheme 2.32

Unexpectedly, when the previous methylation conditions were applied to **3i** instead of taking place the methylation of the thiourea group, a new intramolecular addition occurred by action of the sodium hydride, enabling the reaction between the N-H group of the thiourea and the carboxylate, achieving product **11a** quantitatively. When this adduct was subjected to the conditions reported by Barton and co-workers,[47] an intermediate product **12a** was afforded, that could be transformed to the parent carbonyl function by action of PIFA again, achieving the cleavage of hydrazone moiety and affording the final α-ketoamide pyrrolidine structure **13a** in very good yield and preserving the high enantioselectivity (Scheme 2.33).

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[47] Barton, D. H. R.; Jaszberenyi, J. C.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52*, 14673.
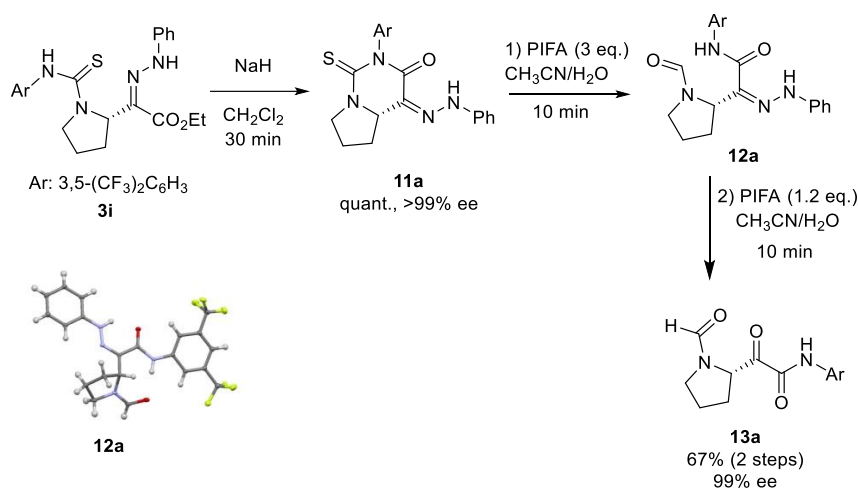
Scheme 2.33

The structure of compound **12a** could be confirmed by single crystal X-ray analysis. It should be mentioned that the conditions of the conversion of **11a** into **12a** and **12a** into **13a** were identical, however, when running the reaction in a single step the yield of the final product **13a** was compromised, indicating that the product was not stable at harsh acidic conditions. As a consequence, we decided to carry out the reaction in two steps, without the purification of product **12a**.

Once a suitable methodology for the cleavage of hydrazone functionality was accomplished, it was applied to a set of hydrazones **3** (Table 2.7). Gratifyingly, the designed sequence was able to proceed efficiently for all the hydrazones tested, providing the final carbonyl compounds in high overall yields and maintaining the high levels of enantioselectivity. It should be pointed out, that the isolated final compounds tend to racemize with the time due to keto-enol tautomerization. This might be the reason why compound **13b** suffered a slight erosion in enantioselectivity from >99 to 90% ee (Entry 4).

Table 2.7: Regeneration of the carbonyl compound.
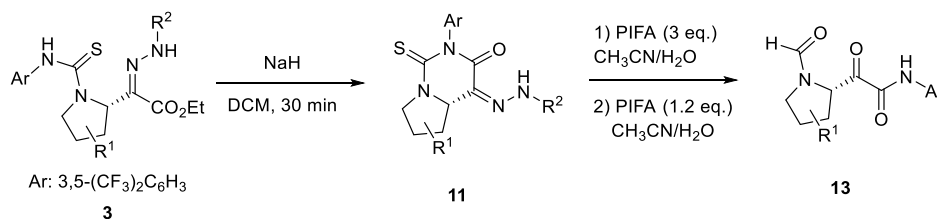
Entry	R^1	R^2	Yield 11 (%)^a	ee 11 (%)^b	Yield 13 (%)^a	ee 13 (%)^b
1	H	Ph (**3i**)	>99 (**11a**)	>99	67(**13a**)	99
2	H	PMP (**3j**)	>99 (**11b**)	96	62 (**13a**)	n.d.^{c}
3	H	*t*Bu (**3k**)	91 (**11c**)	87	60 (**13a**)	n.d.^{c}
4	4,4-(Me)$_2$	Ph (**3aa**)	>99 (**11d**)	>99	63 (**13b**)	90
5	3-(Me)	Ph (**3ab**)	96^d (**11e**)	96	60^d (**13c**)	96

^{a} Isolated product yield of after flash column chromatography. ^{b} Determined by HPLC analysis of the pure product. ^{c} Determined by ^{1}H NMR analysis of the pure product. ^{c} Not determined. ^{d} dr = 3:1.

3.5. Mechanistic proposal

Based on previously explained mechanistic considerations on this activation mode and the obtained stereochemical outcome of the adducts, we propose the general mechanistic pathway presented in Scheme 2.34. The chiral phosphoric acid activates the dihydropyrrole derivative by protonation generating the contact ion pair with the phosphate anion and forming the *N*-thioacyliminium ion **I**. This intermediate is attacked by the azomethine carbon of the hydrazone in a chiral environment due to the close chiral phosphate, affording the azo intermediate **II** and the regeneration of the catalyst. After the [1,3]-hydride shift process of the azo compound, the most stable diastereoisomer of the desired hydrazone product is released.
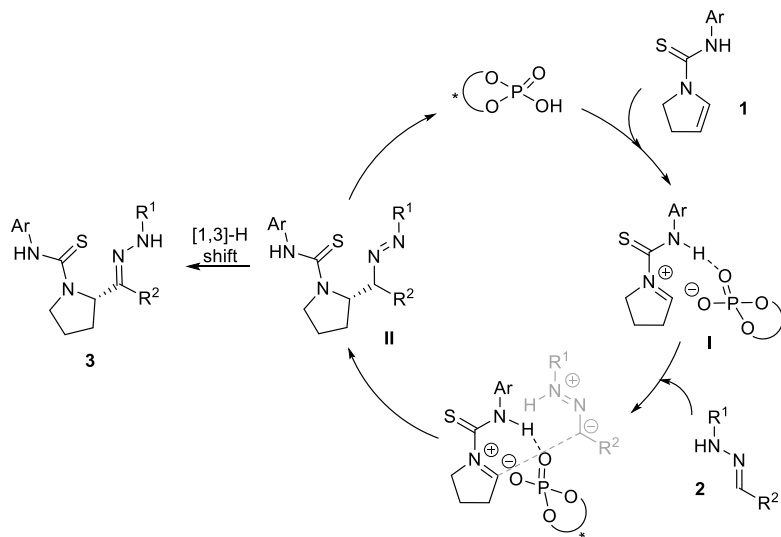
Scheme 2.34

In order to explain the absolute configuration of the adducts **3**, we proposed the approach depicted in Figure 2.9, based on the previous model proposed by Huang and co-workers.[48] In the case of cyclic enethiourea, besides the protonation of the cyclic enamide generating the contact ion pair, its acidic N-H group established a hydrogen-bond with the lewis base site of the catalyst in a dual activation manner. The chiral environment generated by the BINOL backbone and the substituents at the 3,3'-position of the catalyst **4c** leave the *Re* face exposed for the addition of the hydrazone from the top face to furnish the enantioenriched *S*-configured product.
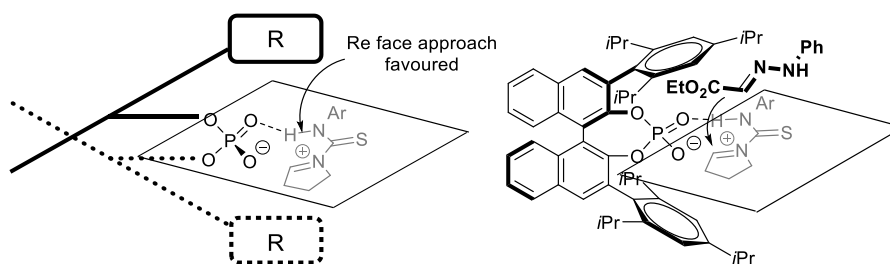
Figure 2.9

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[48] Xie, Y.; Zhao, Y.; Quian, B.; Yang, L.; Xia, C.; Huang, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5682.

For the cases with substitution at the C3-position of the cyclic enethiourea moiety (**3ad** and **3ae**), the relative configuration of the products was assigned to be (2*S*,3*R*), where the two susbtituents of the thiourea structure are placed in the same direction. This configuration could be explained by using the same model system as the one explained above, were the addition of the hydrazone happened from the less hindered face of the catalyst, in this case, the top face. With the enethiourea substrates containing a methyl or ethyl group at C3-carbon, we postulated that the configuration of this carbon will be controlled in the addition step, where the substituent will be placed in the top to avoid destabilizing interactions between the C3-substituent with the 3,3'-substituent of the catalyst (Figure 2.10). Hence, the major isomer will correspond to the product with the configuration (2*S*,3*R*).
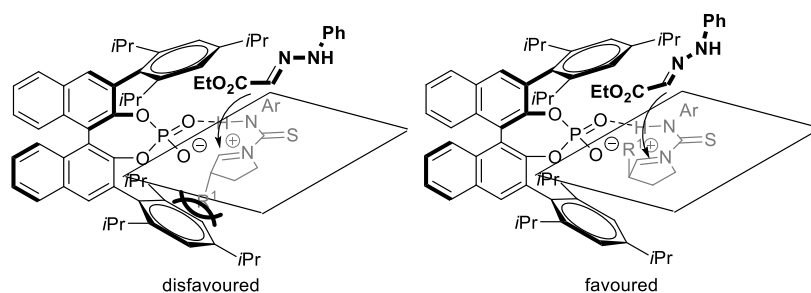
Figure 2.10

4. CONCLUSIONS

Considering the results presented throughout this chapter, the following conclusions can be settled:

1. Chiral Brønsted acid catalysis is an efficient methodology for the activation of cyclic enethioureas and enecarbamates to act as *N*-(thio)acyl iminium ions in asymmetric transformations.

2. Chiral BINOL-derived phosphoric acid catalyst **4d** is the most appropriate one to carry out the reaction in high yields and enantioselectivities.

3. *N*-Monosubstituted hydrazones with substituents of different nature have been proved to be suitable reagents for the addition to cyclic *N*-(thio)acyl iminium ions acting as C nucleophiles providing the final adducts with high optical purity.

4. The 1,2-addition of hydrazones to cyclic enethioureas is an efficient methodology for the construction of enantioenriched α-substituted pyrrolidine derivatives.

5. Hydrazones have been transformed into their parent carbonyl compounds by a simple procedure under mild conditions, confirming their usefulness as acyl anion equivalents.

3

3

Aminocatalytic Vinylogous Iminium Ion Strategy in Organocascade Reactions

1. REMOTE FUNCTIONALIZATION IN AMINOCATALYSIS

In 1926, Ludwig Claisen proposed the concept of vinylogy to explain the acidic properties of formylacetone and β-keto aldehydes.[1] This concept was then further developed by Reynold C. Fuson in 1935.[2] He postulated that a functional group is able to influence the remote points of a molecule when it is conjugated by double bonds. Thus, the principle of vinylogy can be defined as the transmission of electronic effects associated to a functional group through a conjugated π-system. The vinylogy principle has been essential to understand the behaviour of different functional groups and has been the responsible for the expansion of organic reactions giving the opportunity to functionalize remote points of a given molecule.[3] In this sense, numerous vinylogous reactions can be found in the literature that illustrate the possibility to access structures with high level of complexity.

Taking into account the reactivity profile of aminocatalytic activation manifolds (enamine and iminium catalysis) and the vinylogy principle, it was a matter of time for these two concepts to come together. Therefore, by the combination of enamine catalysis and iminium ion catalysis with the vinylogous theory, diverse activation modes have emerged, such as dienaminocatalysis,[4] trienaminocatalysis[5] and vinylogous iminium ion

[1] Claisen, L. *Ber.* **1926**, *59*, 144.

[2] Fuson, R. C.; *Chem. Rev.* **1935**, *16*, 1.

[3] For some reviews on vinylogy, see: a) Krishnamurthy, S. *J. Chem. Educ.* **1982**, 59, 543; b) Bruneau, P.; Taylor, P. J.; Wilkinson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2263.

[4] For some reviews in dienamine catalysis, see: a) Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812; b) Fraile, A.; Alemán, J. *Synlett* **2015**, *26*, 1940; c) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865; for a review on vinylogous organocascade reactions, see: d) Hepburn, H. B.; Dell´Amico, L.; Melchiorre, P. *Chem. Rec.* **2016**, *16*, 1787.

[5] For some reviews in trienamine catalysis, see: a) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709; (c) Xiong, X.-F.; Zhou, Q.; G, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401; (d) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-Y.; Jørgensen K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053; For some examples, see: e) Donslund, B. S.; Nielsen, R. P.; Mønsted, S. M. N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2016**, *129*, 12290; f) Li, Y.; López-Delgado, F. J.; Jørgensen, D. K. B.; Nielsen, R. P.; Jiang, H.; Jørgensen, K. A.; *Chem. Commun.* **2014**, *50*, 15689; g) Zhou, Z.; Feng, X.; Yin, X.; Chen, Y. –C. *Org. Lett.* **2014**, *16*, 2370.

catalysis,[6] allowing the direct functionalization of polyunsaturated carbonyl compounds at remote positions with efficient control of the new stereocentres formed (Figure 3.1).[7]
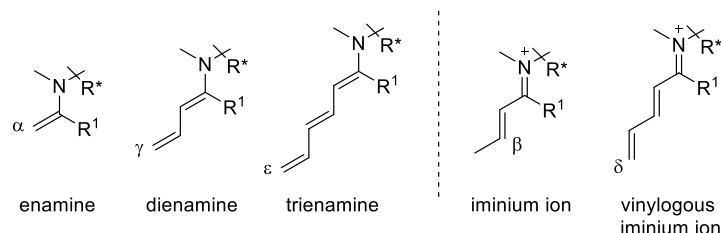
Figure 3.1

1.1 Vinylogous Enamine Activation

Until date, nucleophilic vinylogy is the concept that has found more extensive use in aminocatalytic reactions. Dienamine catalysis is the most studied activation manifold, and since its discovery, numerous organic transformations have been possible to carry out applying this methodology. In this strategy, enones and α,β-unsaturated aldehydes are activated by the HOMO-raising effect through the conjugated π-system, forming a nucleophilic dienamine intermediate capable of reacting with electron-poor substrates. The condensation of a primary or secondary amine catalyst with γ-enolizable α,β-unsaturated carbonyl compounds forms iminium ion that, after γ-deprotonation, leads to a dienamine intermediate ready to react with an electrophile at the γ-position. After hydrolysis of the formed iminium ion, the γ-functionalized product will be released and the catalyst will be regenerated to restart another catalytic cycle (Scheme 3.1).

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[6] a) Chauhan, P.; Kaya, U.; Enders, D. *Adv. Synth. Catal.* **2017**, *359*, 888; b) Lear, M. J.; Hayashi, Y. *ChemCatChem* **2013**, *5*, 3499.

[7] For reviews combining the vinylogy principle with aminocatalysis, see: a) Jurberg, I. D; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869; b) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287; c) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.
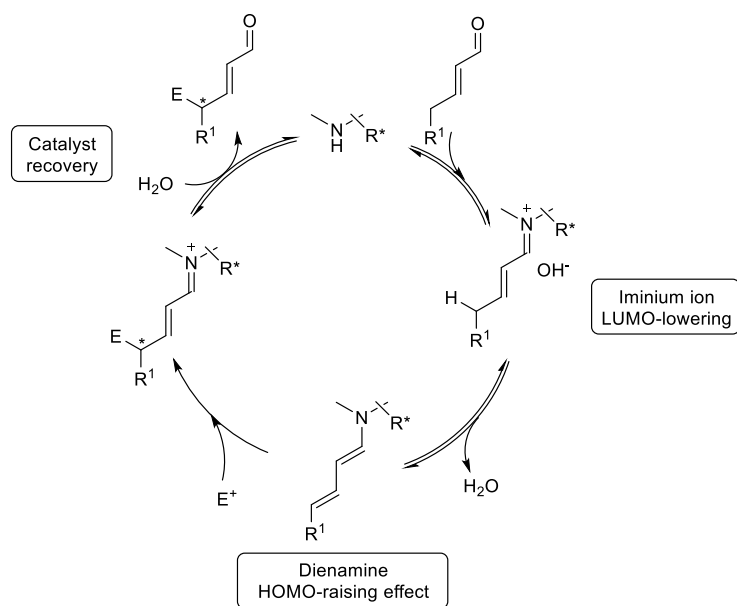
Scheme 3.1

In dienamine catalysis controlling the regioselectivity of the reaction is crucial. In fact, once dienamines are formed, there are different reactive points able to interact with the electrophile due to the polydentate nature of this type of nucleophiles. One of the possibilities is to act *via* enamine pathway to get an α-substituted product. Another possibility is the formation of the γ-substituted product and the third possibility is to participate as an electron-rich diene in a typical [4+2]-cycloaddition reaction that leads to simultaneous *ipso*- and γ-functionalization. The last possibility is the functionalization at the more remote double bond of the dienamine intermediate through β,γ-functionalization, for example acting as an electron-rich alkene that undergoes cycloaddition reactions with dienes or dipoles (Scheme 3.2).

Dienamine reactivity

α-functionalization

ipso,γ-functionalization

γ-functionalization

β,γ-functionalization
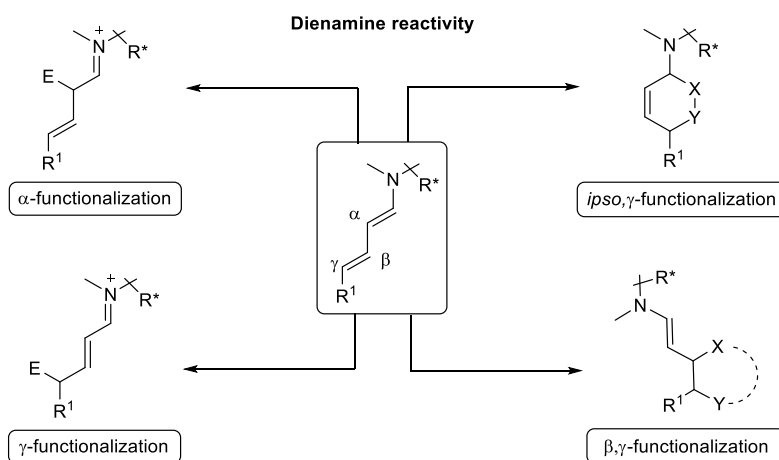
Scheme 3.2

A good example of the reactivity at α- and γ-position was shown by the group of Christmann in 2011. The competition of α- and γ-alkylation of differently substituted α,β-unsaturated aldehydes using stabilized cations as electrophiles was reported employing prolinol-derived catalysts. From these work it was concluded that α-alkylation was favoured when γ-disubstituents were present in the aldehyde, obtaining the corresponding adducts with high enantioselectivities. Alternatively, γ-alkylation was favoured with linear or β-substituted enals, obtaining the corresponding adducts with moderate enantioselectivities (Scheme 3.3).[8]

R^1 = H; R^2 = Me; R^3 = Ph   84%, 73% ee, α/γ: >95/5

R^1 = H; R^2 = R^3 = Me   65%, 93%, ee, α/γ: 78/22

R^1 = R^2 = H; R^3 = Et   48%, 76% ee, α/γ: 17/83

Scheme 3.3
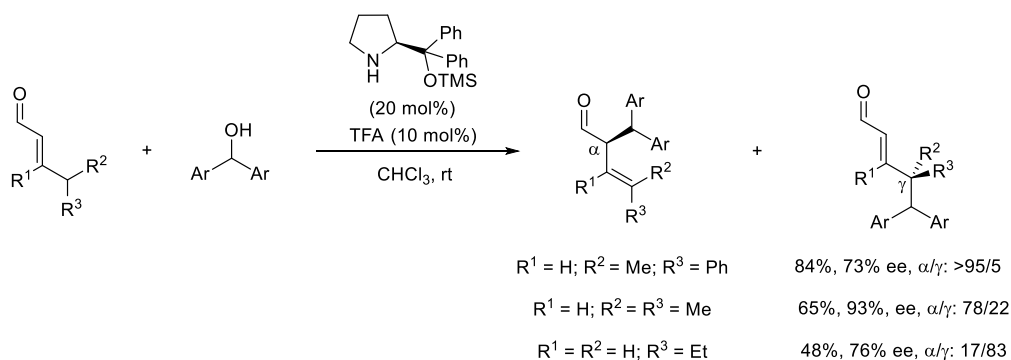
In a similar work, and simultaneously, Melchiorre developed the S_N1-alkylation at γ-position of α-branched enals employing a related type of catalyst. In this case, the observed

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8   Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70.

perfect γ-site selectivity was due to the presence of an α-substituent in the aldehyde.[9] Based on NMR and computational studies the enantioselectivity of the process was explained as a result of the catalyst shielding, as well as the preferential conformation of unsaturated system at dienamine intermediate. Hence, α-branched enals have the appropriate properties to bias the dienamine geometry, making it adopt (*E*)-s-trans-(*E*) conformation predominantly and promoting the alkylation for one face, obtaining high enantioselectivities (Scheme 3.4).
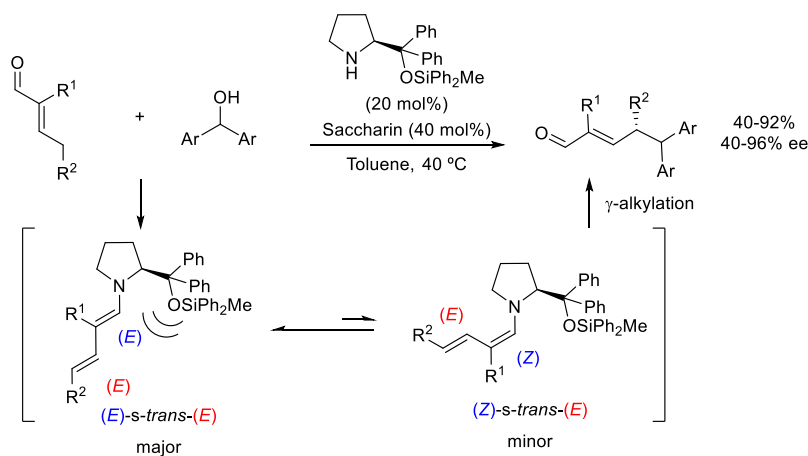
Scheme 3.4

Very recently, Gschwind and colleagues rationalized the enantioselectivities obtained for this type of reactions. Based on NMR studies and theoretical calculations, the kinetics/thermodynamics in the formation of dienamine intermediate was described, concluding that the responsible for the high enantioselectivity obtained is the control of configuration of the remote double bond (*Z* or *E*) as well as the ability of the catalyst for steric shielding of one of the stereogenic faces. The preferred conformations of the dienamine intermediates were found to be (*E*)-s-trans-(*Z*) and (*E*)-s-trans-(*E*) in a 2:1 ratio (*Z/E*), independent of catalyst structure. However, the theoretical and experimental investigations revealed that the main stereodiscrimination is promoted in the adduct formation step, through kinetic preference of the *Z* dienamine to undergo reaction with the electrophile through its less hindered face (Scheme 3.5).[10]

[9] Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. *Helv. Chim. Acta* **2012**, *95*, 1985. For a previous work using a primary amine as catalyst see: Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685.

[10] Seegerer, A; Hioe, J.; Hammer, M. M.; Morana, F.; Fuchs, P. J. W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 9864.
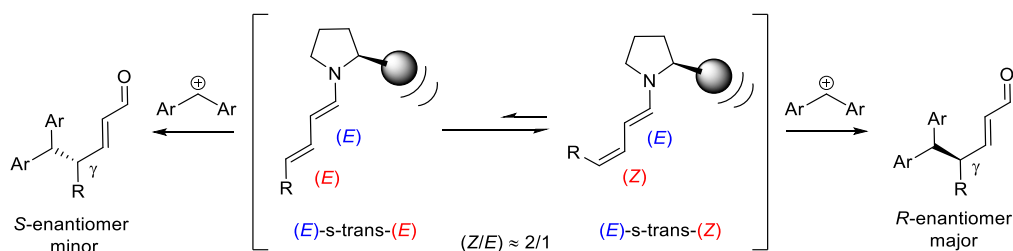
Scheme 3.5

The first example of dienaminocatalysis with *ipso*,γ-functionalization was established in 2006 with the publication of Prof. K. A. Jørgensen and co-workers.[11] In this pioneering work, the enantioselective addition of α,β-unsaturated aldehydes to diethyl azodicarboxylate (DEAD) in the presence of diaryl prolinol-derived catalyst was reported, obtaining the corresponding γ-amination products in good yields and high enantioselectivities (Scheme 3.6).[12] The participation of the dienamine intermediate as electron rich diene undergoing Diels-Alder reaction was key to achieve high stereocontrol because the required s-cis conformation of the diene implies that all issues regarding the high degree of conformational freedom associated to the dienamine intermediate become irrelevant.
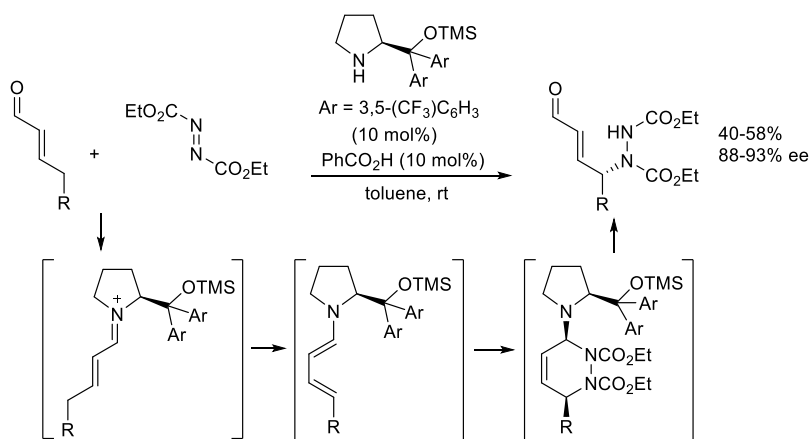
Scheme 3.6

[11] S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[12] For other early works involving dienamine catalysis, see: a) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao J.-J. *Org. Lett.* **2006**, *8*, 2217; b) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458; c) Chen, S.-H.; Hong, B. –C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 8899.

Soon afterwards, the group of Christmann developed an intramolecular asymmetric Diels-Alder reaction under this activation manifold. As it can be seen in Scheme 3.7, the selected starting material underwent clean reaction in the presence of catalytic amounts of diphenyl prolinol trimethylsilyl ether.[13] The catalyst was able to promote the reaction with high enantioselectivities providing an effective facial discrimination of the two stereotopic faces of the dienamine intermediate by steric shielding.
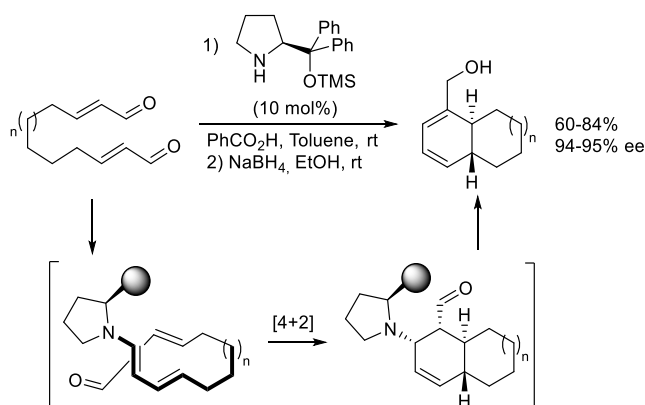
Scheme 3.7

Finally, and regarding the last possibility that dienamine activation offers, the utility of this activation strategy has been extended to the β,γ-functionalization of carbonyl compounds. In particular, the nature of the terminal C=C bond of the dienamine intermediate can be considered as a electron-rich alkene with the potential to participate in cycloaddition reactions with dienes or 1,3-dipoles under inverse electron demand. One representative example of this chemistry is the hetero-Diels-Alder reaction between linear enals and β,γ-unsaturated-α-ketoesters to generate six-member rings in good yields and very good enantioselectivities (Scheme 3.8). Key for the success of this transformation was the use of a bifunctional catalyst that, in addition to activate the enal through dienamine formation, is able to interact with the oxodiene counterpart by hydrogen-bonding. This catalyst was able to approach the two substrates in an efficient way to promote the reaction with high levels of enantioselectivities (Scheme 3.8).[14]

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[13] de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450. For computational studies, see: Duarte, F. J. S.; Gil Santos, A. *J. Org. Chem.* **2012**, *77*, 3252.

[14] Albrecht, Ł.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109.
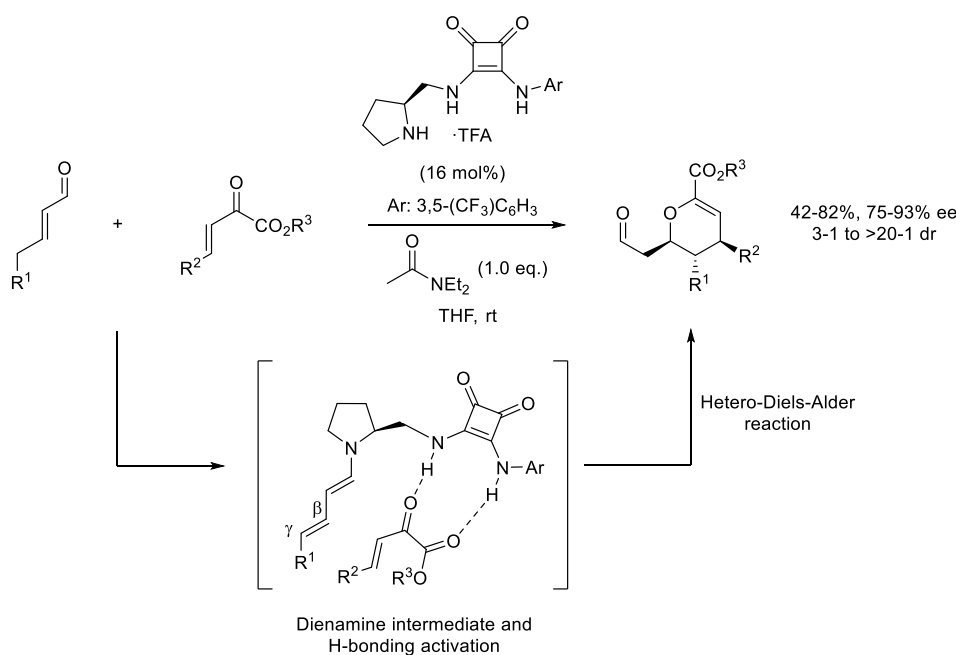
Scheme 3.8

Afterwards, many other cycloaddition reactions have emerged due to the possibilities that this activation mode exhibits, constituting a relevant synthetic methodology for chemistry community. In addition to other related examples of Diels-Alder reactions,[15] [2+2]-,[16] [3+2]-,[17] and [5+2]-cycloadditions[18] have also been reported.

[15] a) Martín-Santos, C.; Jarava-Barrera, C.; del Pozo, S.; Parra, A.; Díaz-Tendero, S.; Mas-Ballesté, R.; Cabrera, S.; Alemán, J. *Angew. Chem., Int. Ed.*, **2014**, *53*, 8184; b) Wang, Z.-Y.; Wong, W.-T.; Yang, D. *Org. Lett.* **2013**,*15*, 4980; c) Ransborg, L. K.; Overgaard, M.; Hejmanowska, J.; Barfüsser, S.; Jørgensen, K. A.; Albrecht, Ł. *Org. Lett.* **2014**, *16*, 4182; d) Halskov, K. S.; Donslund, B. S.; Barfüsser, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 4137; e) Song, A.; Zhang, X.; Song, X.; Chen, X.; Yu, C.; Huang, H.; Li, H.; Wang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 4940; f) Johansen, T. K.; Villegas Gómez, C.; Bak, J. R.; Davis, R. L.; Jørgensen, K. A. *Chem. Eur. J.* **2013**, *19*, 16518; g) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740; h) Hong, B.-C.; Tseng, H.-C.; Chen, S.-H.; *Tetrahedron* **2007**, *63*, 2840; i) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe C. M. H.; *J. Org. Chem.* **2006**, *71*, 9458; j) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217.

[16] a) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685; b) Qi, L.-W.; Yang, Y.; Gui, Y.-Y.; Zhang, Y.; Chen, F.; Tian, F.; Peng, L.; Wang, L.-X. *Org. Lett.* **2014**, 16, 6436; c) Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543; d) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4104.

[17] a) Alemán, J.; Fraile, A. *Synlett* **2015**, 1940; b) Li, W.; Wei, J.; Jia, Q.; Du, Z.; Zhang, K.; Wang, J. *Chem. Eur. J.* **2014**, *20*, 6592; c) Izquierdo, C.; Esteban, F.; Parra, A.; Alfaro, R.; Alemán, J.; Fraile, A.; García Ruano, J. L. *J. Org. Chem.* **2014**, *79*, 10417.

[18] Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3043.

Moreover, and trying to design more sophisticated variants, trienaminocatalysis emerged as a possibility to for promoting the functionalization of unsaturated substrates in a more remote ε-position.5 The first example employing this novel activation strategy was developed by the groups of Chen and Jørgensen in a collaborative project, introducing the first aminocatalytic Diels-Alder reaction between 2,4-hexadienal and 3-alkenyl oxindoles under secondary chiral amine catalysis, furnishing spirocyclic oxindoles in high yields, diastereoslectivities and enantioselectivities (Scheme 3.9).[19]
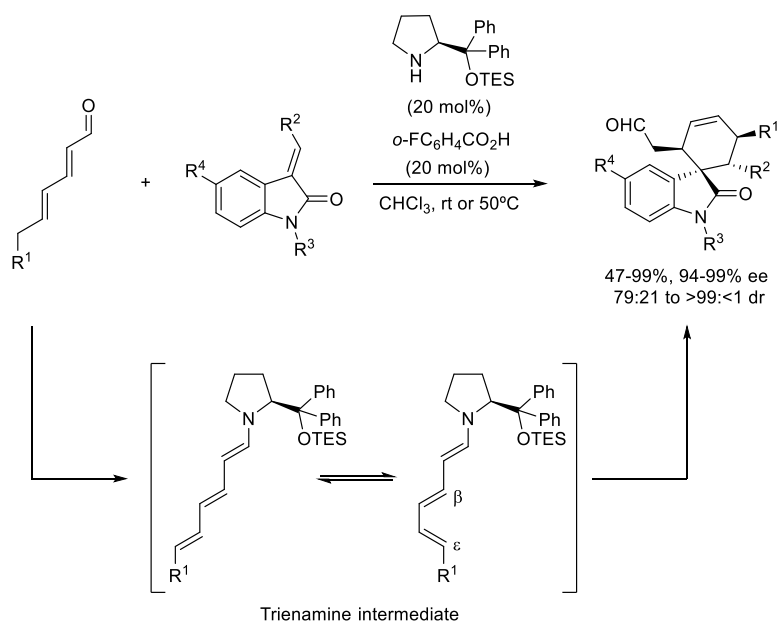
Scheme 3.9

As an alternative to this chemistry, the group of Jørgensen introduced the cross-trienamine intermediate strategy employing 2,4-dienals and 5-alkylidene azlactones as dienophiles through the reaction shown in Scheme 3.10. In this case, condensation of the dienal substrate led to the favoured formation of a cross-conjugated trienamine due to its particular structure. This intermediate was found to react with alkylidene azlactones in a [4+2]-cycloaddition reaction, obtaining the corresponding spirocyclic products in moderate

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[19] 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.

yields, moderate diastereoselectivities and excellent enantioselectivities (Scheme 3.10).[20] Remarkably, the reaction could also be extended to other electron-poor alkenes as dienophiles.
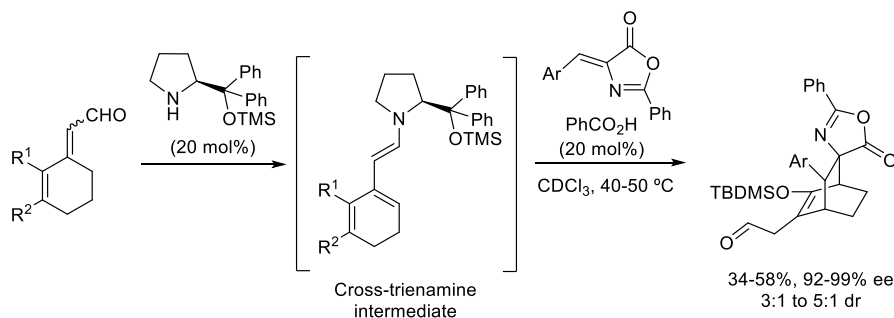
Scheme 3.10

Finally, this activation mode can be further extended to even more conjugated systems *via* tetraenamine intermediates that enables the construction of more complex molecules. This is the case of the formal [4+2]-cycloaddition reaction between 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde and differently functionalized 3-alkylidene oxindoles in the presence of catalytic amounts of the prolinol derived catalyst. After condensation of the catalyst with the aldehyde, the tetraenamine intermediate underwent Diels-Alder reaction with an alkylidene oxindole that after catalyst hydrolysis a cyclization/isomerization sequence occurred to provide the product in high yields and excellent diastereo- and enantioselectivities (Scheme 3.11).[21]
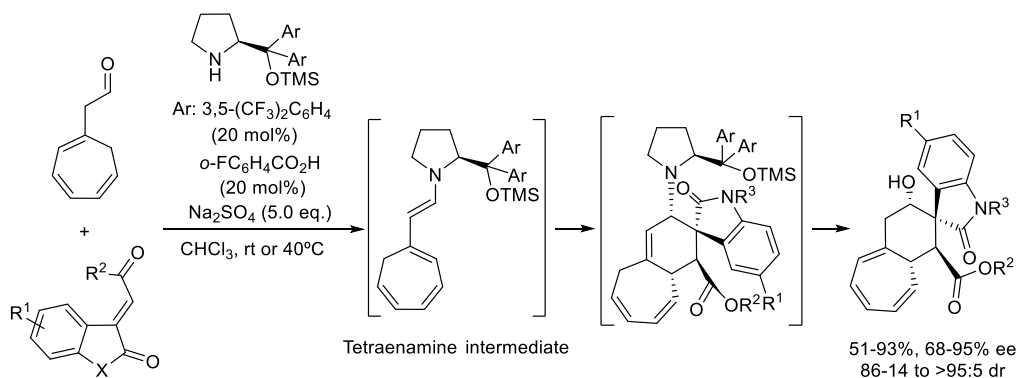
Scheme 3.11

[20] Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943.

[21] Stiller, J.; Poulsen, P. H.; Cruz, D.; Dourado, J.; Davis, R. L.; Jørgensen, K. A. *Chem. Sci.* **2014**, *5*, 2052.

1.2. Vinylogous Iminium Ion Activation

As mentioned earlier, even though the concept of vinylogy has been combined successfully with enamine catalysis across many different examples showing considerable advance in aminocatalytic reactions, it is surprising that this strategy has not been so extensively applied to iminium ion activation. The first example developing this idea was carried out by the group of Melchiorre, gathering all the requirements for δ-site selectivity and high stereocontrol. In this report the asymmetric organocatalytic 1,6-addition reaction of alkyl thiols to β-substituted cyclic dienones under vinylogous iminium ion activation was carried out employing a cinchona alkaloid-based primary amine as catalyst, and furnishing the corresponding adducts in good yields and high enantioselectivities (Scheme 3.12).[22] The success of this reaction resided on the ability of the catalyst to ensure iminium ion formation as well as high stereoinduction. In addition, the inherent rigid structure of the dienone substrate and the substitution pattern at β-position prevented the competitive 1,4-addition of the nucleophile by steric hindrance.
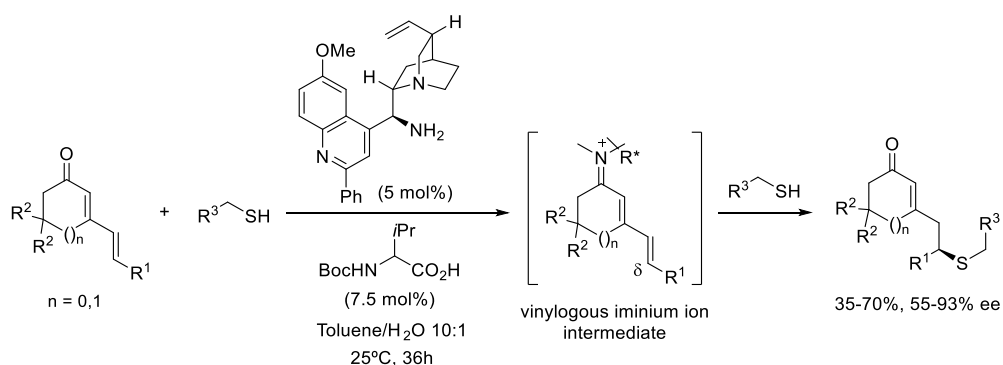
Scheme 3.12

The situation is much more difficult when linear dienals are used as substrates. This is the case of the 1,6-addition of enolizable alkylidene lactones to 2,4-dienals that provided the corresponding adducts in high yields, total regiocontrol and excellent enantioselectivities (Scheme 3.13). An explanation of the high degree of site selectivity and diastereoselectivity obtained was provided by promoting a stable interaction between the negatively charged

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[22] Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439.

oxygen of the alkylidene lactone based nucleophile with the positive charge of the vinylogous iminium ion, aligning the substrates efficiently to attack at δ-carbon.
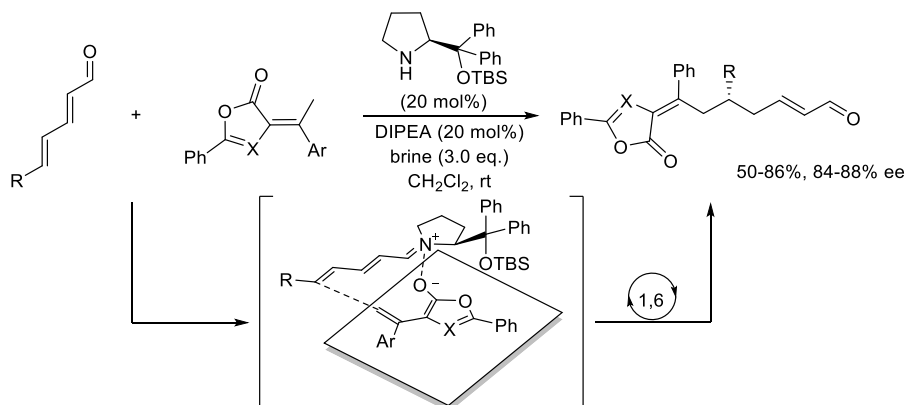
Scheme 3.13

Subsequently, some other examples of asymmetric direct 1,6-addition reactions have been developed under this promising strategy using different nucleophiles to react with activated cyclic dienones that are shown in Scheme 3.14.[23]

Scheme 3.14
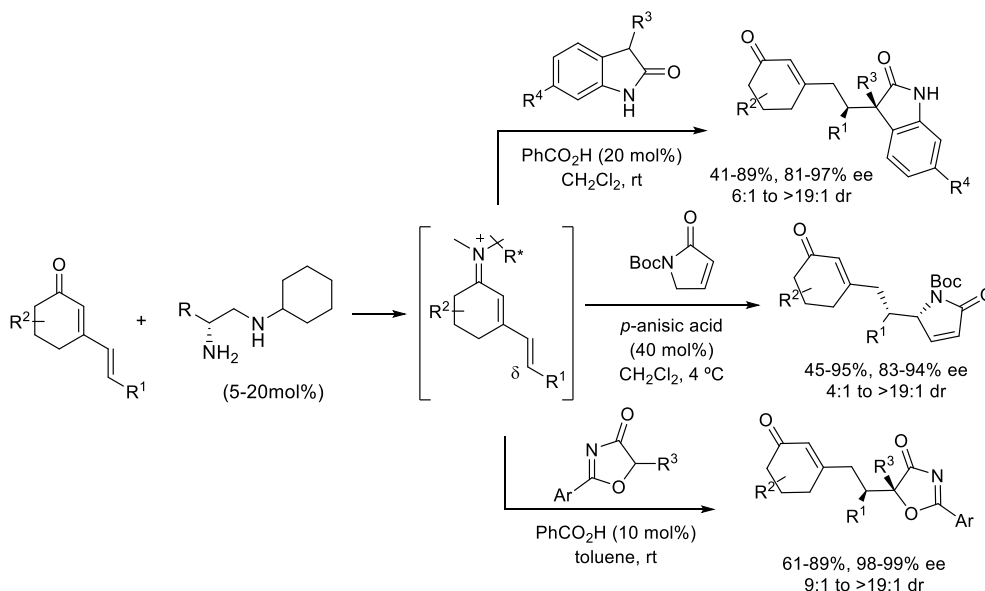
[23] a) Wei, Y.; Liu, Z.; Wu, X.; Fei, J.; Gu, X.; Yuan, X.; Ye, J. *Chem. Eur. J.* **2015**, *21*, 18921; b) Gu, X.; Guo, T.; Dai, Y.; Franchino, A.; Fei, J.; Zou, C.; Dixon, D. J.; Ye, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10249.

One additional example showing the possibility of using dienals with a particular substitution pattern has also been disclosed (Scheme 3.15).[24]
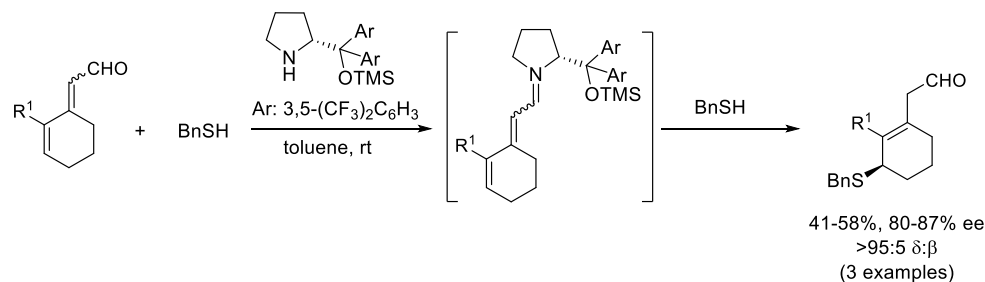
Scheme 3.15

In addition, some publications have been reported in which the vinylogous iminium ion activation has been used for developing sophisticated cascade reactions for the construction of molecules with higher complexity.

The first example of this chemistry was developed by Melchiorre and colleagues in 2013 through the reaction shown in Scheme 3.16. The reaction involved the formation of the key vinylogous iminium ion after condensation of the substrate with the cinchona alkaloid-based catalyst. Next, 1,6-addition of the 3-substituted oxindole occurred, generating a dienamine intermediate ready to react intramolecularly with the carbonyl group incorporated at the lateral chain of the oxindole reagent, forming the final product. Hence, enantioenriched spirocyclopentane oxindole derivatives were obtained in a overall 1,6-addition/aldolization cascade sequence in good yields, from moderate to good diastereoselectivities and excellent enantiocontrol (Scheme 3.16).[25]

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[24] Halskov, K. S.; Naicker, T.; Jensen, M. E.; Jørgensen, K. A. *Chem. Commun.* **2013**, *49*, 6382.
[25] Tian, X.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 5360.
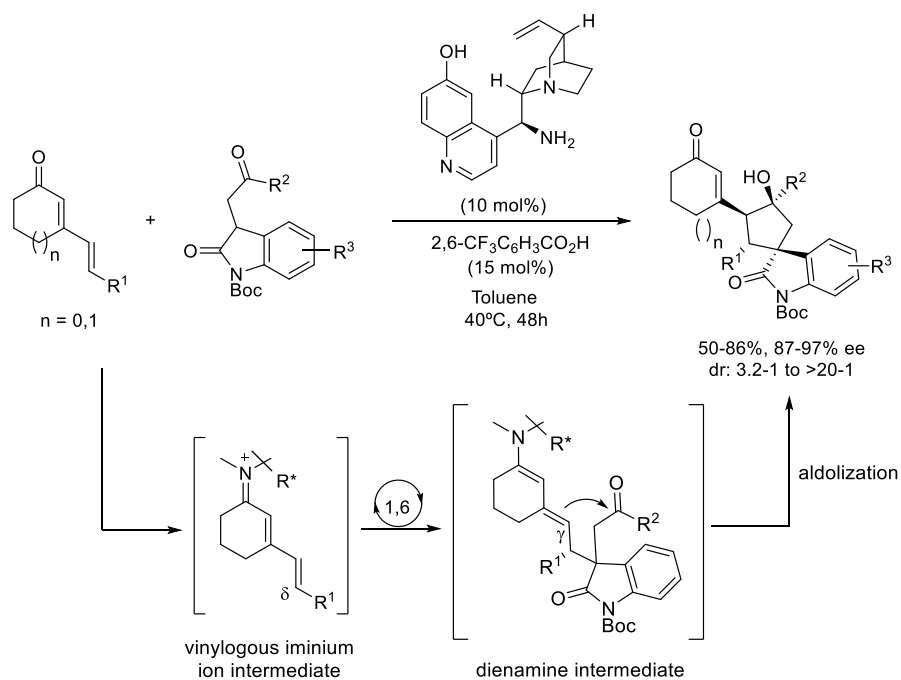
Scheme 3.16

Dienals can also be used as substrates under this reaction scheme. As a representative example of this methodology, Jørgensen *et al*. described the organocatalytic asymmetric 1,6-Friedel-Crafts/1,4-oxa-Michael cascade process for the synthesis of chiral chromans employing linear 2,4-dienals in high yields and enantioselectivities (Scheme 3.17).[26] Computational studies explained the tendency of the phenol reagent to act initially as a C-nucleophile instead of the initially expected O-nucleophile in terms of the formation of a more stable iminium ion intermediate through extended conjugation. This intermediate would form the final product through intramolecular oxa-Michael reaction followed by catalyst release.

[26] Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 8203.
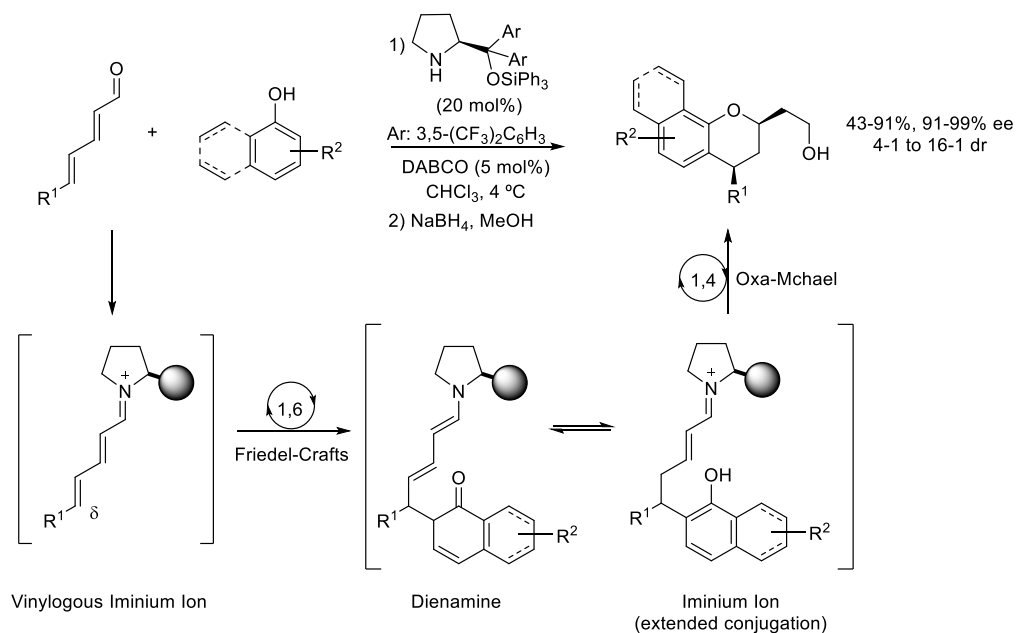
Scheme 3.17

Another example in this area was published by Jørgensen and co-workers showing the use of nitrones for the regio- and enantioselective 1,3-dipolar cycloaddition reaction in the remote position of the vinylogous iminium ion intermediate (Scheme 3.18).[27]
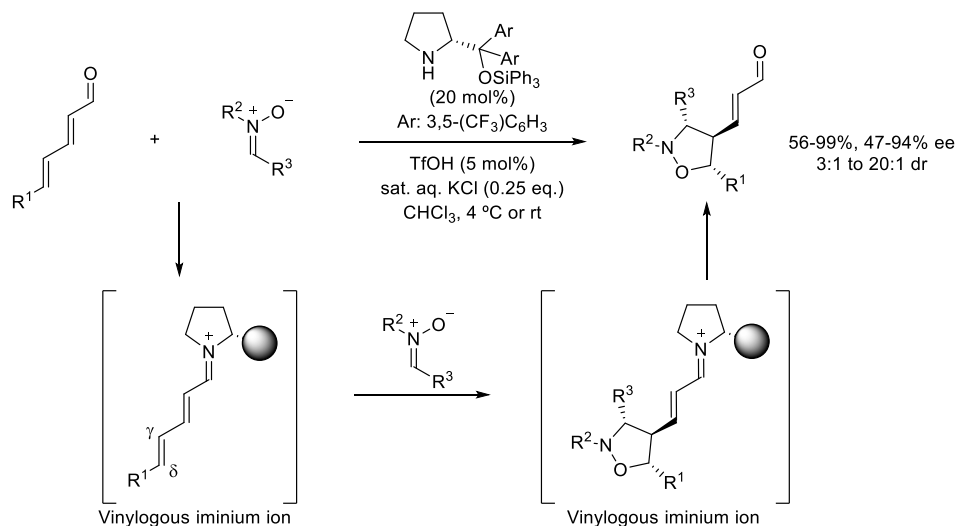
Scheme 3.18

[27] Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2016**, *138*, 6412.

Finally, 2,4,6-trienals can also be used to generate bis-vinylogous iminium ion intermediate which was able to react with three equivalents of a nitrone in an enantioselective triple 1,3-dipolar cycloaddition reaction. Tri-isoxazolidine products with nine stereogenic centres were obtained with low diastereoselectivity, albeit excellent enantioselectivity, showing the possibility to functionalize the α,β,γ,δ,ε,ζ- positions of the starting polyunsaturated aldehyde (Scheme 3.19).[27]
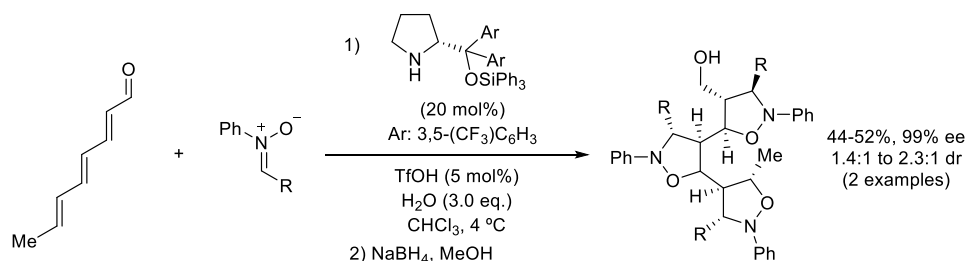
Scheme 3.19

2. SPECIFIC OBJECTIVES AND WORK PLAN

As presented in the introduction part, the examples using vinylogous iminium ion strategy for the functionalization at δ-position are recent and limited, though they are developing fast. In the last years, developing more complex molecules and implementing more sophisticated transformations has been a field of interest research. However, few are the examples involving sequential 1,6-/1,4-addition reactions. In this sense and taking into account the revised literature, we decided to direct our efforts to promote a 1,6-aza-Michael/1,4-Michael cascade reaction using 2-aminomalonates to act as double nucleophiles in combination with cyclic enones, the latter undergoing activation by a chiral primary amine catalyst to generate a vinylogous iminium ion intermediate (Scheme 3.20).
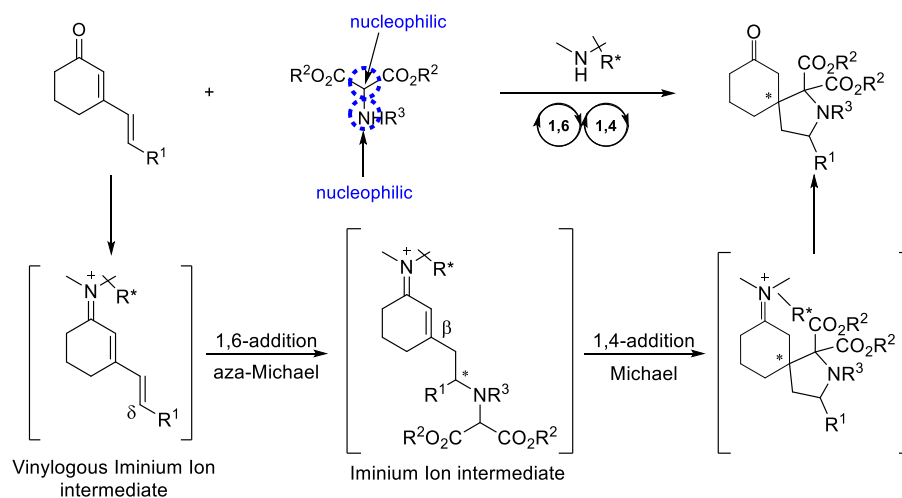
Scheme 3.20

In view of literature precedents, cyclic dienones have been chosen as appropriate unsaturated carbonyl compounds for the generation of the vinylogous iminium ion intermediate. On the other hand, chiral primary amines derived from cinchona alkaloids will be employed as catalysts, due to their proven higher ability to condense easily with ketones and their efficiency to control the stereochemical outcome of the reaction.[28]

It should be mentioned that we have already used this type of aminomalonates as bisnucleophiles in our group in a Michael/1,2-addition cascade sequence in combination with enones under iminium ion activation. This reaction provided pyrrolidine derivatives after diastereoselective reduction in high yields and enantioselectivities (Scheme 3.21).[29]
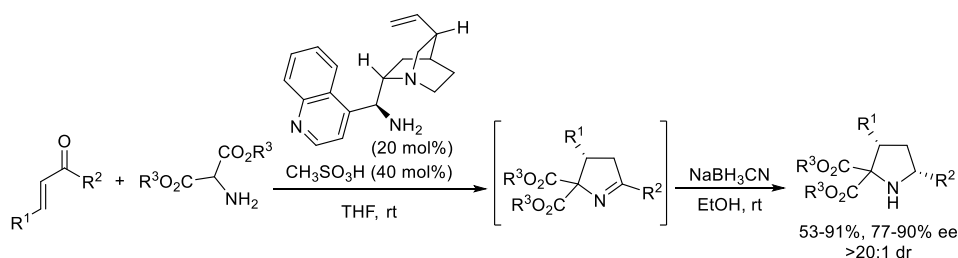
Scheme 3.21

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[28] For some reviews on the use of chiral primary amines in asymmetric organocatalsyis, see: a) Duan, J.; Li, P. *Catal. Sci. Technol.* **2014**, *4*, 311; b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748; c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807; d) Chen, Y.-C. *Synlett* **2008**, *13*, 1919; e) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *12*, 1759.

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

In order to fulfill the mentioned objective, the following work plan was designed:

1. *Proof of concept*: Firstly, the possibility to carry out the 1,6-1,4 cascade reaction under vinylogous iminium ion/iminium ion intermediates will be surveyed using a model system.
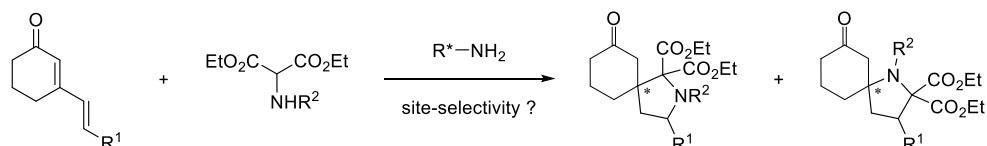
2. *Optimization of the reaction conditions*: Once the feasibility of the reaction is verified, different experimental variables, such as catalyst, solvent, additive, temperature and substituents will be evaluated in an attempt to obtain best results in terms of reactivity and stereocontrol (Scheme 3.22).
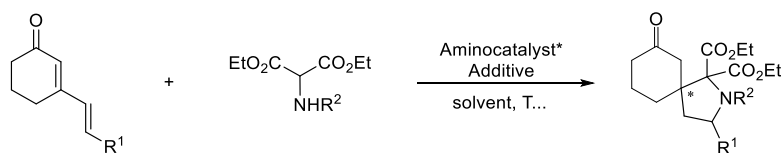
Scheme 3.22

3. RESULTS AND DISCUSSION

After having discussed the methodologies and examples present in the literature regarding this topic, we will continue with the presentation and discussion of the most relevant results obtained in this part or the research.

3.1. Proof of concept

We started our investigations by evaluating the viability of the reaction. Initially, (*E*)-3-(prop-1-en-1-yl)cyclohex-2-en-1-one **14a** and diethyl aminomalonate **15a** were used as a representative model system in the presence of 9-epi-9-amino-9-deoxyquinine **17b** as primary amine catalyst in EtOAc as solvent and at room temperature. In order to favour the condensation of the catalyst with the cyclic enone for the formation of the vinylogous iminium ion, we choose *p*-toluenesulfonic acid as Brønsted acid cocatalyst. To our delight, the corresponding adduct derived from a 1,6-aza-Michael/1,4-Michael cascade sequence was

obtained proceeding with complete regioselectivity, promising enantioselectivity, albeit with low diastereoselectivity, obtaining a 1:1.9 mixture of both diastereoisomers (**16a**:**16a'**). The products derived from the formation of single 1,2-, 1,4- or 1,6-additions were not observed, affording just the product coming from the 1,6-/1,4- cascade sequence, concluding that the cyclic enone was being activated as vinylogous iminium ion/iminium ion cascade sequence. Furthermore, the reaction yielded only one isomer, without observation of 1,6-Michael/1,4-aza-Michael product, showing the ability of 2-aminomalonates to act as double nucleophiles acting firstly as *N*-nucleophiles and then as a C-nucleophiles (Scheme 3.23).
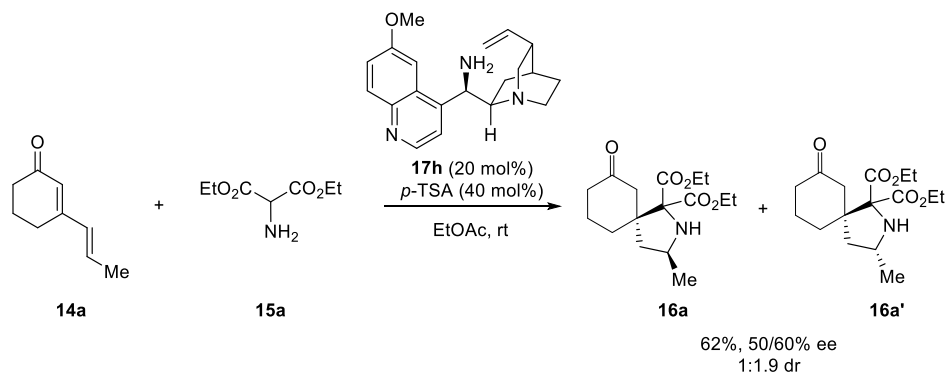
Scheme 3.23

The regioselectivity of the reaction was determined by two dimensional ^{1}H-NMR experiments. As shown in Figure 3.2, in the HMBC experiment correlation between the protons next to the ketone and the quaternary carbon of the malonate can be seen. Moreover, no correlation is seen between the protons of the methyl group and the quaternary malonate carbon indicating that the reaction proceeded through a 1,6-aza-Michael/1,4-Michael cascade pathway to afford the corresponding spirocyclic adduct **16a** (Figure 3.2).
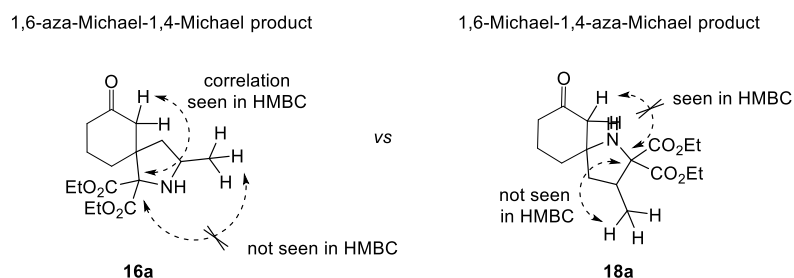
Figure 3.2

The product **16a** was isolated as a mixture of diastereoisomers, and the relative configuration was proposed to be as the one depicted in Scheme 3.23 according to literature precedents.[28b]

Having proved the viability of the reaction with the unprotected 2-aminomalonate, the influence of a *N*-substituent in this substrate was evaluated. Therefore, we synthesize a broad repertoire of *N*-substituted 2-aminomalonates with substituents of different nature, including electron-withdrawing groups, such as nosyl, *tert*-butoxycarbonyl, tosyl, mesyl and acetyl and electron-donating groups, such as benzyl, phenyl, *p*-methoxybenzyl, *n*-butyl or *p*-methoxyphenyl. Disappointingly, none of the substrates were able to promote the reaction recovering the starting material unchanged, thus, proving essential the necessity of the primary amine in the aminomalonate reagent (Scheme 3.24).
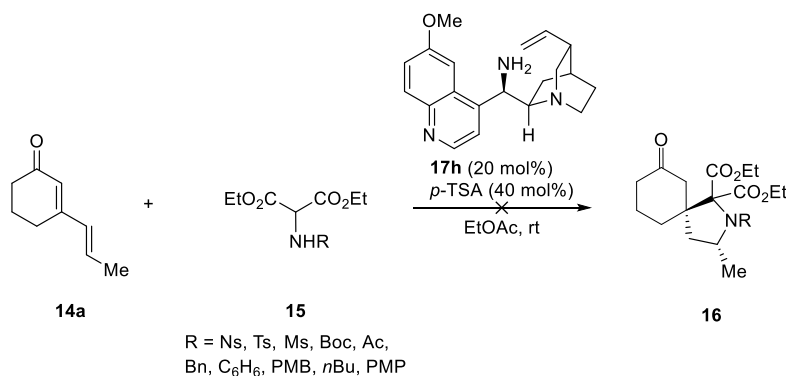
Scheme 3.24

3.2. Optimization of the reaction conditions

This preliminary result encouraged us to evaluate different reaction conditions in order to improve the outcome of the reaction. At this point, we started our investigations using different families of chiral primary amine catalysts of different nature. All the catalysts tested can act as bifunctional catalysts, containing a Brønsted basic site or acidic hydrogen amenable to form hydrogen bonds in the scaffold in addition to the required primary amine moiety. The results obtained are summarized in Table 3.1.

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

Catalyst **17a-o** (20 mol%)
p-TSA (40 mol%)
EtOAc, rt

14a + **15a** → **16a** + **16a'**

17a: $R^1 = R^3 = H$, $R^2 = $ vinyl
17b: $R^1 = $ OMe, $R^2 = $ vinyl, $R^3 = H$
17c: $R^1 = $ OMe, $R^2 = $ Et, $R^3 = H$
17d: $R^1 = $ OH, $R^2 = $ vinyl, $R^3 = H$
17e: $R^1 = $ OMe, $R^2 = $ vinyl, $R^3 = t$Bu
17f: $R^1 = $ OMe, $R^2 = $ vinyl, $R^3 = $ Ph

17g: R = H
17h: R = OMe

17i

17j

17k: $R^1 = R^2 = H$
17l: $R^1 = R^2 = $ -(CH$_2$)$_5$-

17m

17n: $R^1 = i$Pr, $R^2 = H$, $R^3 = $ cyclohexyl
17o: $R^1 = t$Bu, $R^2 = R^3 = $ Et
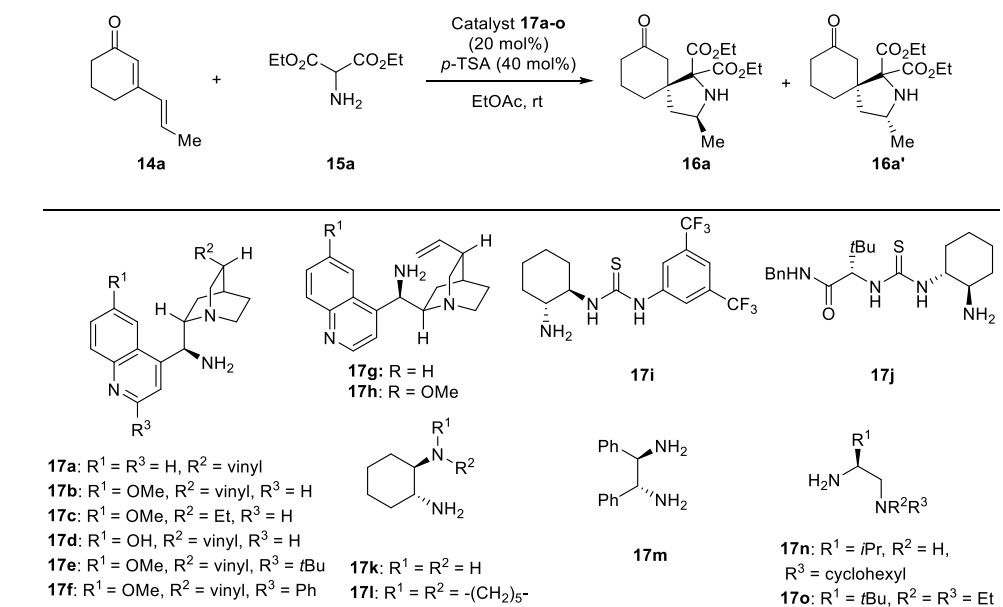
Entry	Catalyst	Yield 16 (%)[b]	dr[c] (16a:16a')	ee 16a (%)[d]	ee 16a' (%)[d]
1[e]	-	n.r.[e]	n.d.[f]	n.d.	n.d.
2	*p*-TSA	25	n.d.	n.d.	n.d.
3[e]	**17h**	4	1:1.4	0	18
4	**17a**	63	1.4:1	36	30
5	**17b**	53	1:1	44	42
6	**17c**	60	1:2.4	46	45
7	**17d**	22	2:1	26	32
8	**17e**	72	1:2[e]	45	61
9	**17f**	63	1:2.4	50	60
10	**17g**	67	1:1.4	54	48
11	**17h**	62	1:1.9	50	60
12	**17i**	61	1:1.9	12	0
13	**17j**	42	1:1.1	0	0
14	**17k**	26	1:2.5[e]	20	42
15	**17l**	16	1:2	20	0
16	**17m**	15	1:1.4	28	10
17	**17n**	35	1:1.5	8	4
18	**17o**	18	1:1	22	9

[a] The reaction was performed in 0.8 mL EtOAc and 0.2 mmol scale of **14a**, using 1.5 eq. of **15a** and 40 mol% of *p*-TSA for 24 h at rt. [b] Isolated product yield of **16a** and **16a'** after flash column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. Preservation of the diastereoisomer ratio in HPLC analysis. [d] Determined by HPLC analysis of the pure product. [e] Reaction carried out without *p*-TSA. [f] No reaction. [g] Not determined.
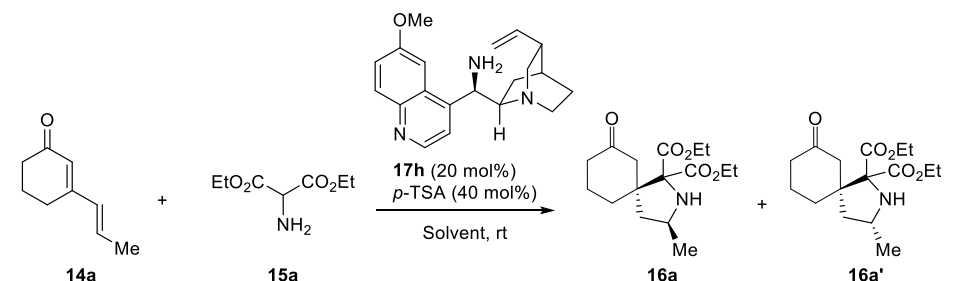
The reaction without the presence of a primary amine catalyst or an acidic additive did not yield any product (Entry 1). However, when running the reaction in the presence of 40 mol% of *p*-TSA, in EtOAc at room temperature, the product was observed in a 25% yield after 24 hours (Entry 2), being a possible competitive racemic pathway necessary to control in the stereoselective transformation. Nevertheless, the use of an acid co-catalyst was proved to be essential in order to take place the reaction, which would favour the condensation between the catalyst and the enone (Entry 3). The first screening of catalysts was carried out in the presence of *p*-TSA and using differently substituted cinchona-based primary amine catalysts. As shown in Table 3.1, modification on the aromatic ring in the R^1 position affected the enantioselectivity of the process in favour of quinine **17b** catalyst (Entries 4-5). If the R^2 substituent was slightly modified, catalyst **17c**, the reaction worked with similar results (Entry 6), however, the introduction of a hydrogen-bond donor group at the aromatic R^1 position of the catalyst disfavoured the enantiocontrol of the reaction affording the product in low yield (Entry 7). On the other hand, the introduction of alkyl or aryl substitution in the R^3 position of the aromatic ring of the catalyst helped in the stereochemical outcome of the reaction, reaching 61% of enantioselectivity for the major diastereoisomer in good yields (Entries 8-9). In the same manner, using the pseudoenantiomers of **17a** and **17b**, the desired products were obtained in good yields in both cases, in the case of **17h**, being comparable to the results obtained with catalyst **17f** (Entry 8 *vs* Entry 11). At this point, other types of bifunctional primary amine catalysts were tested in order to evaluate the influence of the nature of the primary amine. In the case of thiourea based bifunctional catalysts **17i** and **17j**, where hydrogen-bond donor groups are present in the structure, these interactions did not help to induce stereochemical outcome, affording racemic products, regardless the substitution pattern in the catalyst manifold (Entries 12-13). Additionally, different diamine catalysts (**17k-o**) also proceeded with low conversion and stereoinduction regardless the substitution nature of the amine or the presence of additional hydrogen-bond donor groups or Brønsted basic sites (Entries 14-17). Therefore, it was assumed that cinchona alkaloid-based structure with a Brønsted basic site was essential for a higher stereoinduction.

Finally and in order to improve the results obtained regarding yield and stereocontrol, other type of catalysts were checked, such as squaramides or phosphoric acids, although the reactions did not yield better results. Among the different substitution patterns possible within

the cinchona alkaloid-based family, catalyst **17h** was chosen for further reaction condition investigations (Entry 11).

Having selected catalyst **17h** as the best one to perform the reaction in terms of stereocontrol, next we focus on the use of different solvents taking into account their polarity (Table 3.2). More polar solvents than EtOAc, for example DMF or CH$_3$CN, were not well tolerated obtaining the product in low yield and poor enantioselectivity probably due to the solvation of the catalyst (Entries 2-3). Less polar ethereal solvents, worked similarly in terms of enantiocontrol albeit in lower yield (Entries 4-6), as it happened with chloroform (Entry 7). Finally, a non-polar solvent like toluene performed the reaction in moderate yield and enantioselectivity (Entry 8), whereas with hexane the reaction turned out to work with worse results because of the low solubility (Entry 9). As a consequence, we decided to employ ethyl acetate as the optimal solvent to continue with the screening of the reaction.

Table 3.2: Solvent effect on the reaction.[a]

Entry	Solvent	Yield 16 (%)[b]	dr[c] (16a:16a')	ee (%)[d] 16a	ee (%)[d] 16a'
1	EtOAc	62	1:1.9	50	60
2	DMF	20	1:1	7	4
3	CH$_3$CN	24	n.d.[e]	18	20
4	THF	26	1:2	45	62
5	2,2-dimethoxypropane	25	1:1.5	46	46
6	2-methoxyethylether	57	1.5:1	32	36
7	CHCl$_3$	36	1:1.3	50	64
8	Toluene	44	1:2.3	40	63
9	Hexane	38	1:1	14	20

[a] The reaction was performed in 0.8 mL of solvent and 0.2 mmol scale of **14a**, using 1.5 eq. of **15a** and 20 mol% of catalyst **17h** for 24 h at rt.[b] Isolated product yield of **16a** and **16a'** after flash column chromatography.[c] Determined by ^{1}H-NMR analysis of the crude reaction mixture.[d] Determined by HPLC analysis of the pure product.[e] Not determined.

Melchiorre and co-workers described the ability of acids to facilitate the formation of the iminium ion intermediates and also the capacity to modulate the chiral space by acting as a counterion anion, influencing directly into the stereoselectivity of the reaction.[30] Thus, the performance of the reaction in the presence of different Brønsted acid co-catalysts was evaluated (Table 3.3).

Table 3.3: Effect of acid co-catalysts in the reaction.[a]

Entry	Additive	pk_a[b]	Yield 16 (%)[c]	dr[d] (16a:16a')	ee (%)[e] 16a	ee (%)[e] 16a'
1	*p*-TSA	-2.80	62	1:1.9	50	60
2	4-(OMe)C$_6$H$_4$CO$_2$H	4.47	11	1:2	20	27
3	PhCO$_2$H	4.2	11	1:1.7	6	29
4	4-(NO$_2$)C$_6$H$_4$CO$_2$H	3.44	66	1:2.3	4	28
5	2,4-(NO$_2$)$_2$C$_6$H$_4$CO$_2$H	1.43	90	1:2	5	16
6	TFA	-0.2	78	1.7:1	0	0
7	CH$_3$SO$_3$H	-1.9	67	1:1	31	59
8	Tf$_2$NH	-11.9	60	1:1.6	0	0
9	TfOH	-14.9	72	1:1	32	32
10[g]	(*S*)-TRIP	13.6	87	1:1	24	28
11[g]	(*R*)-TRIP	13.6	70	1:1	16	10

[a] The reaction was performed in 0.8 mL EtOAc and 0.2 mmol scale of **14a**, using 1.5 eq. of **15a** and 20 mol% of catalyst **17h** for 24 h at rt.[b] pK$_a$ values measured in H$_2$O. Perrin, D. D.; Serjeant, E. P.; Dempsey, B. pk$_a$ *Predictions for Organic Acids and Bases*, Chapman and Hall, London, **1981**.[c] Isolated product yield of **16a** and **16a'** after flash column chromatography.[d] Determined by ¹H-NMR analysis of the crude reaction mixture.[e] Determined by HPLC analysis of the pure product.[f] Not determined. [g] pk$_a$ measured in CH$_3$CN.

As depicted in Table 3.3 with less acidic co-catalysts, such as 4-methoxyphenylbenzoic acid or benzoic acid, the product was obtained in low yield and enantioselectivities (Entries 2-3), while 4-nitrophenylbenzoic acid afforded the product in slightly higher yield probably due

[30] a) Moran, A.; Hamilton, A.; Bo, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2013**, *135*, 9091; b) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934.

to the background reaction promoted by the acid, because the enantioselectivity of the process was still very low (Entry 4). With more acidic additives, the tendency was confirmed, affording the desired product in very good yields but very low enantioselectivities (Entries 5-6, 8). In the case of CH_3SO_3H and TfOH ambiguities in the results existed regarding the stereocontrol of the reaction. At this point we wondered if a chiral Brønsted acid co-catalyst would be able to yield the final adducts with a better control of stereochemistry in a match effect with the catalyst. We employed (*S*)-TRIP and (*R*)-TRIP as co-catalysts together with catalyst **17h** for the study, but neither of them were able to improve the previously obtained results. We could not either make any deduction of a match-mismatch effect, obtaining in both cases very good yields, but poor enantioselectivities (Entries 10-11). In conclusion, *p*-TSA was proved to be the most suitable co-catalyst for this reaction being a strong acid and providing the product in good yield and good enantioselectivities (Entry 1). Comparing the different acids shown, we can conclude that in general there is a remarkable effect between the pk_a of the acid and the yield of the product probably because of the appearance of the background reaction, although a range of pk_a have been proved to be essential in the outcome of the reaction.

Once the Brønsted acid co-catalyst was optimized, we proceeded to study the effect of other parameters on the reaction, such as the catalytic ratio of the additive and temperature.

Table 3.4: Effect acid co-catalyst equivalents and temperature.[a]

Entry	Acid (eq.)	T (ºC)	Yield 16 (%)[b]	dr[c] (16a:16a')	ee 16a (%)[d]	ee 16a' (%)[d]
1	0.4	25	62	1:1.9	50	60
2	0.2	25	56	1:2	44	64
3	0.3	25	69	1:2	54	63
4	0.6	25	27	n.d.[e]	40	52
5	0.3	50	83	1:1.6	42	45
6	0.3	0	47	1:2	42	65

[a] The reaction was performed in 0.8 mL EtOAc and 0.2 mmol scale of **14a**, using 1.5 eq. of **15a** and 20 mol% of catalyst **17h** for 24 h at rt.[b] Isolated product yield of **16a** and **16a'** after flash column chromatography.[c] Determined by ¹H-NMR analysis of the crude reaction mixture.[d] Determined by HPLC analysis of the pure product.[f] Not determined.

As depicted in Table 3.4, whereas the same amount of catalyst **17h** and *p*-TSA did not have a big impact, with a small excess of additive (0.3 eq.), the reaction turned out to work in higher yield and enantioselectivities (Entry 2 *vs* Entry 1). Nevertheless, 0.6 eq. of acid co-catalyst was proved to have a bad impact in the outcome of the reaction, obtaining the product in lower yield and enantioselectivities (Entry 4). With the aim of improving the dr of the reaction different temperatures were tested as well, observing that at higher temperature, the yield was increased at the expense of enantioselectivity (Entry 5). On the other hand, at lower temperatures, the yield was highly compromised, without observing a big impact in the enantioselectivity of the process (Entry 6).

The variables tested to improve the stereoinduction of the reaction were not efficient enough, affording the final adducts in 69% yield, as a mixture of diastereoisomers in a 1:2 ratio and 54% and 63% enantioselectivity, respectively, being these conditions the best ones until the moment.

These results prompted us to study the influence of the structure of the enone substrate, as it is summarized in Scheme 3.25.
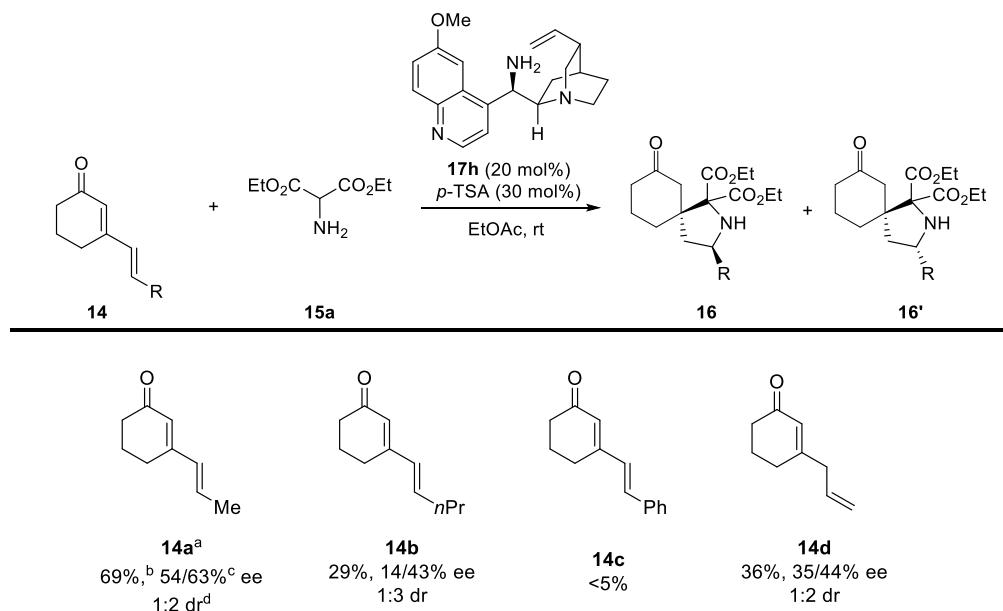
a The reaction was performed in 0.8 mL EtOAc and 0.2 mmol scale of **14**, using 1.5 eq. of **15** and 20 mol% of catalyst **17h** and 30 mol% of *p*-TSA for 24h at rt.[b] Isolated product yield of **16** and **16'** after flash column chromatography.[c] Determined by ¹H-NMR analysis of the crude reaction mixture.[d] Determined by HPLC analysis of the pure product.

Scheme 3.25

Whereas a bulkier alkyl chain as *n*-propyl substituent at δ-position (**14b**) yielded the product in low yield and enantiomeric excess and as a mixture of diastereoisomers, an aromatic substituent became the enone unreactive. Additionally, the unconjugated cyclic dienone (**14d**) was also tested, being a more reactive starting material upon the condensation with the catalyst, though the product was obtained in just 36% yield, in a 1:2 mixture of diastereoisomers and low enanatioselectivities. Thus, none of the new cyclic enones tested improved the already obtained results.

After having examined several reaction variables, we were unable to reach an efficient protocol to carry out the projected reaction between cyclic enones and 2-aminomalonates, affording the spirocycle adduct derived from the 1,6-aza-Michael/1,4-Michael cascade reaction in 69% yield as a mixture of diastereoisomers (1:2) and 63% of enantioselectivity for

the major diastereoisomer. Therefore, further studies on reaction conditions and mechanistic considerations will be necessary to achieve one single diastereoisomer with high optical purity.

3.3. Mechanistic Proposal

Based on literature precedents, we propose the catalytic cycle depicted in Scheme 3.26. The condensation between the chiral primary amine and the cyclic enone would form the vinylogous iminium ion **I** with a lower LUMO-energy. Then, diethyl aminomalonate would react at δ-position through a 1,6-aza-Michael reaction to lead the dienamine intermediate **II** in equilibrium with the iminium ion **III**, now ready for the attack at β-position in a 1,4-Michael reaction, affording the enamine intermediate **IV**. Final hydrolysis would release the catalyst to restart another catalytic cycle and would afford the desired adduct **16**.
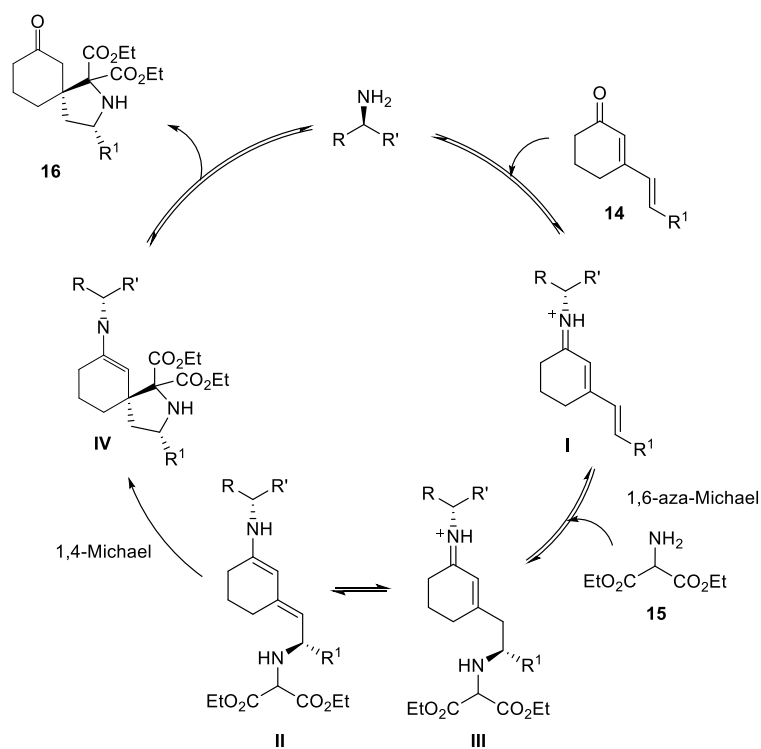
Scheme 3.26

The stereochemistry of the reaction shown is based on previous works where conjugated additions occurred under iminium ion activation, and it is dependent on the effectiveness of the catalyst shielding (Scheme 3.27).
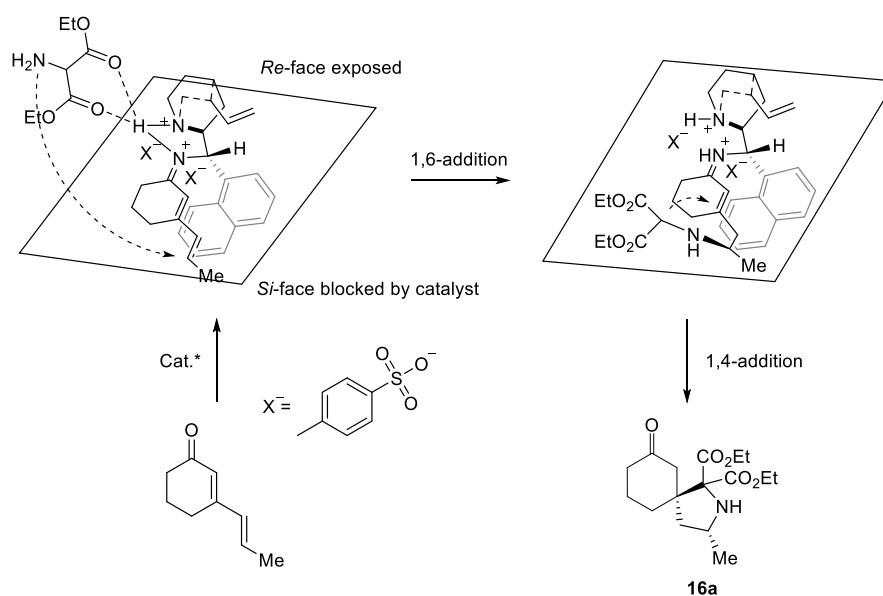
Scheme 3.27

The vinylogous iminium ion will have an *s*-trans conformation and the first 1,6-addition will proceed from the *Re*-face, because *Si*-face is blocked by the catalyst. Hence, the configuration of the new stereocentre formed will be *R*. In the second step, the nucleophile will attack from the opposite face of the catalyst and the same face where the nucleophile is, to release the desired product **16**.

However, in our case we have obtained mixtures of diastereoisomers and poor enantioselectivities. We propose that the reversibility of the aza-Michael reaction is not efficiently controlled, resulting in a drop in the diastereoselectivity and enantioselectivity of the process, although there are other alternatives, such as that the first step of the reaction is efficiently controlled by the catalyst, but the second step is not, or the 1,6-addition is not efficiently controlled, but the 1,4-addition is controlled or alternatively, neither the 1,6-addition nor the 1,4-addition are controlled.

4. CONCLUSIONS

Considering the results obtained in this chapter, the following conclusions can be outlined:

1. Cyclic dienones with diethyl aminomalonates are suitable substrates to accomplish the 1,6-aza-Michael/1,4-Michael cascade reaction obtaining exclusively β,δ-functionalization.

2. Unprotected 2-aminomalonates have been proved to act as double nucleophiles with complete regioselectivity in an 1,6-aza-Michael/1,4-Michael reaction, acting firstly as *N*-donors and subsequently undergoing Michael reaction.

3. Even though we were unable to reach the optimal conditions for the 1,6-aza-Michael-1,4-Michael reaction, the results obtained are promising, having achieved until date 69% yield of the spirocycle adduct, in a diastereomeric ratio of 1:2 and 58% and 62% of enantioselectivity, respectively for a model system.

4. Further evaluation of reaction conditions, such as catalysts, additives or reaction mechanism could be important factors to take into account to finally reach the optimal conditions.

4

4

Synthesis of enantioenriched Hindered Tertiary Boronic Esters through *In Situ* Lithiation-Borylation Conditions

1. INTRODUCTION

Boronic acids and their derivatives have been widely employed as synthetic intermediates in a broad variety of organic transformations. Even though the isolation of boronic acids can be dated back to 1860,[1] the advances on the use of boronic acids and derivatives have been essentially limited to a few number of cases until the development of the palladium-catalyzed cross-coupling reaction of organoboron compounds with carbon halides in 1979 by Miyaura and Suzuki.[2] It was then, when the chemistry community became aware of the usefulness of these organic compounds, together with their stability and ease of handling. Indeed, the utilization of boronic acids and derivatives for the development of new reactions and applications has suffered a representative growth in the last two decades.[3] Due to the limitations that sometimes the alkylboranes typically used in other reactions in boron chemistry exhibit, which are associated to purification and characterization issues, the use of boronic esters as intermediates has been applied with success in numerous organic transformations. The enantioenriched synthesis of these frameworks is also well developed and, moreover, they have shown a widespread ability to be converted into useful functional groups, often with high stereochemical fidelity. Therefore, these compounds have been extensively used for the asymmetric synthesis of C-C and C-heteroatom bond formations (Scheme 4.1).[4]
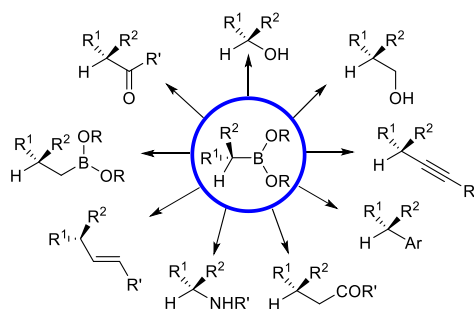
Scheme 4.1

[1] Frankland, E.; Duppa, B. F. *Eur. J .Org. Chem.* **1860**, *115*, 319.

[2] Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866.

[3] a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011; Vols. 1 and 2, 2nd ed.; b) *Stereodirected Synthesis with Organoboranes. Reactivity and Structure Concepts in Organic Chemistry*; Matteson, D. S., Ed.; Springer: Berlin, 1995; Vol. 32.

[4] a) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201; b) Matteson, D. S. *Tetrahedron* **1989**, *45*,1859; c) *Science of Synthesis: Boron Compounds*; Kaufmann, D. E., Matteson, D. S., Ed.; Georg Thieme Verlag: Stuttgart-New York, 2004; d) Crudden, C. M.; Glasspole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, *44*, 6704.

In 1980 Matteson and co-workers developed the substrate-controlled approach for the construction of chiral boronic esters using lithium halomethane reagents and boronic esters derived from a chiral diol. In this strategy, the lithium halomethane species generate a reactive carbenoid, able to react with the boronic ester forming (α-haloalkyl)boronic esters after migration. This can react with a Grignard reagent, that after 1,2-metallate rearrangement, together with loss of halide, provides the enantioenriched boronic ester in which the stereochemistry is controlled exclusively by the chiral architecture of the boronic ester (substrate control) (Scheme 4.2).[5] This strategy has become a powerful method for the stereoselective alkylation of chiral boronic esters, and has been applied for the asymmetric construction of numerous natural products and complex structures and as a key step in total synthesis, due to the effectiveness in inducing high chirality and the ability to generate multiple continuous stereocentres by sequential homologation reactions.[6]
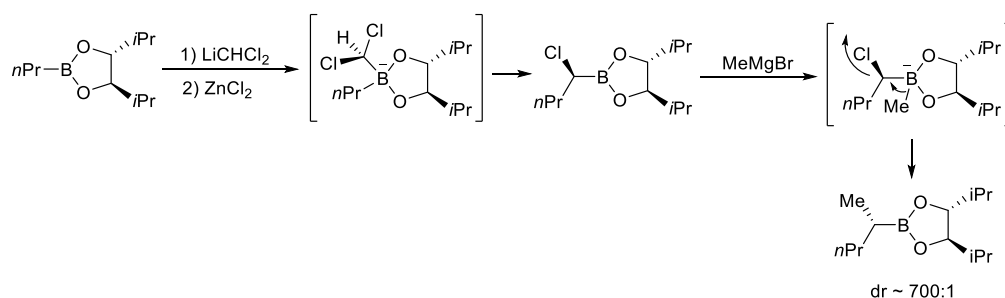
Scheme 4.2

However, this method showed some limitations when applied to construct tertiary alcohols. The enantioselectivities obtained for these compounds were variable and unpredictable. Moreover, as the steroinduction was dictated by the configuration of the chiral boronic ester, in order to furnish the opposite enantiomer, the opposite enantiomer of the boronic ester needed to be synthesized.[7] As a consequence, another type of activation strategy was developed based on the use of chiral homologating agents and achiral boronic esters,

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[5] a) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. S. *Organometallics* **1983**, *2*, 1536; b) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077; c) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41; d) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590.

[6] For some reviews on the use of substrate control methodology, see: a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555; b) Matteson, D. S. *Pure Appl. Chem.* **1991**, *63*, 339; c) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.

[7] Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1996**, *61*, 6047.

giving rise to reagent control approach. In this sense, Blakemore and co-workers used chiral enantoenriched α-chlorosulfoxides for the *in situ* generation of chiral α-chloro lithium carbenoid intermediates that could react with achiral boronic esters and yield enantioenriched boronic esters after the 1,2-migration step (Scheme 4.3).[8] These reagents, however, were difficult to prepare and not very stable.
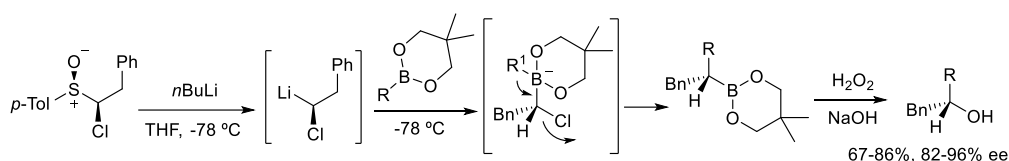
Scheme 4.3

On the other hand, lithiated carbamates have demonstrated to behave as excellent chiral carbanions employed under this protocol. This methodology is based on the initial reports by Hoppe and colleagues,[9] which used for the first time the lithiation and borylation methodology for the generation of a borate ester from the corresponding chiral lithiated carbamate in a stepwise process using Grignard reagents. More recently, Aggarwal *et al.*[10] showed the possibility to perform transformation in a single operation adding the boronic ester directly to the chiral lithiated carbamate (Scheme 4.4).
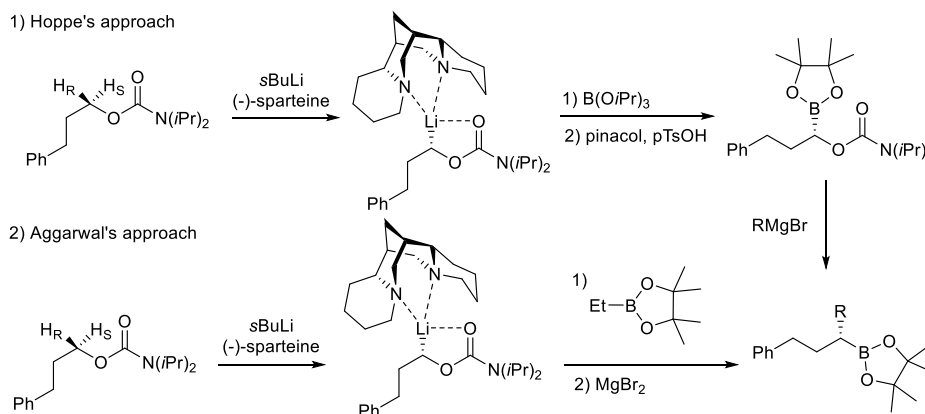
Scheme 4.4

[8] Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773.

[9] a) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, *2*, 217; b) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, *13*, 2275.

[10] Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491; This lithiation-borylation protocol was used previously by Kocienski and co-workers in the synthesis of (*S*)-(-)-*N*-acetylcolchinol: Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193.

Aggarwal and co-workers became utterly interested in this research area and were able to promote the lithiation-borylation methodology in a single step, with a broad substrate scope. As shown in Scheme 4.5, the lithiation-borylation process consists of three different steps: i) lithiation step, where the chiral lithium carbenoid is formed by α-lithiation of the carbamate (or 2,4,6-triisopropylbenzoate (TIB)), ii) borylation step, where the electrophilic quench occurs by addition of the boronic ester, forming a chiral "boron ate" complex. This step needs to be fast and stereospecific (retentive or invertive), and iii) 1,2-metallate rearrangement, where the 1,2-migration of the substituent on the boron takes place in an *anti* periplanar arrangement, the carbamate acting as a leaving group. This reaction proceeds at higher temperatures to avoid over-homologations (Scheme 4.5).[11]
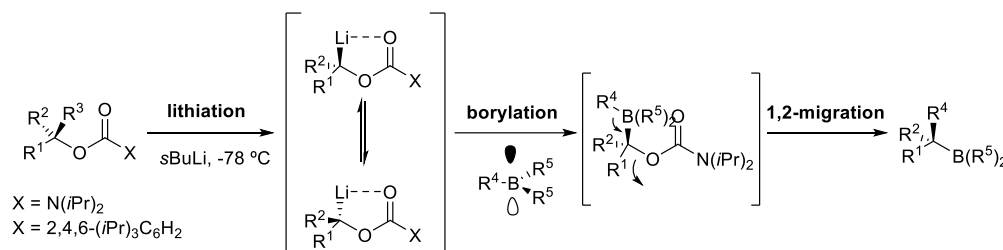
Scheme 4.5

After this useful strategy to synthesize boronic esters with high optical purity, the group of Aggarwal has been devoted to further develop this methodology towards its application in natural product synthesis and to more challenging substrates, such as tertiary boronic esters. Moreover, the ability of this methodology to carry out iterative homologations could be demonstrated, opening a powerful strategy for the synthesis of complex structures containing multiple stereocentres. This introduction will cover some of the most meaningful examples developed in the research group of Prof. Varinder K. Aggarwal.

The first approximation of lithiation-borylation process was carried out using primary carbamates and benzoates. In his sense, these substrates were treated with *s*BuLi and (-)-sparteine at -78 ºC, for the chiral ligand-assisted asymmetric deprotonation that generates the configurationally stable lithium carbamate species. Then, the reaction of these intermediates

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[11] a) Leonori, D.; Aggarwal, V. K. *Reagent-Controlled Lithiation-Borylation* p. 271-295 (Eds.: Fernández, E.; Whiting, A.), Springer, Switzerland, **2015**; b) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174; c) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24.

with organoboranes and boronic ester reagents leaded to boron-ate complexes with retention of configuration. After, 1,2-metallate rearrangement and subsequent oxidation, the desired secondary alcohols were obtained with high yields and excellent enantioselectivities (Scheme 4.6).[10]
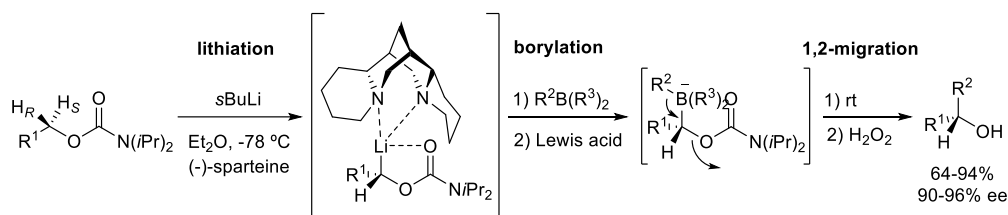
Scheme 4.6

During the investigation of the reaction it was observed that the 1,2-shift was promoted faster with boranes compared to boronic esters, thus higher temperatures were required in the cases were boronic esters were employed. On the other hand, with slow migrating groups, such as phenyl, the incorporation of a lewis acid was proved to be essential in order to occur the 1,2-migration. And in the case of very slow migrating groups, it was found that the use of more hindered triisopropylbenzoate group accelerated the rearrangement being a better leaving group.[12]

Regarding the lithiation conditions, it was shown that another alternative approach for the stereospecific lithiation consisted on the tin-lithium exchange of enantioenriched α-stannilated carbamates or benzoates. This strategy was successfully applied for example, in the total synthesis of solandelactone E.[13]

[12] a) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I. Aggarwal, V. K. *Chem. Commun.* **2011**, *47*, 12592; b) Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215.

[13] a) Robinson, A.; Aggarwal, V. K. *Org. Biomol. Chem.* **2012**, *10*, 1795; b) Robinson, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6673.
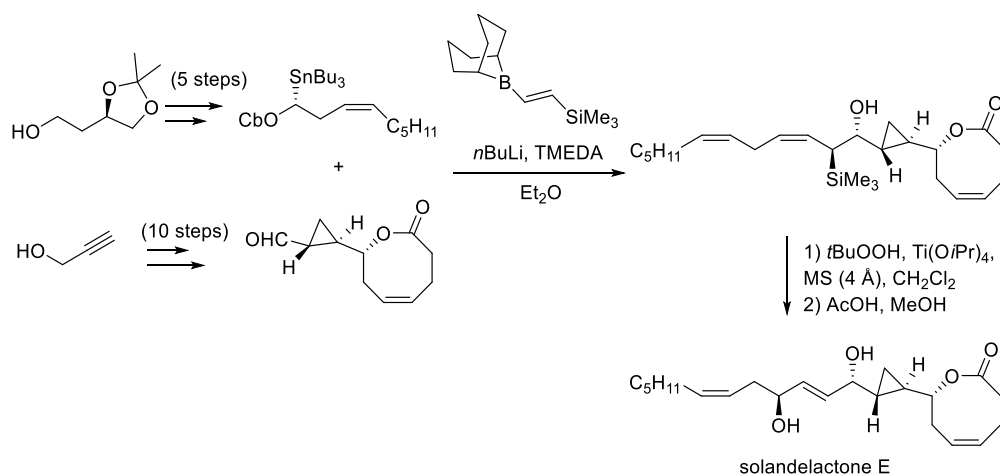
Scheme 4.7

While primary carbamates and benzoates can be employed as reagents in the lithiation-borylation methodology in a plethora of transformations,[14] the synthesis of tertiary boronic esters and boranes is much more limited because these reagents cannot be produced by commonly used methods, such as hydroboration.[15]

In this context, the group of Aggarwal contributed to this goal by using secondary alkyl benzoates,[16] silylated carbamates,[17] allylic/propargylic carbamates[18] and benzylic carbamates as substrates.[19] Secondary alkyl carbamates were found specially challenging substrates due to the low acidity of the proton that needed to be deprotonated as proved by Hoppe and Beak.[20] Nevertheless, Aggarwal and co-workers were able to solve this issue by using again the better leaving group TIB ester together with the employment of neopentyl boronic esters. Using

[14] a) Fletcher, C. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2503; b) Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12444; c) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K.; *Angew. Chem., Int. Ed.* **2010**, *49*, 4264; d) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317.

[15] a) Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124; b) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760.

[16] Pulis, A.P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054.

[17] Aggarwal, V. K.; Binanzer, M.; Ceglie, M. C. d.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vázquez-Romero, A.; Webster, M. P. *Org. Lett.* **2011**, *13*, 1490.

[18] a) Pulis, A. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2012**, *134*, 7570; b) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11795.

[19] a) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142; b) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778.

[20] a) Beak, P.; Carter, L. G. *J. Org. Chem.* **1981**, *46*, 2363; b) Hoppe, D.; Marr, F.; Brüggemann, M. Enantioselective Synthesis by Lithiation Adjacent to Oxygen and Electrophile Incorporation. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer: London, 2003; p. 73.

these new reaction conditions, the deprotonation could be promoted stereoselectively on unactivated secondary alkyl carbamates and the corresponding tertiary alcohols could be obtained in high yields and enantioselectivities for a broad scope of alkylic substituents. Transformations of chiral tertiary boronic esters to different functionalities were accomplished as well, demonstrating the value of this lithiation-borylation methodology (Scheme 4.8).[16]
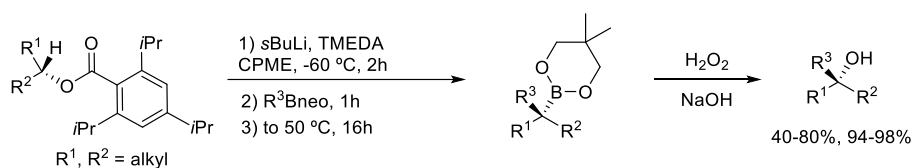
Scheme 4.8

As mentioned before, in order to contribute further to the development of new methods for the synthesis of enantioenriched tertiary boronic esters, the group became highly interested in expanding the lithiation-borylation methodology to secondary benzylic carbamates. In this context it was found that, when using boranes, the borylation step proceeded with inversion of configuration, while using boronic esters retention of configuration was observed (Scheme 4.9).
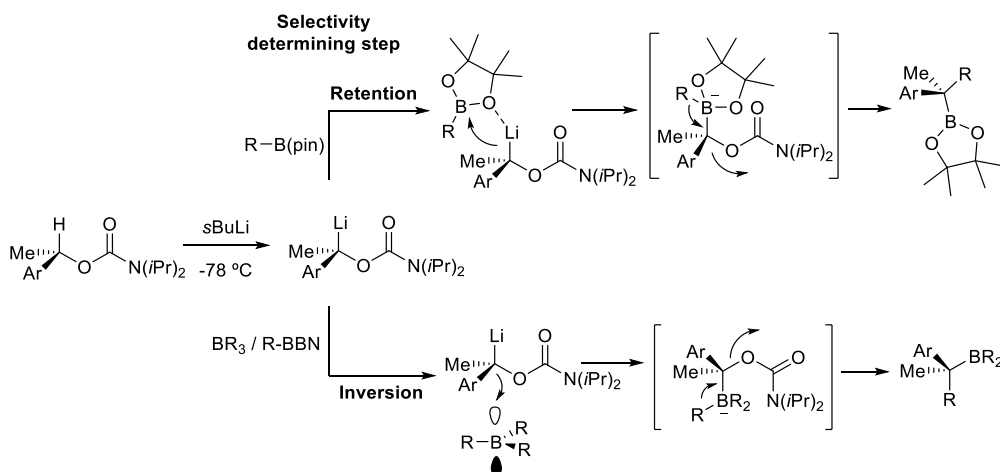
Scheme 4.9

This process as well showed a broad substrate scope being able to introduce alkyl, aryl and heteroaryl groups in high yields and with high stereospecificity.[19b,21] Additionally, this

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[21] Watson, C. G.; Aggarwal, V. K. *Org. Lett.* **2013**, *15*, 1346

strategy was also applied to iterative homologations, that were conducted without purification of the intermediates and affording the final boronic esters with up to ten contiguous methyl substituents with full stereocontrol. Different stereoisomers were able to be synthesized through reagent controlled approach, by combining chiral of lithiated species proceeding with complete stereoinduction and without observing matched and mismatched effects (Scheme 4.10).[22]
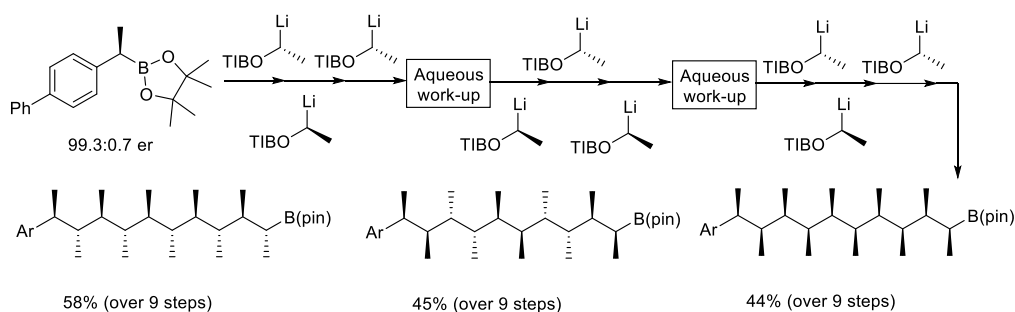
Scheme 4.10

One limitation on the use of secondary carbamates was found when applying these conditions with hindered boronic esters or with carbamates with electron withdrawing groups on the aromatic ring. In these cases, it was shown that the intermediate boronate complexes reverted back to the lithiated carbamate, and due to racemization of these species, an erosion in enantiospecificity was observed (Scheme 4.11).[19a]

[22] Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183.
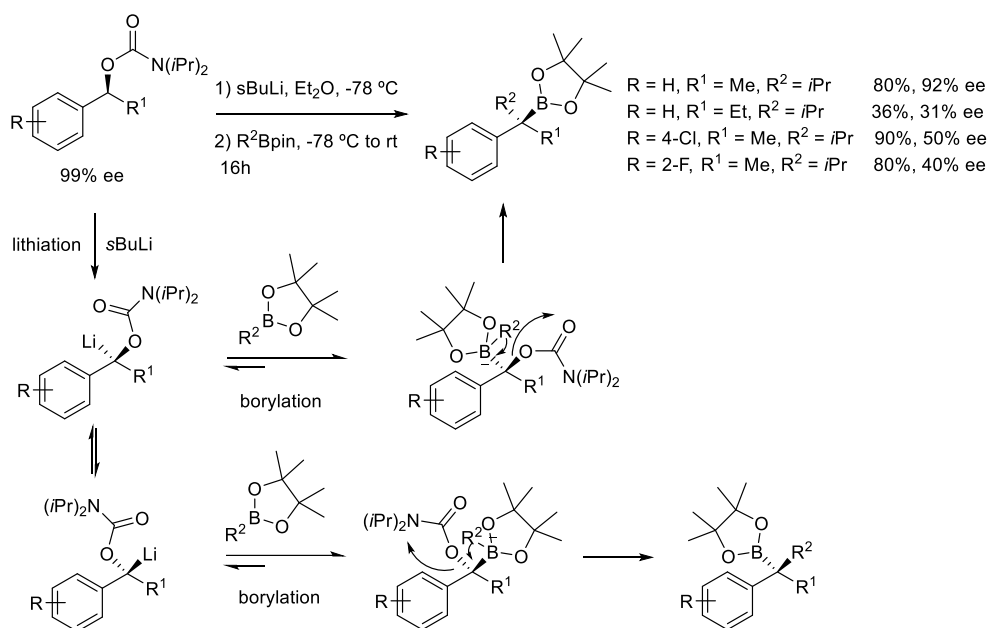
Scheme 4.11

Again, the group of Aggarwal was able to address this inconvenient by adding a lewis acid as an additive when using pinacol boronic esters. This strategy showed a faster 1,2-migration, thus the reversible pathway could be avoided. The reaction could be performed with electron-withdrawing substituents in the aromatic ring of the carbamates and most sterically demanding boronic esters could be used affording tertiary boronic esters in high yields and enantiopurities (Scheme 4.12).[19a] It is thought that the $MgBr_2$ accelerates the 1,2-migration step by coordinating to the carbamate and making it more electron deficient. Moreover, methanol also assisted the reaction by presumably reprotonating any lithiated carbamate generated from the dissociation.
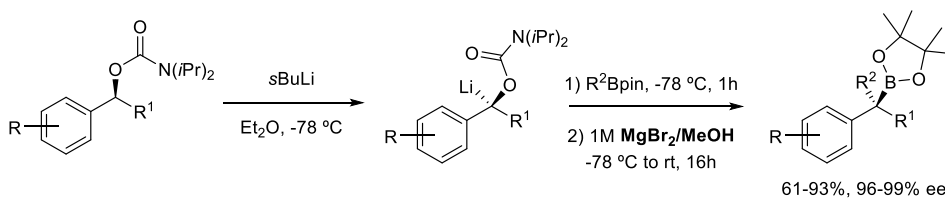
Scheme 4.12

However, the oxidation of this process was very slow and a solvent exchange was necessary prior to oxidation. Hence, it was decided to prove less hindered neopentyl boronic esters for the synthesis of adjacent tertiary benzylic stereocentres and this strategy was successfully applied to the synthesis of fluorohexestrol. By performing the reaction with the less hindered neopentyl boronic ester the synthesis of fluorexestrol could be performed in 5 steps with an overall yield of 18% (Scheme 4.13).[23] In this case, it was expected that the 1,2-rearrangement was enhanced and therefore, the ate complex would suffer less dissociation to starting materials.
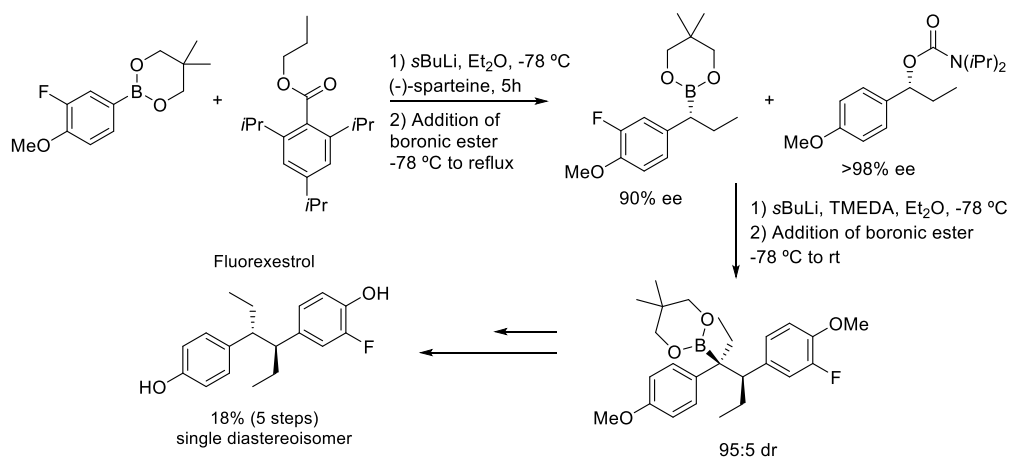
Scheme 4.13

Lithiation-borylation methodology has successfully contributed to synthesize a diverse array of enantioenriched boronic esters, as well as a plethora of natural products and pharmaceuticals, chiral building blocks and large molecules containing contiguous stereocentres with full stereocontrol. However, the usefulness of this strategy to be applied in industry is still limited due to the functional group incompatibility and more precisely, due to the cryogenic conditions that are required. It is in this context that Fandrick *et al.* decided to apply the Aggarwal's lithiation-borylation strategy to secondary benzylic carbamates in multikilogram scale. However, they became aware that the reaction should be modified to avoid the cryogenic conditions and to tolerate more functional groups. Therefore, Fandrick and co-workers further developed the synthesis of chiral tertiary boronic esters with a slight

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[23] Roesner, S.; Blair, D. J.; Aggarwal, V. K. *Chem. Sci.* **2015**, *6*, 3718.

modification of reaction conditions using lithiation-borylation methodology. Aryl bromide and iodide carbamates were proved to be suitable reagents using a weaker base, such as lithium diisoprooylamide (LDA). After some screening of reaction conditions, deuterium labeling experiments and after monitoring the reaction by ReactIR, it was postulated that in the presence of LDA, a more stable LDA-carbamate complex was being generated in equilibrium with the less stable deprotonated lithiated carbamate. This equilibrium was found to occur even at 4 ºC, and conducting the reaction in the presence of the boronic esters it was shown that the desired products were obtained in high yields and enantioselectivities, although some of the more hindered boronic esters were obtained in lower enantioselectivities. By application of these new *in situ* lithiation-borylation conditions at non-cryogenic temperatures and in the presence of the boronic ester, it was possible to avoid the formation of the unstable lithiated carbamate in high concentrations, making it an appropriate process for the application in industrial scale (Scheme 4.14).[24]
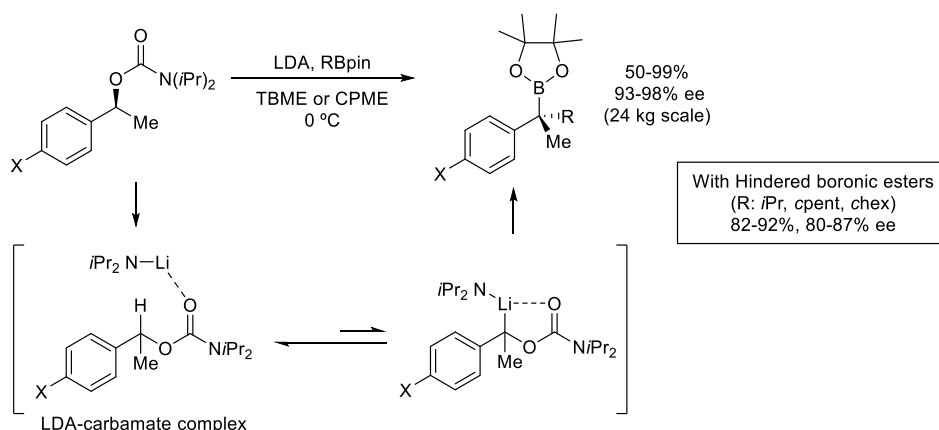
Scheme 4.14

2. SPECIFIC OBJECTIVES

After the work of Fandrick and co-workers, the group of Aggarwal became interested in this *in situ* lithiation-borylation strategy, to enable extending the scope of the reaction to substrates that until date had been impossible to be used with the standard lithiation-borylation

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[24] Fandrick, K. R.; Patel, N. D.; Mulder, J. A.; Gao, J.; Konrad, M.; Archer, E.; Buono, F. G.; Duran, A.; Schmid, R.; Daeubler, J.; Fandrick, D. R.; Ma, S.; Grinberg, N.; Lee, H.; Busacca, C. A.; Song, J. J.; Yee, N. K.; Senanayake, C. S. *Org. Lett.* **2014**, *16*, 4360.

methodology. Moreover, the improvement of conditions to carry out the reaction in higher temperatures demonstrated the applicability of the process in industrial level. Hence, we directed our efforts to develop a methodology for the lithiation-borylation process to furnish high levels of enantioselectivities using sterically hindered boronic esters under non-cryogenic conditions. In particular, neopentyl boronic esters were chosen as substrates, because these have already demonstrated their efficiency to undergo lithiation-borylation reaction with high enantioselectivities (Scheme 4.15).[19a,23]
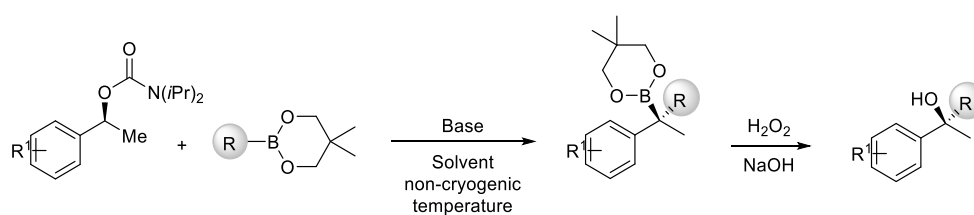
Scheme 4.15

It should be mentioned that this project was performed in collaboration with Daniel Blair, Siying Zhong and Matthew Hesse.

3. RESULTS AND DISCUSSION

Having established the objective of the work, we will outline the representative results achieved in this part of research.

Firstly, the reaction was investigated employing secondary benzylic carbamate **19a** and the hindered boronic ester **20a** in TBME as model system. Based on the work of Fandrick, freshly prepared lithium diisopropylamide (LDA) and lithium tetramethylpiperidine (LTMP) were tested to promote the deprotonation of the carbamate under *in situ* conditions. From the results summarized in Table 4.1, it can be concluded that the reaction proceeded with perfect chirality transfer employing LDA or LTMP at 0 ºC or -20 ºC, confirming our hypothesis that using neopentyl boronic esters the most hindered substrates could be converted into enantioenriched tertiary alcohols. When LDA was used as a base, the yield of the process was slightly compromised, affording the final compound in good yields (Entries 1-2). However, when employing LTMP at -20 ºC the product was isolated in 90% yield (Entry 4). Therefore, we decided to continue to explore the scope of the reaction using LTMP at -20 ºC.

Table 4.1: Reaction conditions for the reaction with neopentyl boronic esters.[a]
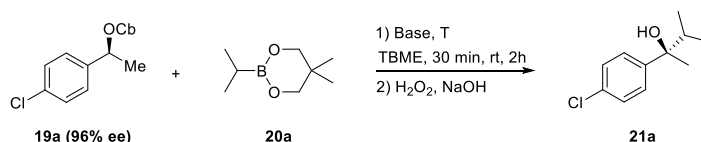
Entry	Base	T (ºC)	Yield (%)[b]	ee (%)[c]
1	**LDA**	0	66	96
2	**LDA**	-20	78	96
3	**LTMP**	0	74	96
4	**LTMP**	-20	90	96

[a] The reaction was performed in 1 mL of dry TBME and 0.5 mmol scale of **19a**, using 1.3 eq. of **20a**. [b] Isolated product yield of **cc** after flash column chromatography. [c] Enantioselectivity determined by HPLC analysis of the pure product.

With the optimized conditions in hand, we proceeded to test the reaction with other challenging carbamates (Table 4.2). The reaction worked well with substrates incorporating different halogen substituents at the *para*-position of the aryl substituent, observing in all cases complete chirality transfer (Entries 1-3). The introduction of a *meta*-substituent in the aryl moiety, also turned out to be possible, all reactions proceeding with very good yields and

maintaining the high enantioselectivities (Entries 4 and 5). However, the reaction employing two *meta*-CF$_3$ groups in the aromatic ring was inefficient furnishing the final compound in low yield and as a mixture of enantiomers (Entry 6). A biphenyl substrate as well turned out to deliver the product in high yield and enantiospecificity. Remarkably, this substrate had already been proved to undergo racemization easily in other conditions which was not happening under our conditions (Entry 7).

Table 4.2: Scope of carbamates in the *In Situ* lithiation-borylation of *i*-PrBneo.[a]
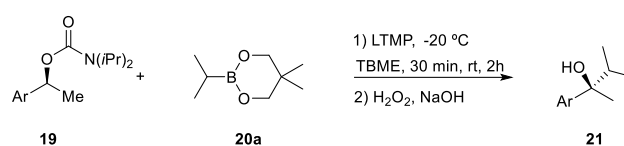
Entry	Ar	ee 19 (%)	Prod. 21	Yield (%)[b]	ee (%)[c]
1	4-ClC$_6$H$_4$ (**19a**)	96	**21a**	90	96
2	4-BrC$_6$H$_4$ (**19b**)	>98	**21b**	95	>98
3	4-IC$_6$H$_4$ (**19c**)	>98	**21c**	90	>98
4	3-CO$_2$*t*BuC$_6$H$_4$ (**19d**)	>98	**21d**	83	98
5	3-CF$_3$C$_6$H$_4$ (**19e**)	>98	**21e**	86	96
6	3,5-(CF$_3$)$_2$C$_6$H$_3$ (**19f**)	>98	**21f**	45	0
7	4-PhC$_6$H$_4$ (**19g**)	96	**21g**	96	96

[a] The reaction was performed in 1 mL of dry TBME and 0.5 mmol scale of **19**, using 1.3 eq. of **20a** and 1.25 eq. of LTMP. [b] Isolated product yield of **cc** after flash column chromatography. [c] Enantioselectivity determined by HPLC analysis of the pure product.

As it was mentioned previously the larger the group that has to rearrange on the boronic ester, the more difficult the 1,2-migration will occur, turning back to the lithiated carbamate and consequently suffering epimerization. In this context, we decied to carry out the reaction employing boronic esters with different steric demand, in particular, with the objective of comparing the presence of the neopentyl boronic esters **20** with the commonly used pinacol boronic esters **22**. The results are summarized in Scheme 4.16. For the less hindered *n*-butyl boronic ester (**23a**), the reaction worked similarly using either pinacol or neopentyl boronic esters, though complete enantiospecificity was observed only in the case where neopentyl boronic ester was used. With the unhindered cyclopropyl pinacol boronic ester also good results were furnished. Unexpectedly, for the allyl boronic esters, the pinacol derivative gave low enantiospecificity, while neopentyl boronic ester was able to undergo the reaction with

almost complete enantiospecificity. In addition, the very bulky 3-pentyl-boronic ester was tested, and in this case the reaction with the pinacol boronic ester only gave traces of product with low enantioselectivity. However, with the less hindered neopentyl boronic ester the yield and the enantioselectivity increased considerably, emphasising the improvement of the reaction with specially hindered boronic esters. It should be noted that the more challenging *tert*-butyl group (**20e**) was also tested in the reaction, but the product was obtained in low yield and as a racemic mixture using neopentyl boronic ester.
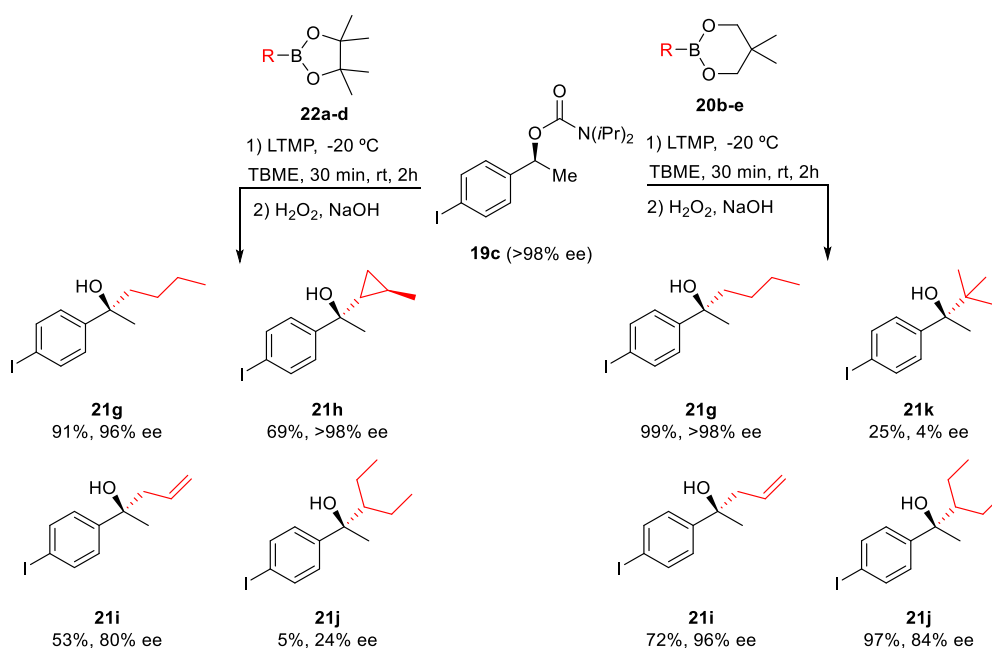
Scheme 4.16

Propargylic carbamates is a group of challenging substrates that are reported to be susceptible to racemisation. We set up the new *in situ* lithiation-borylation conditions with substrate **19h**, and the reaction turned out to proceed in high yield and with almost full chirality transfer. However, when the traditionally used stepwise lithiation-borylation conditions were applied employing neopentyl boronic esters with propargylic carbamates, adduct **21l** was isolated in 78% of enantiomeric excess, which indicated that this brand-new *in situ* lithiation-borylation methodology results a successful approach for even the most challenging substrates (Scheme 4.17).[18b,19]
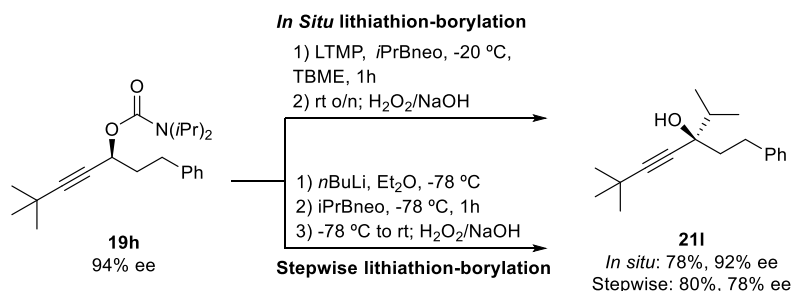
Scheme 4.17

Finally, it was also decided to test these new reaction conditions with chiral enantioeriched secondary benzylic boronic esters, another class of compounds that have shown to be prone to racemisation.[23] When using the optimized *in situ* conditions and comparing pinacol boronic ester with neopentyl boronic ester, we could observe a notable increase in the diastereoisomeric ratio of the process employing (*R*)-1-phenylethyl neopentyl boronic ester, maintaining good yields and enantiospecificities. However, working with the opposite enantiomer of the boronic esters, the reaction worked similarly for both substrates. From these results, it can be deduced that the match/mismatched effect present in the pinacol boronic esters is reduced by employing neopentyl boronic esters, indicating that the reactions were essentially non-reversible under these conditions (Scheme 4.18).
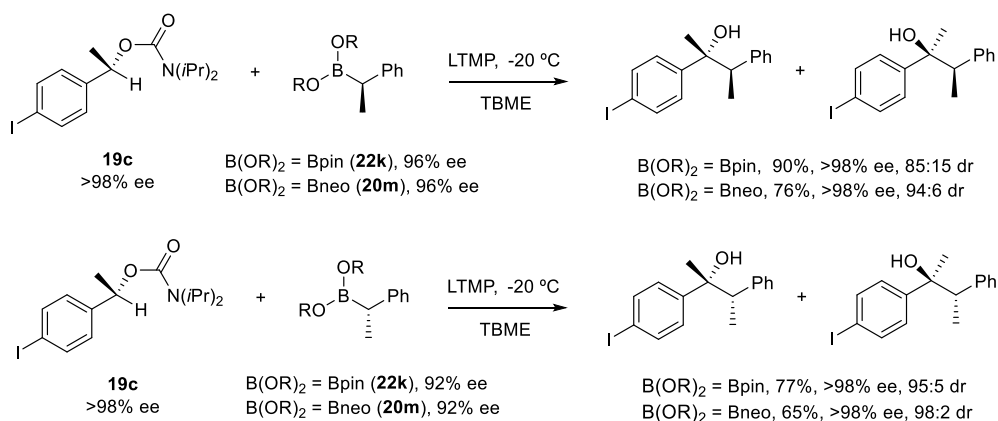
Scheme 4.18

4. CONCLUSIONS

Considering the results presented throughout this chapter, the following conclusions can be outlined:

1. LTMP has been proved to behave as a suitable lithiating reagent for the *in situ* lithiation-borylation of secondary benzylic carbamates, affording the final adducts in high yields and enantiospecificities.

2. The use of neopentyl boronic esters as the borylating reagents allows the methodology to be applied successfully to a broad range of boronic esters and carbamates, including the most hindered boronic esters under non-cryogenic temperatures.

3. It has been possible to improve the problems associated with substrates that are prone to racemisation during the process, such as propargylic carbamates, reducing the reversibility in the step associated with the formation of the boronate complex.

4. With these new *in situ* lithiation-borylation conditions, the number of tertiary boronic esters that can be prepared has been extended, allowing the presence of more functional groups and more steric demanding substituents.

5

5

Final conclusions

CONCLUSIONS

Throughout the present work it has been demonstrated that different organocatalysts are able to activate diverse substrates through different activation mechanisms for the construction of valuable organic molecules of interested synthetic value, showing a relevant role in asymmetric organocatalysis. From the obtained results, we could conclude the following:

a) Hydrazones as acyl anion equivalents in the 1,2-addition to dihydropyrroles. The ability of hydrazones to act as C nucleophiles has been outlined in the 1,2-addition reaction of hydrazones to dihydropyrroles catalyzed by a chiral Brønsted acid catalyst. These catalysts have been able to activate cyclic enecarbamates and enethioureas as *N*-(thio)acyl iminium ions generating the phosphate anion for stereocontrol under counterion catalysisto provide numerous chiral hydrazones in high yields and enantioselectivities. These hydrazones could be converted into the corresponding enantioenriched proline derivatives after hydrazone cleavage, showing their potential as acyl anion equivalents.

b) Enantioselective 1,6-Aza-Michael/1,4-Michael cascade reaction under vinylogous iminium ion activation. Cyclic dienones are known to be activated as vinylogous iminium ions by a chiral cinchona-based primary amine catalyst. This strategy has been applied for the development of more sophisticated cascade sequence. In this sense, employing 2-aminomalonates as double nucleophiles and cyclic dienones as electrophiles, the 1,6-aza-Michael/1,4-Michael cascade reaction has been performed with complete regiocontrol and in high yields. 2-aminomalonates has shown their ability to act as bisnucleophiles, firstly acting as *N*-donors and then, as C-nucleophiles exclusively. This reaction provides highly valuable spirocyclic adducts in high yields, though the diastereoselectivity and enantioselectivity of the process still need to be investigated more thoroughly to achieve better results.

c) Synthesis of enantioenriched hindered tertiary boronic esters. It has been possible to address the problem encountered in the *in situ* lithiation-borylation reaction of secondary benzylic carbamates with hindered boronic esters. LTMP has shown the ability to lithiate secondary carbamates at non-cryogenic temperatures, and react with the more

hindered boronic esters by using neopentyl boronic esters instead of the pinacol derivatives. By applying this methodology, the most hindered tertiary boronic esters have been possible to be synthesized in high yields and enantioselectivities.

6

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Experimental

1. General Methods and Materials

2. Hydrazones as Acyl Anion Equivalents in the Chiral Phosphoric Acid-Catalyzed Enantioselective Addition to Dihydropyrroles

2.1. General structures of cyclic enamides **1a-k**

2.1.1. Synthesis of cyclic enethioureas **1d-i**

2.2. General structures of hydrazones **2a-t**

2.2.1. General Procedures for the Synthesis of Hydrazones **2b, 2e-f and 2j-r,t**

2.3. Synthesis of hydrazones **3a-af**

2.4. Transformations of the adducts

2.4.1. Synthesis of compound **5a**

2.4.2. Synthesis of compounds **6a-b**

2.4.3. Synthesis of compound **7a**

2.4.4. Synthesis of compounds **9a** and **10a**

2.4.5. Synthesis of compounds **11a-e**

2.4.6. Synthesis of compounds **13a-c**

3. Aminocatalytic Vinylogous Iminium Ion Strategy in Organocascade Reactions

3.1. General structures of cyclic dienones **14a-b**

3.2. General structures of *N*-substituted 2-aminomalonates **15a-k**

3.2.1. Synthesis of 2-aminomalonate **15b**

1. General Methods and Materials

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25ºC and 100ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) or a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for ^{1}H NMR, CDCl$_3$, 77.16 ppm for ^{13}C NMR and DMSO, 2.50 ppm for ^{1}H NMR, DMSO-d$_6$, 39.52 ppm for ^{13}C NMR and acetone, 2.05 ppm for ^{1}H NMR, acetone-d$_6$, 206.26 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 assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular configuration and to assist in convoluting complex multiplet signals.[1] Infrared spectra (IR) were measured in a Jasco FT/IR 4100 (ATR), in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer under electronic impact (EI) conditions. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%). High-resolution mass spectra (HRMS) were recorded on an Acquity GC coupled to a TOF mass spectrometer (GCT micromass) using chemical ionization (CI) or on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI+ or ESI-). Melting points (M.p.) were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak AD-H, AS-H, IA, ID-3, IE-3, IC and AY-3 and Chiralcel OZ-3, OD-3 columns were used; specific conditions are indicated for each case. Optical rotations ($[\alpha]_D^{rt}$) were measured at 20ºC on a Jasco P-2000 polarimeter with a sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration are specified in each case. X-ray data collections were performed in an

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

Agilent Supernova diffractometer equipped with an *Atlas* CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 μm FWHM beam size). The sample was kept at 100(1)K with a *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.

Analytical grade solvents and commercially available reagents were used without further purification. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated aluminium-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation and by immersion in phosphomolybdic acid, *p*-anisaldehyde or KMnO$_4$-H$_2$SO$_4$ ethanolic solutions.[2] For flash chromatography Merck 60, 230-400 mesh silica gel was used.[3] Anhydrous solvents were dried with activated molecular sieves prior to use.[4] For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used. For reactions carried out under inert conditions, the argon was previously dried through a column of P$_2$O$_5$ and a column of KOH and CaCl$_2$. All the glassware was dried for 12 hours prior to utilizing in an oven at 140ºC, and allowed to cool under a dehumidified atmosphere.[5] Reactions at reduced temperatures were carried out using an Isotempt refrigerator.

[2] Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlin, **1969**.

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

[4] Armarego, W. L. F.; Chai, C. L. L.; *Purification of Laboratory Chemicals*, Elsevier, Oxford, **2003**.

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

2. HYDRAZONES AS ACYL ANION EQUIVALENTS IN THE CHIRAL PHOSPHORIC ACID-CATALYZED ENANTIOSELECTIVE ADDITION TO DHYDROPYRROLES

2.1. General Structures of cyclic Enamides 1a-k
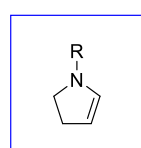
1a: R = Boc
1b: R = Fmoc
1c: R = Ph
1d: R = CSNHBn
1e: R = CSNHAr
Ar: 3,5-$(CF_3)_2C_6H_3$
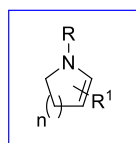
1f: n = 1; R = CSNHAr; R^1 = 4,4-$(Me)_2$
1g: n = 1; R = CSNHAr; R^1 = 3-Me
1h: n = 1; R = CSNHAr; R^1 = 3-Et
1i: n = 2; R = CSNHAr; R^1 = H
1j: n = 2; R = Boc; R^1 = H
1k: n = 3; R = Boc; R^1 = H

Cyclic enecarbamates **1a**, **1j** and **1k** are commercially available. Cyclic enamides **1b**[6] and **1c**[7] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

2.1.1. Synthesis of cyclic enethioureas **1d-i**
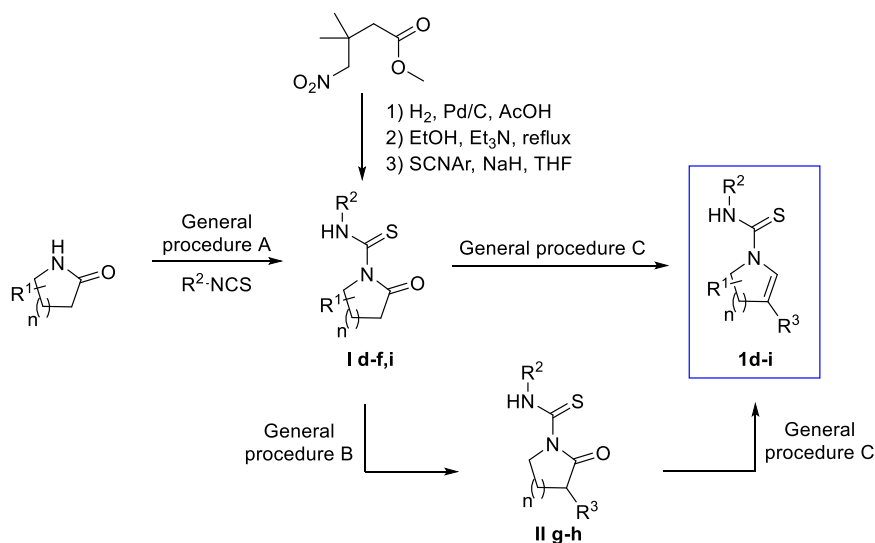
Scheme 6.1. General overview for the synthesis of **1d-i**

[6] Gerard, B.; O´shea, M. W.; Donckele, E.; Kesavan, S.; Akella, L. B.; Xu, H.; Jacobsen, E. N.; Marcaurelle, L. A. *ACS Comb. Sci.* **2012**, *14*, 621.
[7] For the synthesis, see: Hyeok, S.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160; For the spectroscopic data, see: Seto, Y.; Guengerich, F. P. *J. Biol. Chem.* **1993**, *268*, 9986.

General Procedure A: Lactams **I d-e and I i** were prepared according to literature procedure[8] as followed. To a stirred solution of pyrrolidin-2-one (13.4 mmol, 1.0 eq.) in THF (60 mL) at 0 °C, was added portionwise NaH (60%, 20.1 mmol, 1.5 eq.). After stirring at 0°C for 30 min, the corresponding isothiocyanate (20.1 mmol, 1.5 eq.) was slowly added at -78 °C and the reaction was stirred and allowed to warm to room temperature overnight. Then a solution of saturated NH_4Cl was added to quench the reaction, and the mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography on silica gel. Spectroscopic data for lactam **Id**[8] was in agreement with the literature.

General Procedure B: 3-substituted lactams **II g-h** were prepared according to an addapted literature procedure[9] as followed. To a stirred solution of *N*-substituted-pyrroldin-2-one (9.82 mmol, 1.0 eq.) in THF (47 mL) at -78 °C, was added dropwise a solution of lithium bis(trimethylsilyl)amide (LHMDS) (20.6 mmol, 2.1 eq.), followed by stirring for 1 hour. Then, iodomethane or iodoethane (9.82 mmol, 1.0 eq.) was dropwise added. Thereafter, the temperature was gradually raised to -30ºC for 2 hours. 50 mL of EtOAc was added to the solution, and the reaction solution was washed with aqueous NH_4Cl, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, then the residue was purified by flash column chromatography on silica gel.

General Procedure C: Cyclic enethioureas **1d-i** were prepared in two steps according to an addapted literature procedure[8] as followed. 1st step: A solution of *N*-substituted-lactams (6.4 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) was cooled to −78°C under argon atmosphere. Then super-hydride (1 M in THF, 14.1 mmol, 1.1 eq.) was slowly added and the reaction was stirred for 30 min at −78°C and 2 hours at room temperature. Then, a saturated solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude pyrrolidinol derivative which was purified by column chromatography (hexanes/EtOAc gradient from 19:1 to 7:3). 2nd step: To a solution of previously synthesized intermediates (3.33 mmol, 1.0 eq.) in a mixture of tetrahydrofuran/toluene (8 mL/16 mL) and cooled to -78ºC. Then, DMAP (0.128

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[8] Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2012**, *18*, 5869.
[9] Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

mmol, 0.02 eq.), and trifluoroacetic anhydride (7.7 mmol, 1.2 eq.) were added. After 5 minutes Et$_3$N (35.2 mmol, 5.5 eq.) was slowly added during 30 minutes and the reaction mixture was allowed to warm to room temperature for 2 hours. Then, water was added, and the organic layer was dried over Na$_2$SO4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography on silica gel. Spectroscopic data for lactam **1d**[8] was in agreement with the literature.

*Procedure for the synthesis of lactam **If** is indicated.*
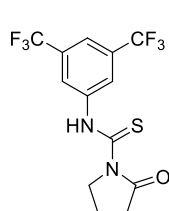
N-(3,5-bis(trifluoromethyl)phenyl)-2-oxopyrrolidine-1-carbothioamide (Ie). Following the general procedure A, **Ie** (2.15 g, 6.0 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 98% yield as colorless cristals starting from pyrrolidin-2-one (0.47 mL, 6.15 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.68 mL, 9.2 mmol) and NaH (0.37 g, 9.2 mmol) in tetrahydrofuran (28 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.86 (bs, 1H, NH), 8.18 (s, 2H, C$_{Ar}$-H), 7.72 (s, 1H, C$_{Ar}$-H), 4.35-4.20 (m, 2H, C$_5$), 2.83 (t, *J* = 8.1 Hz, 2H, C$_3$-H), 2.18-2.04 (m, 2H, C$_4$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 179.5 (CS), 177.3 (C$_2$), 139.7 (C$_{Ar}$-C), 132.2 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2 × CCF$_3$), 124.4 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C$_{Ar}$-H), 123.1 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 119.8 (q, $^3J_{C\text{-}F}$ = 3.9 Hz, C$_{Ar}$-H), 51.4 (C$_5$), 34.7 (C$_3$), 16.6 (C$_4$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.0 (2 × CF$_3$); R$_f$. 0.53 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2992 (NH), 1704 (C=O), 1276 (C=S), 1120 (C-N st); MS (EI) m/z (%): 271 (100), 252 (24), 213 (25), 202 (13), 163 (15), 144 (8), 85 (13), 69 (9); HRMS: Calculated for [C$_{13}$H$_{11}$N$_2$OSF$_6$]$^+$: 357.0496 [(M+H)$^+$]; found: 357.0500; M.p. (CH$_2$Cl$_2$): 101-103 ºC.

N-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-oxopyrrolidine-1-carbothioamide (If).
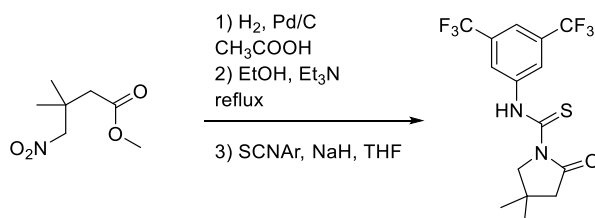
Pd/C (53.2 mg, 10wt%) was added to a solution of methyl 3,3-dimethyl-4-nitrobutanoate[10](1.86 g, 10.6 mmol) in acetic acid (26.5 mL) and the mixture was stirred under a hydrogen atmosphere at room temperature for 12 hours. After that, the mixture was filtered through celite and the solvent was evaporated. Then, the crude product was dissolved in EtOH (20 mL) and Et₃N was added to maintain basic pH. The solution was stirred at reflux overnight. Then, solvent was evaporated and the crude mixture was dissolved in Et₂O and 1M HCl was added. Aqueous phase is extracted with Et₂O (2 × 20 mL), organic phases were collected, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Then, to a stirred solution of the crude product in THF (48 mL) at 0 °C, was added portionwise NaH (0.64 g, 60%, 15.9 mmol). After stirring at 0°C for 30 min, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (3.0 mL, 15.9 mmol) was slowly added at -78 °C and the reaction was stirred and allowed to warm to room temperature overnight. Then a solution of saturated NH₄Cl was added to quench the reaction, and the mixture was extracted with EtOAc, and the organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel (Hexanes/EtOAc) to afford 2.7 g of **If** (7.0 mmol, 66%) as a white solid. ^{1}H NMR (300 MHz, CDCl₃): δ 12.79 (s, 1H, NH), 8.18 (s, 2H, C$_{Ar}$-H), 7.72 (s, 1H, C$_{Ar}$-H), 4.01 (s, 2H, C₅-H), 2.62 (s, 2H, C₃-H), 1.23 (s, 6H, 2 × CH₃); ^{13}C NMR (75 MHz, CDCl₃): δ 179.7 (CS), 176.7 (C₂), 139.8 (C$_{Ar}$-C), 132.2 (q, $^{2}J_{C-F}$ = 33.7 Hz, 2 × **C**CF₃), 123.2 (q, $^{1}J_{C-F}$ = 272.8 Hz, 2 × CF₃), 124.5 (C$_{Ar}$-H), 124.4 (C$_{Ar}$-H), 119.8 (q, $^{3}J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 63.6 (C₅), 49.1 (C₃), 31.2 (C₄), 27.2 (2 × CH₃); ^{19}F NMR (282 MHz, CDCl₃): δ -63.0 (2 × CF₃); R$_f$: 0.88 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2960 (NH), 1709 (C=O), 1276 (C=S), 1127 (C-N st); MS (EI) m/z (%): 271 (100), 252 (24), 213 (25), 202 (13), 163 (15), 143 (8), 113 (10), 69 (10); HRMS: Calculated for [C₁₅H₁₅N₂OSF₆]⁺: 385.0809 [(M+H)⁺]; found: 385.0808; M.p. (CH₂Cl₂): 93-95 ºC.
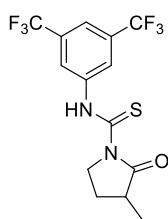
N-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-2-oxopyrrolidine-1-carbothioamide (Ig). Following the general procedure B, **Ig** (3.5 g, 9.45 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) in 96% yield as a colorless oil starting from *N*-3,5-bis(trifluoromethyl)phenyl-pyrroldin-2-one (3.5 g, 9.82 mmol), lithium

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[10] Bunce, R. A.; Drumright, R. E. *The New Journal for Organic Synthesis*, **1987**, *19*, 471.

bis(trimethylsilyl)amide (20.6 mL, 20.6 mmol) and iodomethane (0.62 mL, 9.82 mmol) in THF (47 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.92 (bs, 1H, NH), 8.20 (s, 2H, C$_{Ar}$-H), 7.72 (s, 1H, C$_{Ar}$-H), 4.39 (ddd, J = 11.5, 8.9, 2.5 Hz, 1H, C$_5$-H$_a$), 3.99 (ddd, J = 11.5, 9.5, 7.5 Hz, 1H, C$_5$-H$_b$), 3.03-2.79 (m, 1H, C$_4$-H$_a$), 2.41-2.16 (m, 1H, C$_4$-H$_b$), 1.81-1.64 (m, 1H, C$_3$-H), 1.32 (d, J = 7.0 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 179.9 (CS), 179.5 (C$_2$), 139.8 (C$_{Ar}$-C), 132.2 (q, $^2J_{C-F}$ = 33.7 Hz, 2 × **C**CF$_3$), 124.2 (q, $^3J_{C-F}$ = 2.9 Hz, C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 119.7 (q, $^3J_{C-F}$ = 3.6 Hz, C$_{Ar}$-H), 49.2 (C$_5$), 40.6 (C$_3$), 25.6 (C$_4$), 15.5 (CH$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.0 (2 × CF$_3$); R$_f$: 0.78 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2978 (NH), 2925 (C-H st), 1703 (C=O), 1276 (C=S), 1126 (C-N st); MS (EI) m/z (%): 271 (100), 252 (23), 213 (24), 202 (10), 163 (11), 143 (7), 99 (13), 56 (8); HRMS: Calculated for [C$_{14}$H$_{13}$N$_2$OSF$_6$]$^+$: 371.0653 [(M+H)$^+$]; found: 371.0649.
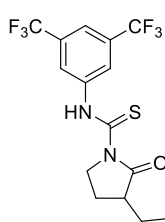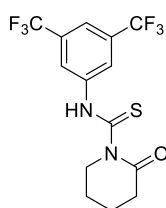

N-(3,5-bis(trifluoromethyl)phenyl)-3-ethyl-2-oxopyrrolidine-1-carbothioamide (Ih). Following the general procedure B, **Ih** (0.84 g, 2.19 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 52% yield as a white solid starting from *N*-3,5-bis(trifluoromethyl)phenyl-pyrroldin-2-one (1.5 g, 4.22 mmol), lithium bis(trimethylsilyl)amide (8.84 mL, 8.84 mmol) and iodoethane (0.342 mL, 4.22 mmol) in THF (20 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.94 (bs, 1H, NH), 8.20 (s, 2H, C$_{Ar}$-H), 7.72 (s, 1H, C$_{Ar}$-H), 4.39 (ddd, J = 11.8, 8.9, 3.1 Hz, 1H, C$_5$-H$_a$), 4.02 (ddd, J = 11.7, 9.0, 7.6 Hz, 1H, C$_5$-H$_b$), 2.79 (ddd, J = 18.5, 8.8, 4.8 Hz, 1H, C$_4$-H$_a$), 2.45-2.15 (m, 1H, C$_3$-H), 2.11-1.87 (m, 1H, C$_4$-H$_b$), 1.87-1.68 (m, 1H, C**H**$_a$H$_b$CH$_3$), 1.68-1.47 (m, 1H, CH$_a$**H**$_b$CH$_3$), 1.05 (t, J = 7.5 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 179.5 (C$_2$), 179.3 (CS), 139.8 (C$_{Ar}$-C), 132.2 (q, $^2J_{C-F}$ = 33.5 Hz, 2 × **C**CF$_3$), 124.3 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 119.7 (q, J = 3.2 Hz, C$_{Ar}$-H), 49.4 (C$_5$), 47.0 (C$_3$), 23.8 (C$_4$), 22.9 (**C**H$_2$CH$_3$), 11.4 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.0 (2 × CF$_3$); R$_f$: 0.83 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2977 (NH), 2877 (C-H st), 1699 (C=O), 1274 (C=S), 1125 (C-N st); MS (EI) m/z (%): 271 (100), 252 (25), 213 (26), 202 (12), 163 (13), 83 (35), 69 (10); HRMS: Calculated for [C$_{15}$H$_{15}$N$_2$OSF$_6$]$^+$: 385.0809 [(M+H)$^+$]; found: 385.0808; M.p. (CH$_2$Cl$_2$): 77-79 °C.
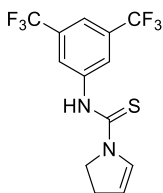
N-(3,5-bis(trifluoromethyl)phenyl)-2-oxopiperidine-1-carbothioamide (Ii). Following the general procedure A, **Ii** (1.1 g, 2.97 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 98% yield as a yellow solid starting from piperidin-2-one (0.306 g, 3.03 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.85 mL, 4.5 mmol) and NaH (0.18 g, 4.5 mmol) in tetrahydrofuran (11 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.12 (bs, 1H, NH), 8.03 (s, 2H, C$_{Ar}$-H), 7.58 (s, 1H, C$_{Ar}$-H), 3.88 (t, J = 5.9 Hz, 2H, C$_6$-H), 2.70-2.60 (m, 2H, C$_3$-H), 2.05-1.79 (m, 4H, C$_4$-H + C$_5$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 176.2 (CS), 152.5 (C$_2$), 139.5 (C$_{Ar}$-C), 132.4 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, 2 × **C**CF$_3$), 123.3 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 120.1 (q, $^3J_{C\text{-}F}$ = 2.7 Hz, C$_{Ar}$-H), 117.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C$_{Ar}$-H), 44.1 (C$_6$), 34.4 (C$_3$), 22.5 (C$_5$), 19.9 (C$_4$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.0 (2 × CF$_3$); R$_f$: 0.61 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2956 (NH), 1662 (C=O), 1275 (C=S), 1125 (C-N st); MS (EI) m/z (%): 271 (100), 252 (26), 213 (25), 202 (13), 163 (15), 143 (9), 83 (23), 69 (10); HRMS: Calculated for [C$_{14}$H$_{13}$N$_2$OSF$_6$]$^+$: 371.0653 [(M+H)$^+$]; found: 371.0657; M.p. (CH$_2$Cl$_2$): 77-79 °C.

N-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (1e). Following the general procedure C, **1e** (862 mg, 2.53 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 76% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2-oxopyrrolidine-1-carbothioamide **Ie** (1.19 g, 3.3 mmol) and LiEt$_3$BH (7.0 mL, 7.0 mmol) in tetrahydrofuran (7 mL). And then, DMAP (8.2 mg, 0.067 mmol), TFAA (0.57 mL, 4.0 mmol) and Et$_3$N (2.57 mL, 18.4 mmol) in tetrahydrofuran/toluene (4 mL/8 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.89 (s, 2H, C$_{Ar}$-H), 7.64 (s, 1H, C$_{Ar}$-H), 7.13 (s, 1H, C$_2$-H), 5.53 (s, 1H, C$_3$-H), 4.14-3.99 (m, 2H, C$_5$-H), 2.93-2.78 (m, 2H, C$_4$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 174.5 (CS), 140.5 (C$_{Ar}$-C), 131.2 (C$_2$), 131.9 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, 2 × **C**CF$_3$), 124.4 (C$_{Ar}$-H), 123.2 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 118.7 (C$_{Ar}$-H), 115.2 (C$_3$), 53.6 (C$_5$), 29.8 (C$_4$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.0 (2 × CF$_3$); R$_f$: 0.46 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}:3197 (NH), 2910 (C-H st), 1537 (C=C), 1277 (C=S), 1125 (C-N st); MS (EI) m/z (%): 271 (100), 252 (26), 213 (24), 202 (12), 163 (16), 143 (9), 83 (34), 69 (10); HRMS: Calculated for [C$_{13}$H$_{11}$N$_2$SF$_6$]$^+$: 341.0547 [(M+H)$^+$]; found: 341.0554; M.p. (CH$_2$Cl$_2$): 142-144 °C.
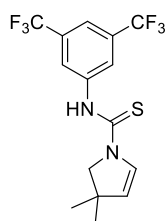
***N*-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (1f).** Following the general procedure E, **1f** (465 mg, 1.26 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 92% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-oxopyrrolidine-1-carbothioamide **If** (530 mg, 1.372 mmol) and LiEt$_3$BH (2.88 mL, 2.88 mmol) in tetrahydrofuran (3 mL). And then, DMAP (3.4 mg, 0.0274 mmol), TFAA (0.23 mL, 1.65 mmol) and Et$_3$N (1.05 mL, 7.55 mmol) in tetrahydrofuran/toluene (1.5 mL/3.5 mL). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 9.53 (s, 1H, NH), 8.26 (s, 2H, C$_{Ar}$-H), 7.69 (s, 1H, C$_{Ar}$-H), 7.21 (d, *J* = 4.2 Hz, 1H, C$_2$-H), 5.46 (d, *J* = 4.6 Hz, 1H, C$_3$-H), 3.86 (s, 2H, C$_5$-H), 1.21 (s, 6H, 2 × CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 174.2 (CS), 142.0 (C$_{Ar}$-C), 129.5 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$), 128.4 (C$_2$), 124.1 (C$_3$), 123.6 (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 273.0 Hz, 2 × CF$_3$), 116.0 (C$_{Ar}$-H), 62.9 (C$_5$), 42.0 (C$_4$), 27.5 (C(**C**H$_3$)$_2$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -63.0 (2 × CF$_3$); R$_f$: 0.80 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2960 (NH), 2931 (C-H st), 1534 (C=C), 1274 (C=S), 1125 (C-N st); MS (EI) m/z (%): 271 (100), 252 (23), 213 (23), 202 (12), 163 (14), 143 (7), 83 (35), 69 (8); HRMS: Calculated for [C$_{15}$H$_{15}$N$_2$SF$_6$]$^+$: 369.0860 [(M+H)$^+$]; found: 369.0866; M.p. (CH$_2$Cl$_2$): 123-125 ºC.

***N*-(3,5-bis(trifluoromethyl)phenyl)-4-methyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide (1g).** Following the general procedure C, **1g** (868 mg, 2.45 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 57% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-2-oxopyrrolidine-1-carbothioamide **IIg** (1.6 g, 4.3 mmol) and LiEt$_3$BH (9.0 mL, 9.0 mmol) in tetrahydrofuran (10 mL). And then, DMAP (10.5 mg, 0.086 mmol), TFAA (0.73 mL, 5.17 mmol) and Et$_3$N (3.3 mL, 23.7 mmol) in tetrahydrofuran/toluene (5.5 mL/11 mL). ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): δ 9.36 (bs, 1H, NH), 8.24 (s, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.08 (s, 1H, C$_2$-H), 4.23-4.05 (m, 2H, C$_5$-H), 2.73-2.65 (m, 2H, C$_4$-H), 1.82 (s, 3H, CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 172.3 (CS), 142.3 (C$_{Ar}$-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$), 125.2 (C$_2$), 123.2 (C$_{Ar}$-H), 122.9 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 115.6 (q, $^3J_{C-F}$ = 4.1 Hz, C$_{Ar}$-H), 49.7 (C$_5$), 32.7 (C$_3$), 13.0 (CH$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.69 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2930 (NH), 2820 (C-H st), 1540 (C=C), 1274 (C=S), 1123 (C-N st); MS (EI)

m/z (%): 271 (100), 252 (22), 213 (22), 202 (10), 163 (12), 143 (7), 83 (31), 69 (6); HRMS: Calculated for $[C_{14}H_{13}N_2SF_6]^+$: 355.0704 $[(M+H)^+]$; found: 355.0712; M.p. (CH$_2$Cl$_2$): 144-146 ºC.
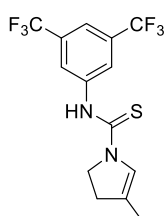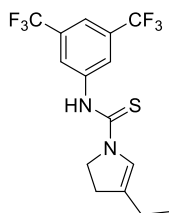
N-(3,5-bis(trifluoromethyl)phenyl)-4-ethyl-2,3-dihydro-1H-pyrrole-1-carbothioamide (1h). Following the general procedure C, **1h** (244 mg, 0.66 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 51% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-ethyl-2-oxopyrrolidine-1-carbothioamide **IIh** (500 mg, 1.3 mmol) and LiEt$_3$BH (2.7 mL, 2.7 mmol) in tetrahydrofuran (3.0 mL). And then, DMAP (3.2 mg, 0.026 mmol), TFAA (0.219 mL, 1.55 mmol) and Et$_3$N (0.99 mL, 7.12 mmol) in tetrahydrofuran/toluene (1.7 mL/3.4 mL). ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): δ 9.38 (bs, 1H, NH), 8.24 (s, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.08 (s, 1H, C$_2$-H), 4.16-4.09 (m, 2H, C$_5$-H), 2.75-2.64 (m, 2H, C$_4$-H), 2.19 (q, *J* = 7.4 Hz, 2H, **CH**$_2$CH$_3$), 1.10 (t, *J* = 7.4 Hz, 3H, CH$_2$**CH**$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 172.4 (CS), 142.3 (C$_{Ar}$-C), 131.4 (C$_3$), 129.5 (q, $^2J_{C-F}$ = 32.8 Hz, 2 × **C**CF$_3$), 124.4 (C$_2$), 123.2 (C$_{Ar}$-H), 122.9 (q, $^1J_{C-F}$ = 272.6 Hz, 2 × CF$_3$), 115.6 (C$_{Ar}$-H), 49.6 (C$_5$), 30.8 (C$_4$), 20.9 (**CH**$_2$CH$_3$), 11.5 (CH$_2$**CH**$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.58 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2971 (NH), 1537 (C=C), 1274 (C=S), 1126 (C-H st); MS (EI) m/z (%): 271 (100), 252 (25), 213 (26), 202 (10), 163 (11), 83 (10), 69 (12); HRMS: Calculated for $[C_{15}H_{15}N_2SF_6]^+$: 369.0860 $[(M+H)^+]$; found: 369.0863; M.p. (CH$_2$Cl$_2$): 133-135 ºC.
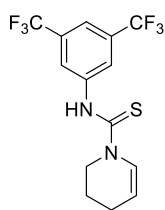
N-(3,5-bis(trifluoromethyl)phenyl)-3,4-dihydropyridine-1(2H)-carbothioamide (1i). Following the general procedure C, **1i** (64.4 mg, 0.18 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 8:2) in 21% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2-oxopiperidine-1-carbothioamide **Ii** (320 mg, 0.86 mmol) and LiEt$_3$BH (1.8 mL, 1.8 mmol) in tetrahydrofuran (2 mL). And then, DMAP (2.1 mg, 0.017 mmol), TFAA (0.146 mL, 1.03 mmol) and Et$_3$N (0.66 mL, 4.72 mmol) in tetrahydrofuran/toluene (1.1 mL/ 2.2 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (s, 2H, C$_{Ar}$-H), 7.60 (s, 1H, C$_{Ar}$-H), 7.49 (bs, 1H, NH), 6.96-6.85 (m, 1H, C$_2$-H), 5.36-5.22 (m, 1H, C$_3$-H), 4.20-3.98 (m, 2H, C$_6$-H), 2.32-2.07 (m, 2H, C$_4$-H), 2.01-1.89 (m, 2H, C$_5$-H); ^{13}C NMR (75

MHz, CDCl$_3$): δ 179.4 (CS), 141.1 (C$_{Ar}$-C), 132.1 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, 2 × **C**CF$_3$), 126.4 (C$_2$), 123.3 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, C$_{Ar}$-H), 123.2 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 118.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C$_{Ar}$-H), 113.5 (C$_3$), 47.7 (C$_6$), 22.3 (C$_5$), 22.0 (C$_4$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.1 (2 × CF$_3$); R$_f$: 0.68 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3198 (NH), 2830 (C-H st), 1530 (C=C), 1274 (C=S), 1124 (C-N st); MS (EI) m/z (%): 271 (100), 252 (25), 213 (25), 202 (12), 163 (15), 143 (8), 83 (24), 69 (9); HRMS: Calculated for [C$_{14}$H$_{13}$N$_2$SF$_6$]$^+$: 355.0704 [(M+H)$^+$]; found: 355.0710; M.p. (CH$_2$Cl$_2$): 112-114 ºC.

2.2. General Structures of Hydrazones 2a-t

2a: R^1 = 4-MeOC$_6$H$_4$; R^2 = CO$_2$Et
2b: R^1 = 4-MeSC$_6$H$_4$; R^2 = CO$_2$Et
2c: R^1 = Ph; R^2 = CO$_2$Et
2d: R^1 = 4-NO$_2$C$_6$H$_4$; R^2 = CO$_2$Et
2e: R^1 = *t*-Bu; R^2 = CO$_2$Et
2f: R^1 = Ph; R^2 = CO$_2$*i*Pr
2g: R^1 = Ph; R^2 = COMe
2h: R^1 = Ph; R^2 = CF$_3$
2i: R^1 = Ph; R^2 = C$_6$F$_5$
2j: R^1 = Ph; R^2 = 4-(CN)C$_6$H$_4$
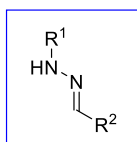
2k: R^1 = Ph; R^2 = 4-F$_3$CC$_6$H$_4$
2l: R^1 = Ph; R^2 = 4-(MeO$_2$C)C$_6$H$_4$
2m: R^1 = Ph; R^2 = 4-BrC$_6$H$_4$
2n: R^1 = Ph; R^2 = 4-ClC$_6$H$_4$
2o: R^1 = Ph; R^2 = 4-FC$_6$H$_4$
2p: R^1 = Ph; R^2 = 3-FC$_6$H$_4$
2q: R^1 = Ph; R^2 = 2-FC$_6$H$_4$
2r: R^1 = R^2 = Ph
2s: R^1 = Ph; R^2 = 4-MeC$_6$H$_4$
2t: R^1 = Ph; R^2 = 4-MeOC$_6$H$_4$

Hydrazone **2g** is commercially available. Hydrazones **2a**,[11] **2c**,[11] **2d**,[11] **2h**[12], **2i**[13] and **2s**[14] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

2.2.1. General Procedures for the Synthesis of Hydrazones **2b, 2e-f and 2j-r,t**
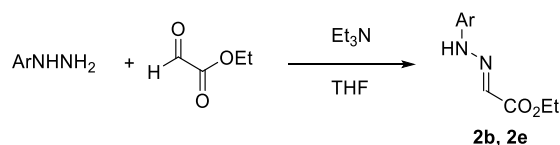
General Procedure D for the synthesis of hydrazones 2b and 2e. Hydrazone derivatives were prepared according to literature procedure[11] as followed. A suspension of the corresponding hydrazine hydrochloride (28.65 mmol, 1.0 eq.) in anhydrous THF (40 mL) was treated with

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[11] Fernandez, M.; Uria, U.; Vicario, J.L.; Reyes, L.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872.
[12] Wojciechowska, A.; Jasiński, M.; Kaszyński, P. *Tetrahedron*, **2015**, *71*, 2349.
[13] Chang, M.-C.; Otten, E. *Chem. Commun.* **2014**, *50*, 7431.
[14] Xu, P.; Wang, G.; Zhu, Y.; Li, W.; Cheng, Y.; Li, S.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2939.

triethylamine (28.65 mmol, 1.0 eq.) before the corresponding aldehyde (28.65 mmol, 1.0 eq.) was added dropwise to the reaction mixture at 0 ºC. The mixture was stirred at this temperature for 30 minutes and then for 12 h at room temperature. The reaction was filtered under vacuum to collect the triethylamine hydrochloride salt. The filtrates were concentrated *in vacuo* and the resulting solids dissolved in dichloromethane (~30 mL) and washed with HCl 1M (2 x 20 mL) and water (2 x 20 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting solids were triturated with diethyl ether or purified by flash column chromatography to obtain the desired hydrazone.
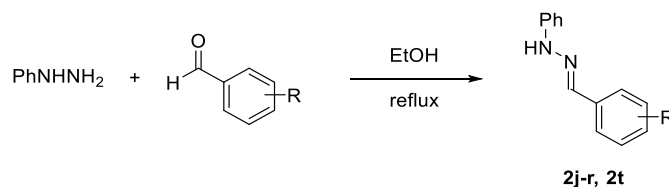
General Procedure E for the synthesis of hydrazones 2j-r and 2t. Hydrazone derivatives were prepared according to literature procedure with some modifications.[15] The corresponding aldehyde (9.25 mmol, 1.0 eq.) was added to a solution of hydrazine (9.25 mmol, 1.0 eq.) in ethanol (9.25 mL). The mixture was stirred and heated to reflux for 3 hours. The precipitated hydrazone was filtered, washed and dried.

Procedures for the synthesis of hydrazones 2f and 2r. Individual procedures are indicated in each case.
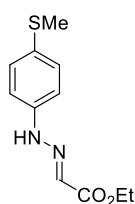
Ethyl (*E*)-2-(2-(4-(methylthio)phenyl)hydrazono)acetate (2b). Following the general procedure D, **2b** (936 mg, 3.9 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) in 75% yield as a yellow solid starting from ethyl glyoxylate (50% *w/v* solution in toluene, 1.04 mL, 5.24 mmol), triethylamine (0.73 mL, 5.24 mmol) and 4-(methylthio)phenylhydrazine hydrochloride (1.0 g, 5.24 mmol) in anhydrous tetrahydrofuran (10 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.45 (bs, 1H, NH), 7.24 (d, *J* = 8.7 Hz, 2H, C$_{Ar}$-H), 7.11 (d, *J* = 8.7 Hz, 2H, C$_{Ar}$-H), 7.06 (s, 1H, CH), 4.31 (q, *J* = 7.1 Hz, 2H, CH$_2$), 2.45 (s, 3H,

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[15] Chen, Z.; Li, H.; Dong, W.; Miao, M.; Ren, H. *Org. Lett.* **2016**, *18*, 1334.

SCH$_3$), 1.35 (t, J = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.3 (COO), 140.8 (C$_{Ar}$-C), 131.2 (C$_{Ar}$-C), 129.4 (C$_{Ar}$-H), 126.0 (CH), 114.8 (C$_{Ar}$-H), 61.1 (CH$_2$), 17.6 (SCH$_3$), 14.5 (CH$_3$); R$_f$: 0.59 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3253 (NH), 2959 (C-H st), 1692 (C=O), 1537 (C=N); MS (EI) m/z (%): 238 (M$^+$, 61), 164 (22), 138 (100), 122 (12); HRMS: Calculated for [C$_{11}$H$_{15}$N$_2$O$_2$S]$^+$: 239.0854 [(M+H)$^+$]; found: 239.0853; M.p. (CH$_2$Cl$_2$): 130-132 °C.
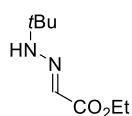
Ethyl (*E*)-2-(2-(*tert*-butyl)hydrazono)acetate (2e). Following the general procedure D, **2e** (315 mg, 1.83 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) in 81% yield as a yellow solid starting from ethyl glyoxylate (50% *w/v* solution in toluene, 0.445 mL, 2.25 mmol), triethylamine (0.314 mL, 2.25 mmol) and *tert*-butylhydrazine hydrochloride (380 mg, 2.25 mmol) in anhydrous tetrahydrofuran (10 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.85 (s, 1H, CH), 6.29 (s, 1H, NH), 4.24 (q, J = 7.1 Hz, 2H, CH$_2$), 1.31 (t, J = 7.1 Hz, 3H, CH$_3$), 1.27 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.6 (COO), 123.3 (CH), 60.3 (CH$_2$), 54.9 (**C**(CH$_3$)$_3$), 28.8 (C(**CH**$_3$)$_3$), 14.4 (CH$_3$); R$_f$: 0.77 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3264 (NH), 2977 (C-H st), 1691 (C=O), 1533 (C=N); MS (EI) m/z (%): 172 (M$^+$, 29), 157 (100), 115 (94), 87 (81), 83 (46), 72 (12), 57 (67); HRMS: Calculated for [C$_8$H$_{17}$N$_2$O$_2$]$^+$: 173.1290 [(M+H)$^+$]; found: 173.1286; M.p. (CH$_2$Cl$_2$): 60-62 °C.
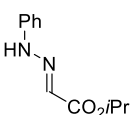
***Iso*-propyl-(*E*)-2-(2-phenylhydrazono)acetate (2f).**[11] To a suspension of phenylhydrazine (1.4 g, 12.9 mmol) in anhydrous tetrahydrofuran (12.9 mL) *iso*propyl glyoxylate (1.5 g, 12.9 mmol) was added dropwise at 0 °C. The mixture was stirred at this temperature for 30 minutes and then for 12 hours at room temperature. Solvents were removed *in vacuo* and the resulting solid was purified by flash column chromatography (hexanes/EtOAc gradient from 19:1 to 7:3) to afford 1.4 g of **2f** (6.8 mmol, 53%) as a light brown solid. ^{1}H NMR (300 MHz, CDCl$_3$): (8:1 *E*/*Z* ratio, *denotes minor isomer resonances) δ 8.61 (bs, 1H, NH), 7.32-7.23 (m, 2H, C$_{Ar}$-H), 7.22-7.11 (m, 2H, C$_{Ar}$-H), 7.07 (s, 1H, NCH), 6.97 (t, J = 7.3 Hz, 1H, C$_{Ar}$-H), 5.18 (hept, J = 6.3 Hz, 1H, C**H**(CH$_3$)$_2$), 1.32 (d, J = 6.3 Hz, 6H, CH(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.6 (COO), 143.1 (C$_{Ar}$-C), 142.7* (C$_{Ar}$-C), 129.5 (C$_{Ar}$-H), 126.4* (NCH), 122.7 (C$_{Ar}$-H), 122.5* (C$_{Ar}$-H), 119.1 (NCH), 114.1* (C$_{Ar}$-H), 114.0 (C$_{Ar}$-H), 68.5* (**C**H(CH$_3$)$_2$), 68.3 (**C**H(CH$_3$)$_2$), 22.1*

(CH(**CH**$_3$)$_2$), 22.0 (CH(**CH**$_3$)$_2$); R$_f$: 0.55 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3255 (NH), 3052 (C-H st), 1689 (C=O), 1539 (C=N); MS (EI) m/z (%): 206 (M$^+$, 54), 164 (56), 118 (100), 91 (94), 77 (22), 65 (43), 51 (9); HRMS: Calculated for [C$_{11}$H$_{15}$N$_2$O$_2$]$^+$: 207.1134 [(M+H)$^+$]; found: 207.1136; M.p. (EtOH): 124-126 ºC.
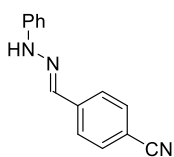
(*E*)-4-((2-phenylhydrazono)methyl)benzonitrile (2j). Following the general procedure E, **2j** (1.7 g, 7.7 mmol) was isolated in 83% yield as a yellow solid starting from 4-formylbenzonitrile (1.27 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.69 (bs, 1H, NH), 7.77-7.69 (m, 2H, C$_{Ar}$-H), 7.68-7.59 (m, 3H, CH + C$_{Ar}$-H), 7.31 (ddd, *J* = 8.5, 5.5, 1.7 Hz, 2H, C$_{Ar}$-H), 7.18-7.10 (m, 2H, C$_{Ar}$-H), 6.99-6.90 (m, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.9 (C$_{Ar}$-C), 139.9 (C$_{Ar}$-C), 134.4 (CH), 132.5 (C$_{Ar}$-H), 129.5 (C$_{Ar}$-H), 126.4 (C$_{Ar}$-H), 121.2 (C$_{Ar}$-H), 119.2 (CN), 113.2 (C$_{Ar}$-H), 111.1 (C$_{Ar}$-C); R$_f$: 0.36 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3273 (NH), 3038 (C-H st), 2221 (*p*-CN), 1577 (C=N); MS (EI) m/z (%): 221 (M$^+$, 66), 207 (38), 128 (100), 102 (13), 92 (66), 77 (13), 65 (27), 51 (14); HRMS: Calculated for [C$_{14}$H$_{12}$N$_3$]$^+$: 222.1031 [(M+H)$^+$]; found: 222.1021; M.p. (EtOH): 151-153 ºC.
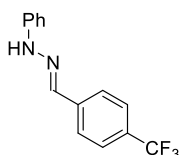
(*E*)-1-phenyl-2-(4-(trifluoromethyl)benzylidene)hydrazine (2k). Following the general procedure E, **2k** (1.35 g, 5.1 mmol) was isolated in 55% yield as a light yellow solid starting from 4-(trifluoromethyl)benzaldehyde (1.3 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.79-7.70 (m, 3H, NH + C$_{Ar}$-H), 7.67-7.57 (m, 3H, CH + C$_{Ar}$-H), 7.32 (ddd, *J* = 8.6, 5.7, 2.2 Hz, 2H, C$_{Ar}$-H), 7.18-7.10 (m, 2H, C$_{Ar}$-H), 6.94 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.2 (C$_{Ar}$-C), 138.9 (C$_{Ar}$-C), 135.3 (CH), 129.9 (q, $^2J_{C-F}$ = 32.1 Hz, **C**CF$_3$), 129.5 (C$_{Ar}$-H), 126.2 (C$_{Ar}$-H), 125.7 (q, $^3J_{C-F}$ = 3.9 Hz, C$_{Ar}$-H), 122.9 (q, $^1J_{C-F}$ = 272.5 Hz, CF$_3$), 120.9 (C$_{Ar}$-H), 113.1 (C$_{Ar}$-H); ^{19}F NMR (300 MHz, CDCl$_3$): δ -62.5 (CF$_3$); R$_f$: 0.68 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3292 (NH), 1594 (C=N); MS (EI) m/z (%): 264 (M$^+$, 100), 207 (13), 171 (78), 152 (36), 121 (44), 92 (88), 75 (20), 65 (37), 51 (17); HRMS: Calculated for [C$_{14}$H$_{12}$N$_2$F$_3$]$^+$: 265.0953 [(M+H)$^+$]; found: 265.0948; M.p. (EtOH): 132-134 ºC.
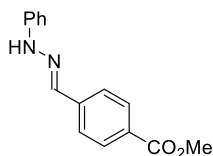
Methyl (*E*)-4-((2-phenylhydrazono)methyl)benzoate (2l). Following the general procedure E, **2l** (1.9 g, 7.5 mmol) was isolated in 80% yield as a yellow solid starting from methyl 4-formylbenzoate (1.53 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.03 (d, *J* = 8.4 Hz, 2H, C$_{Ar}$-H), 7.82 (bs, 1H, NH), 7.78-7.63 (m, 3H, CH + C$_{Ar}$-H), 7.36-7.24 (m, 2H, C$_{Ar}$-H), 7.19-7.09 (m, 2H, C$_{Ar}$-H), 6.91 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H), 3.93 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 167.0 (COO), 144.2 (C$_{Ar}$-C), 139.9 (C$_{Ar}$-C), 135.7 (CH), 130.0 (C$_{Ar}$-H), 129.5 (C$_{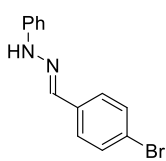Ar}$-H), 125.9 (C$_{Ar}$-H), 120.7 (C$_{Ar}$-H), 113.0 (C$_{Ar}$-H), 52.2 (CH$_3$); R$_f$: 0.42 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3288 (NH), 3042 (C-H st), 1690 (C=O), 1578 (C=N); MS (EI) m/z (%): 254 (M$^+$, 83), 207 (28), 161 (26), 130 (100), 102 (40), 92 (57), 77 (19), 65 (26), 51 (18); HRMS: Calculated for [C$_{15}$H$_{15}$N$_2$O$_2$]$^+$: 255.1134 [(M+H)$^+$]; found: 255.1132; M.p. (EtOH): 142-144 ºC.

(*E*)-1-(4-bromobenzylidene)-2-phenylhydrazine (2m). Following the general procedure E, **2m** (1.1 g, 3.99 mmol) was isolated in 49% yield as a light yellow solid starting from 4-bromobenzaldehyde (1.52 g, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.64 (s, 1H, NH), 7.60 (s, 1H, CH), 7.56-7.46 (m, 4H, C$_{Ar}$-H), 7.33-7.24 (m, 2H, C$_{Ar}$-H), 7.11 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 6.95-6.86 (m, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.5 (C$_{Ar}$-C), 136.0 (CH), 134.4 (C$_{Ar}$-C), 131.9 (C$_{Ar}$-H), 129.5 (C$_{Ar}$-H), 127.7 (C$_{Ar}$-H), 122.3 (C$_{Ar}$-C), 120.5 (C$_{Ar}$-H), 113.0 (C$_{Ar}$-H); R$_f$: 0.56 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3308 (NH), 3051 (C-H st), 1591 (C=N); MS (EI) m/z (%): 274 (M$^+$, 91), 207 (93), 183 (100), 102 (69), 92 (95), 75 (37), 65 (47), 51 (27); HRMS: Calculated for [C$_{13}$H$_{12}$N$_2$Br]$^+$: 275.0184 [(M+H)$^+$]; found: 275.0185; M.p. (EtOH): 120-122 ºC.
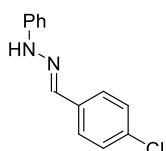
(*E*)-1-(4-chlorobenzylidene)-2-phenylhydrazine (2n). Following the general procedure E, **2n** (1.35 g, 5.9 mmol) was isolated in 63% yield as a white solid starting from 4-chlorobenzaldehyde (1.32 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.66-7.54 (m, 4H, NH + CH + C$_{Ar}$-H), 7.38-7.24 (m, 4H, C$_{Ar}$-H), 7.11 (d, *J* = 7.6 Hz, 2H, C$_{Ar}$-H), 6.90 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.5 (C$_{Ar}$-C), 135.9 (CH), 134.1 (C$_{Ar}$-C), 134.0 (C$_{Ar}$-C), 129.5 (C$_{Ar}$-H), 129.0 (C$_{Ar}$-H), 127.4 (C$_{Ar}$-H),

120.5 (C_{Ar}-H), 112.9 (C_{Ar}-H); R_f: 0.64 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3312 (NH), 3055 (C-H st), 1598 (C=N), 747 (CCl); MS (EI) m/z (%): 230 (M$^+$, 66), 207 (57), 137 (100), 102 (30), 92 (54), 65 (24); HRMS: Calculated for [$C_{13}H_{12}N_2Cl$]$^+$: 231.0689 [(M+H)$^+$]; found: 231.0689; M.p. (EtOH): 126-128 ºC.

(*E*)-1-(4-fluorobenzylidene)-2-phenylhydrazine (2o). Following the general procedure E, **2o** (1.28 g, 5.97 mmol) was isolated in 65% yield as a white solid starting from 4-fluorobenzaldehyde (1.32 g, 9.25 mmol) and phenylhydrazine (0.91 mL, 9.25 mmol) in ethanol (9.25 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.70-7.49 (m, 4H, NH + CH + C_{Ar}-H), 7.29 (t, *J* = 7.9 Hz, 2H, C_{Ar}-H), 7.16-7.00 (m, 4H, C_{Ar}-H), 6.89 (t, *J* = 6.8 Hz, 1H, C_{Ar}-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.0 (d, $^1J_{C-F}$ = 248.2 Hz, CF), 144.7 (C_{Ar}-C), 136.3 (CH), 131.7 (d, $^4J_{C-F}$ = 3.2 Hz, C_{Ar}-C), 129.5 (C_{Ar}-H), 127.9 (d, $^3J_{C-F}$ = 8.1 Hz, C_{Ar}-H), 120.4 (C_{Ar}-H), 116.0 (d, $^2J_{C-F}$ = 21.9 Hz, C_{Ar}-H), 112.9 (C_{Ar}-H); ^{19}F NMR (282 MHz, CDCl$_3$): δ -112.7 (CF); IR (ATR) cm^{-1}: 3311 (NH), 3053 (C-H st), 1597 (C=N), 1230 (CF); MS (EI) m/z (%): 214 (M$^+$, 87), 121 (100), 92 (52), 77 (11), 65 (27), 51 (9); HRMS: Calculated for [$C_{13}H_{12}N_2F$]$^+$: 215.0985 [(M+H)$^+$]; found: 215.0988; R_f: 0.64 (hexanes/EtOAc 8:2); M.p. (EtOH): 145-147 ºC.
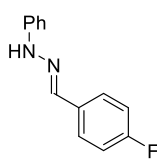
(*E*)-1-(3-fluorobenzylidene)-2-phenylhydrazine (2p). Following the general procedure E, **2p** (1.4 g, 6.5 mmol) was isolated in 81% yield as a light yellow solid starting from 3-fluorobenzaldehyde (0.88 mL, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.68 (bs, 1H, NH), 7.63 (s, 1H, CH), 7.49-7.25 (m, 5H, C_{Ar}-H), 7.20-7.08 (m, 2H, C_{Ar}-H), 7.04-7.95 (m, 1H, C_{Ar}-H), 6.91 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.3 (d, $^1J_{C-F}$ = 245.3 Hz, CF), 144.4 (C_{Ar}-C), 137.8 (d, $^3J_{C-F}$ = 8.0 Hz, C_{Ar}-C), 135.8 (d, $^4J_{C-F}$ = 3.2 Hz, CH), 130.2 (d, $^3J_{C-F}$ = 8.4 Hz, C_{Ar}-H), 129.5 (C_{Ar}-H), 122.3 (d, $^4J_{C-F}$ = 2.7 Hz, C_{Ar}-H), 120.6 (C_{Ar}-H), 115.3 (d, $^2J_{C-F}$ = 21.7 Hz, C_{Ar}-H), 113.0 (C_{Ar}-H), 112.4 (d, $^2J_{C-F}$ = 22.8 Hz, C_{Ar}-H); ^{19}F NMR (282 MHz, CDCl$_3$): δ -113.2 (CF); R_f: 0.86 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3311 (NH), 3008 (C-H st), 1594 (C=N), 1262 (CF); MS (EI) m/z (%): 214 (M$^+$, 100), 121 (88), 107 (11), 92 (75), 75 (18), 65 (37), 51 (14); HRMS: Calculated for [$C_{13}H_{12}N_2F$]$^+$: 215.0985 [(M+H)$^+$]; found: 215.0981; M.p. (EtOH): 115-117 ºC.
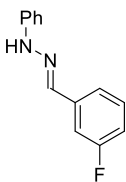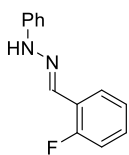
(*E*)-1-(2-fluorobenzylidene)-2-phenylhydrazine (2q). Following the general procedure E, **2q** (1.7 g, 7.9 mmol) was isolated in 98% yield as an orange solid starting from 2-fluorobenzaldehyde (0.88 mL, 8.1 mmol) and phenylhydrazine (0.8 mL, 8.1 mmol) in ethanol (8.1 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.01 (td, J = 7.6, 1.8 Hz, 1H, C$_{Ar}$-H), 7.94 (s, 1H, CH), 7.77 (bs, 1H, NH), 7.36-7.22 (m, 3H, C$_{Ar}$-H), 7.20-7.10 (m, 3H, C$_{Ar}$-H), 7.10-7.00 (m, 1H, C$_{Ar}$-H), 6.89 (t, J = 7.3 Hz, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 160.6 (d, $^1J_{C\text{-}F}$ = 249.5 Hz, CF), 114.5 (C$_{Ar}$-C), 130.2 (d, $^3J_{C\text{-}F}$ = 4.9 Hz, CH), 129.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, C$_{Ar}$-H), 129.5 (C$_{Ar}$-H), 126.3 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, C$_{Ar}$-H), 124.4 (d, $^3J_{C\text{-}F}$ = 3.4 Hz, C$_{Ar}$-H), 123.3 (d, $^2J_{C\text{-}F}$ = 10.2 Hz, C$_{Ar}$-C), 120.5 (C$_{Ar}$-H), 115.7 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, C$_{Ar}$-H), 112.9 (C$_{Ar}$-H); ^{19}F NMR (282 MHz, CDCl$_3$): δ -122.5 (CF); R$_f$: 0.78 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3307 (NH), 3055 (C-H st), 1598 (C=N), 1258 (CF); MS (EI) m/z (%): 214 (M$^+$, 99), 121 (100), 107 (11), 92 (65), 75 (21), 65 (35), 51 (13); HRMS: Calculated for [C$_{13}$H$_{12}$N$_2$F]$^+$: 215.0985 [(M+H)$^+$]; found: 215.0982; M.p. (EtOH): 86-88 ºC.

(*E*)-1-benzylidene-2-phenylhydrazine (2r).[16] To a solution of phenylhydrazine (0.91 mL, 9.25 mmol) in MeOH (8 mL) was added benzaldehyde (0.9 mL, 8.8 mmol) slowly. The mixture was stirred at room temperature for 6h. MeOH was evaporated *in vacuo,* and the residue was recristallized from MeOH to afford (*E*)-1-benzylidene-2-phenylhydrazine **2r** (1.36 g, 6.9 mmol) in 79% yield as a light yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.73-7.64 (m, 3H, CH + C$_{Ar}$-H), 7.59 (bs, 1H, NH), 7.44-7.25 (m, 5H, C$_{Ar}$-H), 7.14 (d, J = 7.7 Hz, 2H, C$_{Ar}$-H), 6.90 (t, J = 7.3 Hz, 1H, C$_{Ar}$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.8 (C$_{Ar}$-C), 137.4 (CH), 135.4 (C$_{Ar}$-C), 129.4 (C$_{Ar}$-H), 128.7 (C$_{Ar}$-H), 128.6 (C$_{Ar}$-H), 126.3 (C$_{Ar}$-H), 120.2 (C$_{Ar}$-H), 112.9 (C$_{Ar}$-H); R$_f$: 0.9 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3313 (NH), 2924 (C-H st), 1592 (CN); MS (EI) m/z (%): 196 (M$^+$, 100), 103 (51), 92 (43), 77 (41), 65 (30), 51 (24); HRMS: Calculated for [C$_{13}$H$_{13}$N$_2$]$^+$: 197.1079 [(M+H)$^+$]; found: 197.1078; M.p. (EtOH): 155-157 ºC.
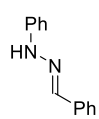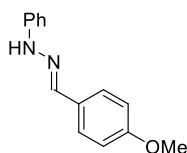
(*E*)-1-(4-methoxybenzylidene)-2-phenylhydrazine (2t). Following the general procedure E, **2t** (2.05 g, 8.0 mmol) was isolated in 99% yield as a white solid starting from 4-methoxybenzaldehyde (0.99 mL, 8.1 mmol)

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and phenylhydrazine (0.88 mL, 8.1 mmol) in ethanol (8.1 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.71-7.56 (m, 3H, C$_{Ar}$-H), 7.48 (bs, 1H, NH), 7.33-7.23 (m, 2H, C$_{Ar}$-H), 7.10 (d, J = 7.6 Hz, 2H, C$_{Ar}$-H), 6.98-6.81 (m, 3H, CH + C$_{Ar}$-H), 3.84 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 160.1 (C$_{Ar}$-C), 145.1 (C$_{Ar}$-C), 137.5 (CH), 129.4 (C$_{Ar}$-H), 128.3 (C$_{Ar}$-C), 127.7 (C$_{Ar}$-H), 119.9 (C$_{Ar}$-H), 114.3 (C$_{Ar}$-H), 112.8 (C$_{Ar}$-H), 55.5 (OCH$_3$); R$_f$: 0.64 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3314 (NH), 3024 (C-H st), 1594 (C=N); MS (EI) m/z (%): 226 (M$^+$, 100), 207 (41), 133 (58), 107 (11), 92 (37), 77 (31), 65 (24), 51 (13); HRMS: Calculated for [C$_{14}$H$_{15}$N$_2$O]$^+$: 227.1184 [(M+H)$^+$]; found: 227.1188; M.p. (EtOH): 145-147 ºC.

2.3. Synthesis of hydrazones 3a-af
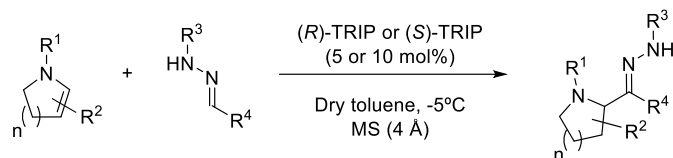
General procedure F: An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **(R)-TRIP or (S)-TRIP** (0.009 mmol, 0.01 eq.), dry toluene (0.18 mL) and smashed molecular sieves (4Å, 27 mg). The reaction was cooled to -5ºC and the corresponding enecarbamte/enethiourea (0.135 mmol, 1.5 eq.) and the corresponding hydrazone (0.09 mmol, 1.0 eq.) were added and the reaction mixture was stirred at -5ºC until completion of reaction. The crude reaction mixture was directly charged onto silica gel and subjected to flash chromatography, affording the corresponding adducts **3a-af**.

The ^{1}H NMR and ^{13}C NMR spectra of products **3i-3ac** were performed in DMSO-d$_6$ and at 100 ºC to get rid of rotamers and simplified the spectra as shown in Figure 5.1 for compound **3i**. It should be pointed out as well that ^{13}C NMR for these compounds was assigned by 2D NMR experiments (HSQC, HMBC), due to the low signal intensities in the ^{13}C NMR spectra.
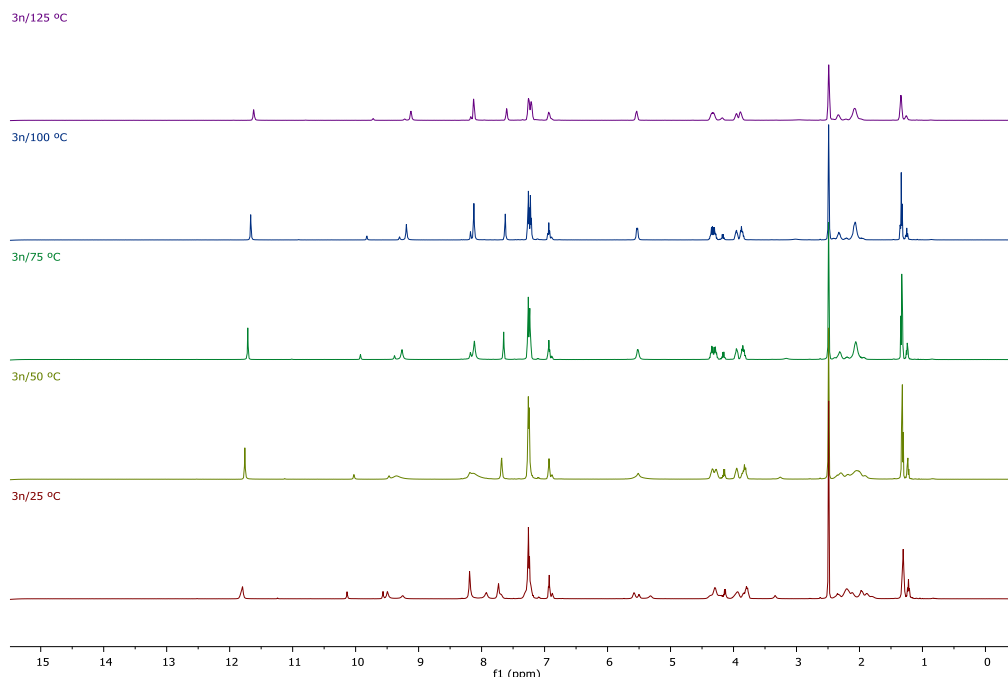
Figure 5.1: ^{1}H NMR temperature experiment in DMSO-d$_6$ for the elimination of rotamers.
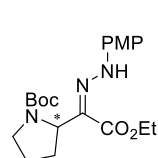
(*S/R*)-*N*-Boc-(*Z*)-2-(2-ethoxy-1-(2-(4-(methoxyphenyl)hydrazono)-2-oxoethyl)pyrrolidine (3a). Following the general procedure F with a slight modification, **3a** (30.8 mg, 0.079 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 24h in 60% yield as a yellow oil starting from *N*-Boc-2,3-dihydro-1*H*-pyrrole **1a** (23.2 mg, 0.13 mmol) and ethyl (*E*)-2-(2-(4-(methoxy)phenyl)hydrazono)acetate **2a** (34.4 mg, 0.156 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): (1.45:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.01 (bs, 1H, NH), 11.98* (bs, 1H, NH), 7.08 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 6.84 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 5.03-4.90* (m, 1H, C$_2$-H), 4.81 (dd, *J* = 7.8, 3.2 Hz, 1H, C$_2$-H), 4.27 (q, *J* = 7.2 Hz, 2H, C**H$_2$**CH$_3$), 3.77 (s, 3H, OCH$_3$), 3.68-3.33 (m, 2H, C$_5$-H), 2.30-1.68 (m, 4H, C$_3$-H + C$_4$-H), 1.58-1.23 (m, 12H, CH$_2$C**H$_3$** + C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.1 (COO), 155.2 (C$_{Ar}$-C), 154.4 (NCOO), 137.4 (CN), 127.7 (C$_{Ar}$-C), 114.8 (C$_{Ar}$-H), 114.8 (C$_{Ar}$-H), 79.1 (**C**(CH$_3$)$_3$), 60.6 (**C**H$_2$CH$_3$), 58.0 (C$_2$), 55.7 (OCH$_3$), 46.6 (C$_5$), 32.5 (C$_3$), 28.6 (C(**C**H$_3$)$_3$), 22.8 (C$_4$), 14.4 (CH$_2$**C**H$_3$); R$_f$: 0.72 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2977 (NH), 2930 (C-H

st), 1691 (C=O), 1548 (C=N); MS (EI) *m/z* (%): 281 (16), 207 (57), 149 (100), 134 (62), 108 (50), 93 (14), 78 (52), 52 (40); HRMS: Calculated for $[C_{20}H_{30}N_3O_5]^+$: 392.2185 $[(M+H)^+]$; found: 392.2188; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 5.295 min, τ_{minor} = 6.207 min (86% ee); $[\alpha]_D^{20}$: +88.5 (*c* = 1.0, CH_2Cl_2).

(S/R)-N-Boc-(Z)-2-(2-ethoxy-1-(2-(4-(methylthio)phenyl)hydrazono)-2-oxoethyl)pyrrolidine (3b). Following the general procedure F, **3b** (mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 24h in 78% yield as a yellow oil starting from *N*-Boc-2,3-dihydro-1*H*-pyrrole **1a** (6 × 5.9 μL every 1h 30 min, 0.195 mmol) and ethyl (*E*)-2-(2-(4-(methylthio)phenyl)hydrazono)acetate **2b** (31.0 mg, 0.13 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): (1.25:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.02 (bs, 1H, NH), 7.24 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 7.09 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 5.01-4.92* (m, 1H, C$_2$-H), 4.86-4.77 (m, 1H, C$_2$-H), 4.29 (q, *J* = 7.1 Hz, 2H, C**H$_2$**CH$_3$), 3.68-3.35 (m, 2H, C$_5$-H), 2.45 (s, 3H, SCH$_3$), 2.25-2.07 (m, 1H, C$_3$-H$_a$), 2.02-1.77 (m, 3H, C$_3$-H$_b$ + C$_4$-H), 1.52-1.27 (m, 12H, CH$_2$**CH$_3$** + C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.0 (COO), 163.0* (COO), 154.3 (NCO), 142.1* (C$_{Ar}$-C), 141.6 (C$_{Ar}$-C), 130.5* (C$_{Ar}$-C), 129.7* (C$_{Ar}$-H), 129.6 (C$_{Ar}$-H), 129.0 (C$_{Ar}$-C), 127.9 (CN), 114.4 (C$_{Ar}$-H), 114.4* (C$_{Ar}$-H), 79.2* (**C**(CH$_3$)$_3$), 79.1 (**C**(CH$_3$)$_3$), 60.8 (**C**H$_2$CH$_3$), 58.1 (C$_2$), 57.7* (C$_2$), 47.0* (C$_5$), 46.6 (C$_5$), 32.4 (C$_3$), 31.3* (C$_3$), 28.8* (C(**C**H$_3$)$_3$), 28.5 (C(**C**H$_3$)$_3$), 22.9* (C$_4$), 22.8 (C$_4$), 17.9* (SCH$_3$), 17.7 (SCH$_3$), 14.4 (CH$_2$**C**H$_3$), 14.3* (CH$_2$**C**H$_3$); R$_f$: 0.52 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2976 (NH), 2820 (C-H st), 1693 (C=O), 1551 (C=N); MS (EI) *m/z* (%): 281 (20), 238 (16), 207 (89), 191 (11), 165 (100), 150 (61), 138 (37), 124 (53), 106 (27), 78 (29), 69 (33), 56 (28); HRMS: Calculated for $[C_{20}H_{30}N_3O_4S]^+$: 408.1957 $[(M+H)^+]$; found: 408.1938; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 5.036 min, τ_{minor} = 5.915 min (92% ee); $[\alpha]_D^{20}$: +158.7 (*c* = 1.0, CH_2Cl_2).
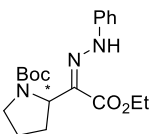
(S/R)-N-Boc-(Z)-2-(2-ethoxy-1-(2-(phenyl)hydrazono)-2-oxoethyl)pyrrolidine (3c). Following the general procedure F, **3c** (45.1 mg, 0.125 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3)

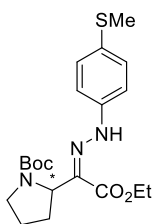after 24h in 96% yield as an orange oil starting from *N*-Boc-2,3-dihydro-1*H*-pyrrole **1a** (6 × 5.9 μL every 1h 30 min, 0.195 mmol) added in portions and ethyl (*E*)-2-(2-phenylhydrazono)acetate **2c** (25.0 mg, 0.13 mmol) in the presence of catalyst (*R*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent.^{1}H NMR (300 MHz, CDCl$_3$): (1.5:1 rotamer ratio, *denotes minor rotamer resonances, #overlapped signals) δ 12.02 (s, 1H, NH), 11.99* (s, 1H, NH), 7.43-7.22 (m, 2H, C$_{Ar}$-H), 7.22-7.07 (m, 2H, C$_{Ar}$-H), 7.05-6.83 (m, 1H, C$_{Ar}$-H), 5.02-4.94* (m, 1H, C$_2$-H), 4.82 (dd, *J* = 7.5, 3.3 Hz, 1H, C$_2$-H), 4.29 (q, *J* = 6.9 Hz, 2H, C**H$_2$**CH$_3$), 3.72-3.30 (m, 2H, C$_5$-H), 2.30-1.73 (m, 4H, C$_3$-H + C$_4$-H), 1.45* (s, 9H, C(CH$_3$)$_3$), 1.40-1.19# (m, 12H, CH$_2$C**H$_3$** + C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.0 (COO), 154.3 (NCO), 143.7* (CN), 143.4 (CN), 129.4 (C$_{Ar}$-H), 129.2* (C$_{Ar}$-H), 128.8 (C$_{Ar}$-C), 127.6* (C$_{Ar}$-C), 122.1 (C$_{Ar}$-H), 121.9* (C$_{Ar}$-H), 113.8 (C$_{Ar}$-H), 79.2* (**C**(CH$_3$)$_3$), 79.1 (**C**(CH$_3$)$_3$), 60.8 (**C**H$_2$CH$_3$), 58.1 (C$_2$), 57.6* (C$_2$), 46.6 (C$_5$), 32.4 (C$_3$), 31.3* (C$_3$), 28.7* (C(**C**H$_3$)$_3$), 28.4 (C(**C**H$_3$)$_3$), 22.9* (C$_4$), 22.7 (C$_4$), 14.3 (CH$_2$**C**H$_3$), 14.3* (CH$_2$**C**H$_3$); R$_f$: 0.79 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2976 (NH), 2920 (C-H st), 1694 (C=O),1550 (C=N); MS (EI) *m/z* (%): 281 (16), 207 (57), 149 (100), 134 (62), 108 (50), 93 (14), 78 (52), 52 (40); HRMS: Calculated for [C$_{19}$H$_{28}$N$_3$O$_4$]$^+$: 362.2080 [(M-H)$^+$]; found: 362.2081; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 4.754 min, τ$_{minor}$ = 3.825 min (93% ee); [α]$_D^{20}$: -177.8 (*c* = 1.0, CH$_2$Cl$_2$).
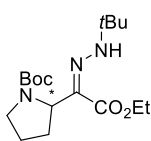
(*S/R*)-*tert*-butyl-(*E/Z*)-2-(1-(2-(*tert*-butyl)hydrazono)-2-ethoxy-2-oxoethyl)pyrrolidine-1-carboxylate (3e). Following the general procedure F, **3e** (38.6 mg, 0.113 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 5h in 87% yield as a light yellow oil starting from *N*-Boc-2,3-dihydro-1*H*-pyrrole **1a** (23.6 μL, 0.13 mmol) and ethyl (*E*)-2-(2-(*tert*-butyl)hydrazono)acetate **2e** (26.9 mg, 0.156 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): (1.3:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.99 (s, 1H, NH), 9.92* (s, 1H, NH), 4.88* (d, *J* = 7.1 Hz, 1H, C$_2$-H), 4.75 (dd, *J* = 7.5, 2.9 Hz, 1H, C$_2$-H), 4.19 (q, *J* = 7.2 Hz, 2H, C**H$_2$**CH$_3$), 3.58-3.22 (m, 2H, C$_5$-H), 2.16-1.73 (m, 4H, C$_3$-H + C$_4$-H), 1.43* (s, 9H, OC(CH$_3$)$_3$), 1.33 (s, 9H, OC(CH$_3$)$_3$), 1.31-1.24 (m, 3H, CH$_2$CH$_3$), 1.20 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 162.9 (COO), 162.8* (COO), 154.3 (NCO), 154.1*

(NCO), 125.4 (CN), 124.0* (CN), 78.6 (O**C**(CH$_3$)$_3$), 59.9* (**C**H$_2$CH$_3$), 59.8 (**C**H$_2$CH$_3$), 57.5 (C$_2$), 57.2* (C$_2$), 54.5 (**C**(CH$_3$)$_3$), 54.4* (**C**(CH$_3$)$_3$), 46.5 (C$_5$), 32.7 (C$_3$), 31.5* (C$_3$), 28.9 (OC(**C**H$_3$)$_3$), 28.8* (OC(**C**H$_3$)$_3$), 28.7* (C(**C**H$_3$)$_3$), 28.6 (C(**C**H$_3$)$_3$), 22.8* (C$_4$), 22.6 (C$_4$), 14.5 (CH$_2$**C**H$_3$), 14.4* (CH$_2$**C**H$_3$); R$_f$: 0.70 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2977 (NH), 2876 (C-H st), 1695 (C=O), 1537 (C=N); MS (EI) *m/z* (%): 341 (M$^+$, 8), 184 (40), 169 (38), 156 (30), 114 (47), 95 (17), 70 (38), 57 (100); HRMS: Calculated for [C$_{17}$H$_{32}$N$_3$O$_4$]$^+$: 342.2393 [(M+H)$^+$]; found: 342.2394; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 5.957 min, τ_{minor} = 7.067 min (72% ee); [α]$_D^{20}$: +42.5 (*c* = 1.0, CH$_2$Cl$_2$).
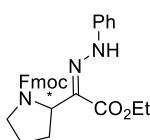
(*S*/*R*)-(9*H*-fluoren-9-yl)methyl-(*Z*)-2-(2-ethoxy-2-oxo-1-(2-phenylhydrazono)ethyl)pyrrolidine-1-carboxylate (3f). Following the general procedure F, **3f** (58.2 mg, 0.120 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 72h in 93% yield as an orange oil starting from *N*-Fmoc-2,3-dihydro-1*H*-pyrrole **1b** (5 × 9.5 mg + 1 × 9.3 mg every 1h 30 min, 0.195 mmol) added in portions and ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **2c** (24.9 mg, 0.13 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent at 10ºC. ^{1}H NMR (300 MHz, CDCl$_3$): (1.2:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.05* (s, 1H, NH), 11.93 (s, 1H, NH), 7.78 (d, *J* = 7.5 Hz, 1H, C$_{Ar}$-H), 7.72-7.61 (m, 2H, C$_{Ar}$-H), 7.50-7.27 (m, 5H, C$_{Ar}$-H), 7.23-7.06 (m, 4H, C$_{Ar}$-H), 7.01-6.85 (m, 1H, C$_{Ar}$-H), 5.09* (dd, *J* = 7.5, 2.3 Hz, 1H, C$_2$-H), 4.89-4.77 (m, 1H, C$_2$-H), 4.58-4.44 (m, 1H, C**H**CH$_2$O), 4.40-4.00 (m, 4H, CHC**H**$_2$O + C**H**$_2$CH$_3$), 3.85-3.44 (m, 2H, C$_5$-H), 2.30-1.80 (m, 4H, C$_3$-H + C$_4$-H), 1.38-1.32 (m, 3H, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.4 (**C**OO), 162.9* (N**C**O), 162.6 (N**C**O), 154.9 (CN), 154.7* (CN), 144.5* (C$_{Ar}$-C), 144.2 (C$_{Ar}$-C), 144.2 (C$_{Ar}$-C), 144.2* (C$_{Ar}$-C), 143.5* (C$_{Ar}$-C), 143.3 (C$_{Ar}$-C), 142.8* (C$_{Ar}$-C), 141.4 (C$_{Ar}$-C), 141.2 (C$_{Ar}$-C), 129.5 (C$_{Ar}$-H), 129.4 (C$_{Ar}$-H), 129.3* (C$_{Ar}$-H), 127.7 (C$_{Ar}$-H), 127.5 (C$_{Ar}$-H), 127.5* (C$_{Ar}$-H), 127.1* (C$_{Ar}$-H), 127.1 (C$_{Ar}$-H), 127.0 (C$_{Ar}$-H), 126.9* (C$_{Ar}$-H), 125.8 (C$_{Ar}$-H), 125.3 (C$_{Ar}$-H), 124.8* (C$_{Ar}$-H), 122.3* (C$_{Ar}$-H), 122.2 (C$_{Ar}$-H), 122.1 (C$_{Ar}$-H), 120.1 (C$_{Ar}$-H), 120.0* (C$_{Ar}$-H), 119.8 (C$_{Ar}$-H), 114.0 (C$_{Ar}$-H), 113.8 (C$_{Ar}$-H), 113.7* (C$_{Ar}$-H), 67.3* (CH**C**H$_2$O), 66.6 (CH**C**H$_2$O), 60.9 (**C**H$_2$CH$_3$), 60.8* (**C**H$_2$CH$_3$), 58.0* (C$_2$), 57.7 (C$_2$), 47.6* (**C**HCH$_2$O), 47.4 (**C**HCH$_2$O), 47.0 (C$_5$), 46.6* (C$_5$), 32.2 (C$_3$), 31.4* (C$_3$), 23.2* (C$_4$), 22.0 (C$_4$), 14.4* (CH$_2$**C**H$_3$), 14.3 (CH$_2$**C**H$_3$); R$_f$: 0.54

(hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2980 (NH), 2810 (C-H st), 1695 (C=O), 1551 (C=N); MS (EI) m/z (%): 178 (100), 152 (12), 88 (9), 76 (13); HRMS: Calculated for $[C_{29}H_{30}N_3O_4]^+$: 484.2236 $[(M+H)^+]$; found: 484.2238; The ee was determined by HPLC using a Chiralcel OD-3 column [$n$hexane/iPrOH (80:20)]; flow rate 1.00 mL/min; τ_{major} = 21.319 min, τ_{minor} = 61.500 min (92% ee); $[\alpha]_D^{20}$: +5.5 (c = 1.0, CH$_2$Cl$_2$).
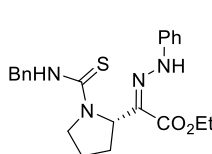
(S)-Ethyl-(Z)-2-(1-(benzylcarbamothioyl)pyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate (3h). Following the general procedure F, **3h** (36.2 mg, 0.088 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 98% yield as a yellow solid starting from N-benzyl-2,3-dihydro-1H-pyrrole-1-carbothioamide **1d** (29.5 mg, 0.135 mmol) and ethyl (E)-2-(2-phenylhydrazono)acetate **2c** (17.2 mg, 0.09 mmol) in the presence of catalyst (R)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): **(**5.8:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.68 (s, 1H, NN**H**), 9.70* (s, 1H, NN**H**), 7.56* (s, 1H, CSN**H**), 7.48 (s, 1H, CSN**H**), 7.35-7.13 (m, 7H, C$_{Ar}$-H + C$_{Ar}$-H*), 7.13-7.01 (m, 2H, C$_{Ar}$-H + C$_{Ar}$-H*), 6.95 (dd, J = 6.5, 1.2 Hz, 1H, C$_{Ar}$-H), 6.90-6.85* (m, 1H, C$_{Ar}$-H), 5.49* (dd, J = 8.2, 5.8 Hz, 1H, C$_2$-H), 5.45-5.38 (m, 1H, C$_2$-H), 4.88-4.66 (m, 2H, NHC**H$_2$** + NHC**H$_2$***), 4.38-4.20 (m, 2H, C**H$_2$**CH$_3$), 4.15* (q, J = 7.1 Hz, 2H, C**H$_2$**CH$_3$), 3.81 (ddd, J = 11.8, 8.7, 3.3 Hz, 1H, C$_5$-H$_a$), 3.85-3.61 (m, 1H, C$_5$-H$_a$* + C$_5$-H$_b$ + C$_5$-H$_b$*), 2.37-2.27* (m, 1H, C$_3$-H$_a$), 2.27-2.18 (m, 1H, C$_3$-H$_a$), 2.18-2.12* (m, 1H, C$_3$-H$_b$), 2.12-1.92 (m, 3H, C$_3$-H$_b$ + C$_4$-H + C$_4$-H$_a$*), 1.92-1.81* (m, 2H, C$_4$-H$_b$), 1.33 (t, J = 7.1 Hz, 3H, CH$_3$), 1.24* (t, J = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 179.0 (CS), 178.5* (CS), 162.8* (CO), 161.4 (CO), 144.2 (CN), 143.1 (C$_{Ar}$-C), 139.4 (C$_{Ar}$-C), 139.4* (C$_{Ar}$-C), 128.6 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 127.3* (C$_{Ar}$-H), 127.3 (C$_{Ar}$-H), 126.5* (C$_{Ar}$-H), 126.4 (C$_{Ar}$-H), 125.8* (C$_{Ar}$-H), 125.7 (C$_{Ar}$-H), 121.1 (C$_{Ar}$-H), 120.2* (C$_{Ar}$-H), 113.3* (C$_{Ar}$-H), 113.2 (C$_{Ar}$-H), 60.3 (C$_2$), 60.1 (**C**H$_2$CH$_3$), 59.2* (**C**H$_2$CH$_3$), 57.5* (C$_2$), 48.9 (C$_5$), 48.4* (C$_5$), 47.5 (NHCH$_2$), 30.4 (C$_3$), 28.4* (C$_3$), 23.9* (C$_4$), 22.0 (C$_4$), 13.6* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$); R$_f$: 0.35 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3264 (NH), 2977 (NH), 2820 (C-H st), 1679 (C=O), 1530 (C=N), 1236 (C=S), 1149 (C-N st); MS (EI) m/z (%): 149 (17), 91 (100), 83 (10), 65 (16), 51 (5); HRMS: Calculated for $[C_{22}H_{27}N_4O_2S]^+$: 411.1855 $[(M+H)^+]$; found: 411.1858; The ee was determined by HPLC using a Chiralpak IC

column [*n*hexane/*i*PrOH (85:15)]; flow rate 1.00 mL/min; τ_{major} = 18.766 min, τ_{minor} = 27.998 min (92% ee); $[\alpha]_D^{20}$: -119.9 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 124-126 °C.

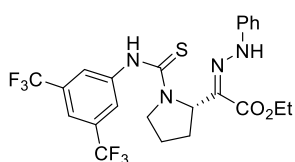**(*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate (3i).** Following the general procedure F, **3i** (47 mg, 0.088 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 98% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and ethyl (*E*)-2-(2-phenyl)hydrazono)acetate **2c** (17.2 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (1.7 mg, 0.00225 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100°C): (5.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.68 (s, 1H, NNH), 9.83* (s, 1H, NNH), 9.31* (s, 1H, CSNH), 9.20 (s, 1H, CSNH), 8.18* (s, 2H, C$_{Ar}$-H), 8.13 (s, 2H, C$_{Ar}$-H), 7.64* (s, 1H, C$_{Ar}$-H), 7.63 (s, 1H, C$_{Ar}$-H), 7.30-7.20 (m, 4H, C$_{Ar}$-H), 6.97-6.92 (m, 1H, C$_{Ar}$-H), 6.91-6.86* (m, 1H, C$_{Ar}$-H), 5.58-5.50 (m, C$_2$-H), 4.41-4.25 (m, 2H, C**H**$_2$CH$_3$), 4.18* (q, *J* = 7.1 Hz, 2H, C**H**$_2$CH$_3$), 4.02-3.92 (m, 1H, C$_5$-H$_a$), 3.92-3.82 (m, 1H, C$_5$-H$_b$), 2.45-2.37* (m, 1H, C$_3$-H$_a$), 2.37-2.27 (m, 1H, C$_3$-H$_a$), 2.27-2.17* (m, 1H, C$_3$-H$_b$), 2.17-2.00 (m, 3H, C$_3$-H$_b$ + C$_4$-H), 2.00-1.90* (m, 2H, C$_4$-H), 1.35 (t, *J* = 7.1 Hz, 3H, CH$_3$), 1.26* (t, *J* = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100°C): δ 177.7 (CS), 176.7* (CS), 162.7* (CO), 161.3 (CO), 144.1 (C$_{Ar}$-C), 143.0 (CN), 142.5 (C$_{Ar}$-C), 142.4* (C$_{Ar}$-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$), 128.6 (C$_{Ar}$-H), 128.4* (C$_{Ar}$-H), 124.0 (q, $^3J_{C-F}$ = 3.9 Hz, C$_{Ar}$-H), 123.3* (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 121.3 (C$_{Ar}$-H), 120.5* (C$_{Ar}$-H), 115.9 (q, $^3J_{C-F}$ = 3.9 Hz, C$_{Ar}$-H), 115.7* (C$_{Ar}$-H), 113.5* (C$_{Ar}$-H), 113.2 (C$_{Ar}$-H), 61.1 (C$_2$), 60.2 (**C**H$_2$CH$_3$), 59.3* (**C**H$_2$CH$_3$), 57.8* (C$_2$), 50.1 (C$_5$), 30.6 (C$_3$), 28.5* (C$_3$), 24.0* (C$_4$), 22.2 (C$_4$), 13.5* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.3* (2 × CF$_3$), -61.7 (2 × CF$_3$); R$_f$: 0.67 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3262 (NH), 2983 (NH), 2830 (C-H st), 1683 (C=O), 1550 (C=N), 1277 (C=S), 1132 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (25), 213 (24), 202 (13), 163 (16), 143 (9), 83 (29), 69 (10); HRMS: Calculated for [C$_{23}$H$_{23}$N$_4$O$_2$SF$_6$]$^+$: 533.1446 [(M+H)$^+$]; found: 533.1451; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} =

15.395 min, τ_{minor} = 5.896 min (>99% ee); $[\alpha]_D^{20}$: -157.6 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 127-129 ºC.

(*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-(4-methoxyphenyl)hydrazono)acetate (3j). Following the general procedure F, **3j** (43.1 mg, 0.0766 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 85% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and ethyl (*E*)-2-(2-(4-(methoxy)phenyl)hydrazono)acetate **2a** (20.0 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (6.7:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.67 (s, 1H, NNH), 9.71* (s, 1H, NNH), 9.28* (s, 1H, CSNH), 9.17 (s, 1H, CSNH), 8.18* (s, 2H, C$_{Ar}$-H), 8.13 (s, 2H, C$_{Ar}$-H), 7.63 (s, 1H, C$_{Ar}$-H), 7.18 (d, *J* = 8.7 Hz, 2H, C$_{Ar}$-H), 6.88 (d, *J* = 8.7 Hz, 2H, C$_{Ar}$-H), 5.55-5.49 (m, 1H, C$_2$-H), 4.39-4.22 (m, 2H, **CH$_2$**CH$_3$), 4.16* (q, *J* = 7.1 Hz, 2H, **CH$_2$**CH$_3$), 4.00-3.81 (m, 2H, C$_5$-H), 3.73 (s, 3H, OCH$_3$), 2.44-2.26 (m, 1H, C$_3$-H$_a$), 2.26-1.91 (m, 3H, C$_3$-H$_b$ + C$_4$-H), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_2$**CH$_3$**), 1.25* (t, *J* = 7.1 Hz, 3H, CH$_2$**CH$_3$**); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 177.7 (CS), 176.7* (CS), 162.8* (CO), 161.4 (CO), 154.7 (C$_{Ar}$-C), 154.0* (C$_{Ar}$-C), 142.5 (CN), 142.4* (CN), 138.0* (C$_{Ar}$-C), 136.9 (C$_{Ar}$-C), 132.5 (C$_{Ar}$-C), 129.4 (q, $^2J_{C-F}$ = 32.7 Hz, 2 × **C**CF$_3$), 124.0 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 123.9* (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 273.1 Hz, 2 × CF$_3$), 115.9 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 115.6* (C$_{Ar}$-H), 114.6* (C$_{Ar}$-H), 114.5 (C$_{Ar}$-H), 114.4 (C$_{Ar}$-H), 114.2* (C$_{Ar}$-H), 61.1 (C$_2$), 60.0 (**C**H$_2$CH$_3$), 59.2* (**C**H$_2$CH$_3$), 57.7* (C$_2$), 55.1 (OCH$_3$), 50.1 (C$_5$), 30.7 (C$_3$), 28.5* (C$_3$), 24.0* (C$_4$), 22.1 (C$_4$), 13.5* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.59 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3231 (NH), 2955 (NH), 2830 (C-H st), 1679 (C=O), 1550 (C=N), 1275 (C=S), 1131 (C-N st); MS (EI) *m/z* (%): 149 (17), 91 (100), 83 (10), 65 (16); HRMS: Calculated for [C$_{23}$H$_{25}$N$_4$O$_3$SF$_6$]$^+$: 563.1552 [(M+H)$^+$]; found: 563.1566; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 14.567 min, τ_{minor} = 9.426 min (98% ee); $[\alpha]_D^{20}$: -96.0 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 128-130 ºC.
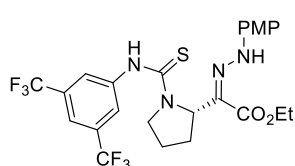
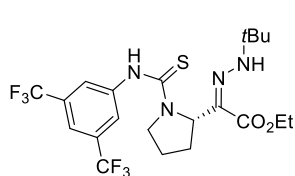**(S)-ethyl-(Z)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-(*tert*-butyl)hydrazono)acetate (3k).** Following the general procedure F, **3k** (36.9 mg, 0.072 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 80% yield as a white solid starting from N-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1H-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and ethyl (E)-2-(2-(*tert*-butyl) hydrazono)acetate **2e** (15.5 mg, 0.09 mmol) in the presence of catalyst (R)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC): δ 9.75 (bs, 1H, NH), 9.03 (bs, 1H, CSNH), 8.12 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 5.44-5.37 (m, 1H, C_2-H), 4.30-4.13 (m, 2H, **CH$_2$**CH$_3$), 3.88-3.73 (m, 2H, C_5-H), 2.29-2.17 (m, 1H, C_3-H$_a$), 2.05-1.92 (m, 3H, C_3-H$_b$ + C_4-H), 1.29 (t, J = 7.1 Hz, 3H, CH$_2$**CH$_3$**), 1.19 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (125 MHz, DMSO-d_6, 100ºC): δ 177.4 (CS), 161.2 (CO), 142.6 (CN), 130.5 (C_{Ar}-C), 129.3 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, 2 × **C**CF$_3$), 123.9 (C_{Ar}-H), 122.9 (q, $^1J_{C\text{-}F}$ = 272.1 Hz, 2 × CF$_3$), 115.7 (C_{Ar}-H), 60.8 (C_2), 59.3 (**C**H$_2$CH$_3$), 53.6 (**C**(CH$_3$)$_3$), 50.2 (C_5), 30.8 (C_3), 27.8 (C(**C**H$_3$)$_3$), 21.8 (C_4), 13.5 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (2 × CF$_3$); R$_f$: 0.69 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3266 (NH), 2976 (NH), 2850 (C-H st), 1678 (C=O), 1537 (C=N), 1275 (C=S), 1126 (C-N st); MS (EI) m/z (%): 271 (100), 252 (23), 213 (23), 202 (9), 163 (12), 83 (13); HRMS: Calculated for [C$_{21}$H$_{27}$N$_4$O$_2$SF$_6$]$^+$: 513.1759 [(M+H)$^+$]; found: 513.1779; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 3.761 min, τ_{minor} = 4.230 min (91% ee); [α]$_D^{20}$: -46.9 (c = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 76-78 ºC.

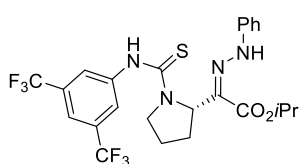**(S)-*iso*-propyl-(Z)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate (3l).** Following the general procedure F, **3l** (42.8 mg, 0.078 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 2h in 87% yield as a light yellow solid starting from N-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1H-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and *iso*-propyl (E)-2-(2-phenylhydrazono)acetate **2f** (18.6 mg, 0.09 mmol) in the presence of catalyst (R)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d_6,

100ºC): (7.8:1 diasteroisomer ratio, *denotes minor diastereoisomer resonances) δ 11.72 (s, 1H, NNH), 9.77* (s, 1H, NNH), 9.20 (s, 1H, CSNH), 8.18* (s, 2H, C_{Ar}-H), 8.14 (s, 2H, C_{Ar}-H), 7.65* (s, 1H, C_{Ar}-H), 7.63 (s, 1H, C_{Ar}-H), 7.34-7.13 (m, 4H, C_{Ar}-H), 6.98-6.92 (m, 1H, C_{Ar}-H), 6.91-6.86* (m, 1H, C_{Ar}-H), 5.56-5.49 (m, 1H, C_2-H), 5.19-5.09 (m, 1H, C**H**(CH$_3$)$_2$), 5.04-4.96* (m, 1H, C**H**(CH$_3$)$_2$), 4.05-3.77 (m, 2H, C_5-H), 2.46-2.38* (m, 1H, C_3-H$_a$), 2.38-2.27 (m, 1H, C_3-H$_a$), 2.26-2.18* (m, 1H, C_3-H$_b$), 2.18-1.90 (m, 3H, C_3-H$_b$ + C_4-H), 1.35 (d, J = 6.1 Hz, 6H, CH(C**H**$_3$)$_2$), 1.27* (d, J = 6.3 Hz, 3H, CH(C**H**$_3$)), 1.25* (d, J = 6.3 Hz, 3H, CH(C**H**$_3$)); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 177.7 (CS), 176.6* (CS), 162.2* (COO), 160.9 (COO), 144.2* (C_{Ar}-C), 143.0 (C_{Ar}-C), 142.5 (CN), 142.3* (CN), 134.5 (C_{Ar}-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$), 128.6 (C_{Ar}-H), 128.3* (C_{Ar}-H), 124.0 (C_{Ar}-H), 123.4* (C_{Ar}-H), 123.9 (2 × CF$_3$), 121.3 (C_{Ar}-H), 120.3* (C_{Ar}-H), 115.9 (tt, J = 6.9, 3.3 Hz, C_{Ar}-H), 113.4* (C_{Ar}-H), 113.2 (C_{Ar}-H), 68.3 (**C**H(CH$_3$)$_2$), 66.7* (**C**H(CH$_3$)$_2$), 61.3 (C_2), 57.9* (C_2), 50.0 (C_5), 30.6 (C_3), 28.4* (C_3), 24.0* (C_4), 22.3 (C_4), 21.0 (CH(**C**H$_3$)$_2$), 21.0 (CH(**C**H$_3$)$_2$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.67 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3227 (NH), 2985 (NH), 2924 (C-H st), 1676 (C=O), 1551 (C=N), 1273 (C=S), 1133 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (10), 163 (12), 83 (20); HRMS: Calculated for [C$_{24}$H$_{25}$N$_4$O$_2$SF$_6$]$^+$: 547.1602 [(M+H)$^+$]; found: 547.1588; The ee was determined by HPLC using a Chiralpak IA column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 9.683 min, τ$_{minor}$ = 5.086 min (99% ee); [α]$_D^{20}$: -84.3 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 139-141 ºC.
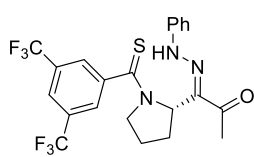
(*S*)-(*E*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxo-1-(2-phenylhydrazono)propyl)pyrrolidine-1-carbothioamide (3m). Following the general procedure F, **3m** (39.4 mg, 0.078 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 1h in 87% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and pyruvic aldehyde 1-phenylhydrazone **2g** (14.6 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (1:10 diastereoisomer ratio, *denotes minor diastereoisomer resonances, #overlapped signals) δ 13.24* (s, 1H, NNH), 9.98 (s, 1H, NNH), 9.27 (s, 1H, CSNH), 8.20 (s, 2H, C_{Ar}-H), 8.15* (s, 2H, C_{Ar}-H), 7.64* (s, 1H, C_{Ar}-H), 7.62 (s, 1H, C_{Ar}-H),

7.36-7.22 (m, 4H, C_{Ar}-H), 7.02-6.96* (m, 1H, C_{Ar}-H), 6.94 (tt, J = 6.6, 1.6 Hz, 1H, C_{Ar}-H), 5.61-5.56* (m, 1H, C_2-H), 5.49-5.41 (m, 1H, C_2-H), 3.99-3.76 (m, 2H, C_5-H), 2.40-2.29# (m, 4H, C_3-H_a + CH_3), 2.24-2.14 (m, 1H, C_4-H_a), 2.06-1.95 (m, 1H, C_4-H_b), 1.92-1.83 (m, 1H, C_3-H_b); ^{13}C NMR (125 MHz, DMSO-d_6, 100ºC): δ 194.8 (CO), 176.1 (CS), 143.9 (C_{Ar}-C), 142.4 (C_{Ar}-C), 141.1 (CN), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$), 128.7* (C_{Ar}-H), 128.6* (C_{Ar}-H), 128.5 (C_{Ar}-H), 123.0 (q, $^3J_{C-F}$ = 3.5 Hz, C_{Ar}-H), 122.9 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 121.1* (C_{Ar}-H), 120.9 (C_{Ar}-H), 115.5 (q, $^3J_{C-F}$ = 3.9 Hz, C_{Ar}-H), 113.7* (C_{Ar}-H), 113.6 (C_{Ar}-H), 57.3 (C_2), 57.1* (C_2), 51.7* (C_5), 50.0 (C_5), 28.3 (C_3), 24.6 (CH_3), 24.2 (C_4); ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.6 (2 × CF$_3$); R_f: 0.49 (hexanes/EtOAc 6:4); IR (ATR) cm^{-1}: 3296 (NH), 2968 (NH), 2850 (C-H st), 1645 (C=O), 1559 (C=N), 1269 (C=S), 1127 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (21), 202 (11), 163 (12), 83 (25); HRMS: Calculated for $[C_{22}H_{21}N_4OSF_6]^+$: 503.1340 [(M+H)$^+$]; found: 503.1341; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ_{major} = 6.033 min, τ_{minor} = 6.533 min (98% ee); $[α]_D^{20}$: +287.1 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 190-192 ºC.
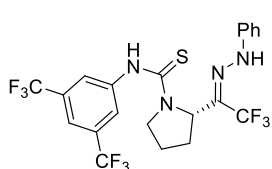
(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-(2,2,2-trifluoro-1-(2-phenylhydrazono)ethyl)pyrrolidine-1-carbothioamide (3n). Following the general procedure G, **3n** (34.9 mg, 0.066 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 73% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-phenyl-2-(2,2,2-trifluoroethylidene)hydrazine **2h** (16.9 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d_6, 100ºC): (16.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.86 (s, 1H, NNH), 9.70* (s, 1H, NNH), 9.53 (s, 1H, CSNH), 9.37* (s, 1H, CSNH), 8.22 (s, 2H, C_{Ar}-H), 8.16* (s, 2H, C_{Ar}-H), 7.69 (s, 1H, C_{Ar}-H), 7.66* (s, 1H, C_{Ar}-H), 7.27 (t, J = 7.8 Hz, 2H, C_{Ar}-H), 7.21 (d, J = 7.8 Hz, 2H, C_{Ar}-H), 6.90 (t, J = 7.2 Hz, 1H, C_{Ar}-H), 5.83-5.70 (m, 1H, C_2-H), 5.51-5.44* (m, 1H, C_2-H), 4.00-3.90 (m, 1H, C_5-H_a), 3.83-3.70 (m, 1H, C_5-H_b), 2.51-2.39 (m, 1H, C_3-H_a), 2.23-2.12 (m, 1H, C_4-H_a), 2.11-2.01 (m, 1H, C_4-H_b), 2.00-1.92 (m, 1H, C_3-H_b); ^{13}C NMR (125 MHz, DMSO-d_6, 100ºC): δ 178.8 (CS), 143.9 (C_{Ar}-C), 142.2 (CN), 129.6 (q, $^2J_{C-F}$ = 33.0 Hz, 2 × **C**CF$_3$), 128.4 (C_{Ar}-H), 123.6 (C_{Ar}-H),

122.8 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 122.1 (q, $^1J_{C-F}$ = 274.1 Hz, CF$_3$), 120.5 (C$_{Ar}$-H), 116.1 (q, $^3J_{C-F}$ = 3.5 Hz, C$_{Ar}$-H), 113.2 (C$_{Ar}$-H), 57.1 (C$_2$), 49.9 (C$_5$), 28.3 (C$_3$), 23.8 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.37 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3285 (NH), 2924 (NH), 2853 (C-H st), 1536 (C=N), 1276 (C=S), 1175 (C-F st), 1124 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (24), 213 (24), 202 (10), 163 (12), 83 (29); HRMS: Calculated for [C$_{21}$H$_{18}$N$_4$OSF$_9$]$^+$: 529.1108 [(M+H)$^+$]; found: 529.1119; The ee was determined by HPLC using a Chiralpak AS-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 59.265 min, τ$_{minor}$ = 15.983 min (99% ee); [α]$_D{}^{20}$: +125.7 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 129-131 ºC.
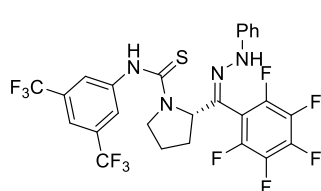
(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((perfluorophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3o). Following the general procedure F, **3o** (44.0 mg, 0.070 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 78% yield as a white foam starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-((perfluorophenyl)methylene)-2-phenylhydrazine **2i** (25.8 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (>20:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.66* (s, 1H, NNH), 9.43* (s, 1H, CSNH), 9.31 (s, 1H, CSNH), 9.12 (s, 1H, NNH), 8.21* (s, 2H, C$_{Ar}$-H), 8.13 (s, 2H, C$_{Ar}$-H), 7.64 (s, 1H, C$_{Ar}$-H), 7.23-7.16 (m, 2H, C$_{Ar}$-H), 7.11 (d, *J* = 7.9 Hz, 2H, C$_{Ar}$-H), 6.86-6.79 (m, 1H, C$_{Ar}$-H), 5.88-5.82* (m, 1H, C$_2$-H), 5.73-5.66 (m, 1H, C$_2$-H), 3.98-3.75 (m, 2H, C$_5$-H), 2.37-2.30 (m, 1H, C$_3$-H$_a$), 2.26-2.08 (m, 3H, C$_3$-H$_b$ + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.6 (CS), 144.4 (C$_{Ar}$-C), 143.4 (dm, J_{C-F} = 245.9 Hz, C$_6$-F$_5$), 142.4 (CN), 142.3 (C$_{Ar}$-C), 137.1 (dm, J_{C-F} = 249.8 Hz, C$_6$-F$_5$), 129.5 (q, $^2J_{C-F}$ = 32.8 Hz, 2 × **C**CF$_3$), 128.3 (C$_{Ar}$-H), 123.1 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 119.7 (C$_{Ar}$-H), 115.7 (C$_{Ar}$-H), 112.7 (C$_{Ar}$-H), 107.3 (dm, C$_{Ar}$-C), 63.8 (C$_2$), 49.4 (C$_5$), 28.4 (C$_3$), 22.4 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$), -137.4 (m, C$_6$F$_5$ *m*-F), -154.3 (m, C$_6$F$_5$ *p*-F), -162.1 (m, C$_6$F$_5$ *o*-F); R$_f$: 0.49 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3269 (NH), 2926 (NH), 1520 (C=N), 1277 (C=S), 1171 (C-F st), 1132 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202

(10), 163 (11); HRMS: Calculated for $[C_{26}H_{18}N_4SF_{11}]^+$: 627.1077 $[(M+H)^+]$; found: 627.1086; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ_{major} = 47.899 min, τ_{minor} = 57.949 min (97% ee); $[\alpha]_D^{20}$: +15.7 (*c* = 1.0, CH_2Cl_2); M.p. (CH_2Cl_2): 157-159 ºC.
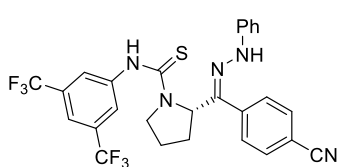
(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((4-cyanophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3p). Following the general procedure F, **3p** (45.6 mg, 0.081 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 90% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-4-((2-phenylhydrazono)methyl)benzonitrile **2j** (19.9 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (1.4:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.37 (s, 1H, NNH), 9.31 (s, 1H, CSNH), 8.60 (s, 1H, C$_{Ar}$-H), 8.19 (s, 2H, C$_{Ar}$-H), 7.99-7.86 (m, 2H, C$_{Ar}$-H), 7.74-7.59 (m, 2H, C$_{Ar}$-H), 7.26-7.20* (m, 4H, C$_{Ar}$-H), 7.16-7.10 (m, 2H, C$_{Ar}$-H), 7.10-7.06 (m, 2H, C$_{Ar}$-H), 6.87-6.79* (m, 1H, C$_{Ar}$-H), 6.77-6.70 (m, 1H, C$_{Ar}$-H), 5.72-5.66* (m, 1H, C$_2$-H), 5.48-5.42 (m, 1H, C$_2$-H), 4.05-3.78 (m, 2H, C$_5$-H), 2.69-2.60* (m, 1H, C$_3$-H$_a$), 2.27-1.90 (m, 3H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.4* (CS), 178.0 (CS), 145.2* (C$_{Ar}$-C), 145.1 (C$_{Ar}$-C), 142.4 (CNNH), 142.1* (CNNH), 141.8 (C$_{Ar}$-C), 141.3* (C$_{Ar}$-C), 137.8 (C$_{Ar}$-C), 132.4 (C$_{Ar}$-H), 131.0* (C$_{Ar}$-H), 129.4 (q, $^2J_{C-F}$ = 32.5Hz, 2 × **C**CF$_3$), 128.9 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 128.1 (C$_{Ar}$-H), 127.0* (C$_{Ar}$-H), 123.9 (C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 119.4* (C$_{Ar}$-H), 118.8 (C$_{Ar}$-H), 118.2* (CN), 117.9 (CN), 116.0 (C$_{Ar}$-H), 112.9* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 111.3 (C$_{Ar}$-C), 111.2* (C$_{Ar}$-C), 65.2 (C$_2$), 59.4* (C$_2$), 50.9 (C$_5$), 49.8* (C$_5$), 29.2 (C$_3$), 28.6* (C$_3$), 23.9* (C$_4$), 22.2 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.43 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3308 (NH), 2928 (NH), 2231 (*p*-CN), 1600 (C=N), 1276 (C=S), 1128 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (22), 213 (22), 202 (11), 163 (12), 83 (17); HRMS: Calculated for $[C_{27}H_{22}N_5SF_6]^+$: 562.1500 $[(M+H)^+]$; found: 562.1495; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 17.194 min, τ_{minor} = 11.594 min (88% ee); $[\alpha]_D^{20}$: +47.0 (*c* = 1.0, CH_2Cl_2); M.p. (CH_2Cl_2): 97-99 ºC.

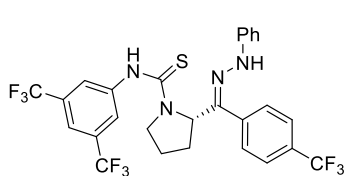**(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((2-phenylhydrazono)(4-(trifluoromethyl)phenyl)methyl)pyrrolidine-1-carbothioamide (3q).** Following the general procedure F, **3q** (32.7 mg, 0.054 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 60% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-phenyl-2-(4-(trifluoromethyl)benzylidene)hydrazine **2k** (23.8 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (2.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.33* (s, 1H, NNH), 9.30 (s, 1H, CSNH + CSNH*), 8.58 (s, 1H, NNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.89* (s, 2H, C$_{Ar}$-H), 7.86 (d, *J* = 8.0 Hz, 2H, C$_{Ar}$-H), 7.75-7.68 (m, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.63* (s, 2H, C$_{Ar}$-H), 7.26-7.17* (m, 4H, C$_{Ar}$-H), 7.17-7.03 (m, 4H, C$_{Ar}$-H), 6.86-6.77* (m, 1H, C$_{Ar}$-H), 6.77-6.70 (m, 1H, C$_{Ar}$-H), 5.76-5.68* (m, 1H, C$_2$-H), 5.51-5.44 (m, 1H, C$_2$-H), 4.05-3.73 (m, 2H, C$_5$-H), 2.75-2.59* (m, 1H, C$_3$-H$_a$), 2.29-1.94 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.4* (CS), 178.0 (CS), 145.2 (C$_{Ar}$-C), 142.4* (C$_{Ar}$-C), 142.1 (CN), 141.3 (CN), 137.1 (C$_{Ar}$-C), 129.6 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × **C**CF$_3$ + *p*-**C**CF$_3$), 128.7 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 127.1* (C$_{Ar}$-H), 125.4 (q, $^3J_{C-F}$ = 3.9 Hz, C$_{Ar}$-H), 123.9* (C$_{Ar}$-H), 123.8 (C$_{Ar}$-H), 123.6* (C$_{Ar}$-H), 123.7 (q, $^1J_{C-F}$ = 272.2 Hz, 2 × CF$_3$), 122.9 (q, $^1J_{C-F}$ = 272.2 Hz, 2 × CF$_3$), 121.7 (C$_{Ar}$-C), 121.6* (C$_{Ar}$-C), 119.2* (C$_{Ar}$-H), 118.7 (C$_{Ar}$-H), 115.9 (C$_{Ar}$-H), 112.8* (C$_{Ar}$-H), 112.6 (C$_{Ar}$-H), 65.2 (C$_2$), 59.4* (C$_2$), 50.8* (C$_5$), 49.9 (C$_5$), 29.2 (C$_3$), 28.7* (C$_3$), 23.9* (C$_4$), 22.2 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.2 (CF$_3$), -61.6 (2 × CF$_3$) R$_f$: 0.56 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3340 (NH), 2981 (NH), 1601 (C=N), 1276 (C=S), 1169 (C-F st), 1124 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (6); HRMS: Calculated for [C$_{27}$H$_{22}$N$_4$SF$_9$]$^+$: 605.1421 [(M+H)$^+$]; found: 605.1434; The ee was determined by HPLC using a Chiralpak IA column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 6.290 min, τ$_{minor}$ = 6.940 min (86% ee); [α]$_D^{20}$: +125.9 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 81-83 ºC.
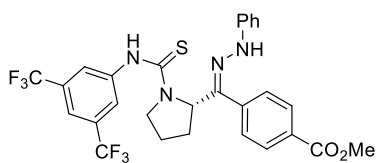
(*S*)-methyl-(*Z*)-4-((1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)(2-phenylhydrazono)methyl)benzoate (3r). Following the general procedure F, **3r** (34.7 mg, 0.058 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 65% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and methyl (*E*)-4-((2-phenylhydrazono)methyl)benzoate **2l** (22.9 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (2.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances, # overlapped signals) δ 9.32* (s, 1H, NNH), 9.30 (bs, 1H, NNH), 8.48 (s, 1H, CSNH), 8.19 (s, 2H, C$_{Ar}$-H), 8.08 (d, *J* = 8.0 Hz, 2H, C$_{Ar}$-H), 7.90 (d, *J* = 8.3 Hz, 1H, C$_{Ar}$-H), 7.66-7.56 (m, 2H, C$_{Ar}$-H), 7.25-7.18* (m, 4H, C$_{Ar}$-H), 7.16-7.03 (m, 4H, C$_{Ar}$-H), 6.85-6.78* (m, 1H, C$_{Ar}$-H), 6.75-6.71 (m, 1H, C$_{Ar}$-H), 5.75-5.68* (m, 1H, C$_2$-H), 5.49 (dd, *J* = 7.8, 2.0 Hz, 1H, C$_2$-H), 4.05-3.82# (m, 5H, C$_5$-H + OCH$_3$), 2.71-2.59* (m, 1H, C$_3$-H$_a$), 2.26-1.97 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.3* (CS), 178.0 (CS), 165.6* (COO), 165.5 (COO), 145.2* (C$_{Ar}$-C), 145.1 (C$_{Ar}$-C), 142.4 (CN), 137.5 (C$_{Ar}$-C), 129.8 (C$_{Ar}$-C), 129.6 (q, $^2J_{C-F}$ = 33.0 Hz, 2 × **C**CF$_3$), 129.4 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 128.1 (C$_{Ar}$-H), 128.1* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 126.5* (C$_{Ar}$-H), 123.8 (q, $^3J_{C-F}$ = 3.3 Hz, C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 273.1 Hz, 2 × CF$_3$), 119.2* (C$_{Ar}$-H), 118.7 (C$_{Ar}$-H), 115.9 (q, $^3J_{C-F}$ = 2.9 Hz, C$_{Ar}$-H), 112.8* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.0 (C$_2$), 59.5* (C$_2$), 51.5 (OCH$_3$), 51.2* (OCH$_3$), 50.9* (C$_5$), 50.0 (C$_5$), 29.2 (C$_3$), 28.7* (C$_3$), 23.9* (C$_4$), 22.2 (C$_4$); ^{19}F NMR (300 MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.45 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3308 (NH), 2959 (NH), 1717 (C=O), 1601 (C=N), 1275 (C=S), 1129 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (24), 202 (11), 163 (13), 83 (25); HRMS: Calculated for [C$_{28}$H$_{25}$N$_4$O$_2$SF$_6$]$^+$: 595.1602 [(M+H)$^+$]; found: 595.1607; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 10.350 min, τ$_{minor}$ = 12.245 min (83% ee); [α]$_D^{20}$: +102.4 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 77-79 ºC.
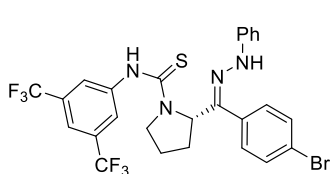
(S)-(Z)-N-(3,5-bis(trifluoromethyl)phenyl)-2-((4-bromophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3s). Following the general procedure F, **3s** (43.9 mg, 0.071 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 79% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(4-bromobenzylidene)-2-phenylhydrazine **2m** (24.8 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.2:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.32* (s, 1H, NNH), 9.28 (s, 1H, NNH), 9.18* (s, 1H, CSNH), 8.47 (s, 1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.96* (s, 2H, C$_{Ar}$-H), 7.71 (d, J = 8.4 Hz, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.52-7.47* (m, 2H, C$_{Ar}$-H), 7.47-7.40 (m, 2H, C$_{Ar}$-H), 7.25-7.17* (m, 4H, C$_{Ar}$-H), 7.16-7.05 (m, 4H, C$_{Ar}$-H), 6.82-6.77* (m, 1H, C$_{Ar}$-H), 6.75-6.69 (m, 1H, C$_{Ar}$-H), 5.74-5.66* (m, 1H, C$_2$-H), 5.47-5.40 (m, 1H, C$_2$-H), 4.01-3.76 (m, 2H, C$_5$-H), 2.66-2.56* (C$_3$-H$_a$), 2.27-1.93 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.3* (CS), 178.0 (CS), 145.4* (CN), 145.2 (CN), 142.4 (C$_{Ar}$-C), 142.1* (C$_{Ar}$-C), 136.6 (C$_{Ar}$-C), 131.8 (C$_{Ar}$-C), 131.7 (C$_{Ar}$-H), 130.1* (C$_{Ar}$-H), 129.9 (C$_{Ar}$-H), 129.4 (q, $^2J_{C-F}$ = 33.6 Hz, 2 × **C**CF$_3$), 128.6* (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 123.8 (C$_{Ar}$-H), 123.6* (C$_{Ar}$-H), 123.0 (q, $^1J_{C-F}$ = 272.3 Hz, 2 × CF$_3$), 123.8 (C$_{Ar}$-H), 121.7 (C$_{Ar}$-C), 119.0* (C$_{Ar}$-H), 118.6 (C$_{Ar}$-H), 115.9 (q, $^3J_{C-F}$ = 4.3 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.3 (C$_2$), 59.5* (C$_2$), 49.9 (C$_5$), 29.2 (C$_3$), 28.7* (C$_3$), 23.9* (C$_4$), 22.1 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.58 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3341 (NH), 2971 (NH), 2930 (C-H st), 1591 (C=N), 1276 (C=S), 1129 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (27), 213 (24), 202 (10), 163 (13), 83 (25), 69 (9); HRMS: Calculated for [C$_{26}$H$_{22}$N$_4$SF$_6$Br]$^+$: 615.0653 [(M+H)$^+$]; found: 615.0647; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ$_{major}$ = 4.597 min, τ$_{minor}$ = 4.956 min (92% ee); [α]$_D^{20}$: +114.7 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 88-90 ºC.
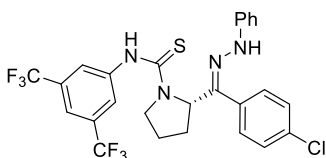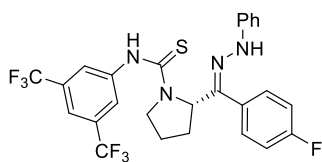
(S)-(Z)-N-(3,5-bis(trifluoromethyl)phenyl)-2-((4-chlorophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3t). Following the general procedure F, **3t** (42.3 mg, 0.074 mmol) was isolated by FC (petroleum
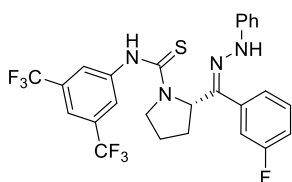
ether/EtOAc gradient from 19:1 to 7:3) after 20h in 82% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(4-chlorobenzylidene)-2-phenylhydrazine **2n** (20.8 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.4:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.32* (s, 1H, NNH), 9.29 (s, 1H, NNH), 9.17* (s, 1H, CSNH), 8.46 (s, 1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.96* (s, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.57 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 7.52-7.47 (m, 2H, C$_{Ar}$-H), 7.34* (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 7.25-.716 (m, 1H, C$_{Ar}$-H), 7.15-7.02 (m, 3H, C$_{Ar}$-H), 6.82-6.77* (m, 1H, C$_{Ar}$-H), 6.75-6.70 (m, 1H, C$_{Ar}$-H), 5.74-5.69* (m, 1H, C$_2$-H), 5.47-5.39 (m, 1H, C$_2$-H), 4.02-3.74 (m, 2H, C$_5$-H), 2.65-2.57* (C$_3$-H$_a$), 2.28-1.94 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.3* (CS), 178.0 (CS), 145.4* (C$_{Ar}$-C), 145.2 (C$_{Ar}$-C), 142.4 (CN), 142.2* (CN), 136.2 (C$_{Ar}$-C), 133.4 (C$_{Ar}$-C), 131.4 (C$_{Ar}$-C), 129.6 (C$_{Ar}$-H), 129.4 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, 2 × **C**CF$_3$), 128.7 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 127.2* (C$_{Ar}$-H), 123.8 (C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 122.8 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2 × CF$_3$), 119.0* (C$_{Ar}$-H), 118.6 (C$_{Ar}$-H), 115.9 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.3 (C$_2$), 59.5* (C$_2$), 50.7* (C$_5$), 50.0 (C$_5$), 29.2 (C$_3$), 28.7* (C$_3$), 23.9* (C$_4$), 22.1 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.55 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2984 (NH), 1601 (C=N), 1278 (C=S), 1134 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (24), 213 (23), 202 (11), 163 (14), 143 (9), 83 (34), 69 (9); HRMS: Calculated for [C$_{26}$H$_{22}$N$_4$SF$_6$Cl]$^+$: 571.1158 [(M+H)$^+$]; found: 571.1157; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 9.354 min, τ$_{minor}$ = 11.676 min (90% ee); [α]$_D^{20}$: +145.3 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 81-83 ºC.

(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((4-fluorophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3u). Following the general procedure F, **3u** (47.8 mg, 0.086 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 95% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(4-fluorobenzylidene)-2-phenylhydrazine **2o** (19.3 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry

toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (4.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.30 (s, 1H, NNH*), 9.28 (s, 1H, NNH), 9.12* (s, 1H, CSNH), 8.37 (s, 1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.95* (s, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.57-7.48 (m, 2H, C$_{Ar}$-H), 7.36-7.29 (m, 2H, C$_{Ar}$-H), 7.25-7.15 (m, 1H, C$_{Ar}$-H), 7.15-7.02 (m, 3H, C$_{Ar}$-H), 6.81-6.76* (m, 1H, C$_{Ar}$-H), 6.75-6.69 (m, 1H, C$_{Ar}$-H), 5.75-5.68* (m, 1H, C$_2$-H), 5.47-5.40 (m, 1H, C$_2$-H), 4.01-3.72 (m, 2H, C$_5$-H), 2.67-2.57* (C$_3$-H), 2.26-1.95 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.2* (CS), 178.0 (CS), 161.9 (d, $^1J_{C\text{-}F}$ = 246.4 Hz, CF), 145.5* (C$_{Ar}$-C), 145.2 (C$_{Ar}$-C), 142.4 (CN), 142.2* (CN), 130.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, C$_{Ar}$-H), 129.4 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, 2 × CCF$_3$), 128.6 (C$_{Ar}$-C), 128.2* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 123.8 (C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 122.8 (q, $^1J_{C\text{-}F}$ = 272.6 Hz, 2 × CF$_3$), 118.8* (C$_{Ar}$-H), 118.6 (C$_{Ar}$-H), 115.9 (C$_{Ar}$-H), 115.6 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, C$_{Ar}$-H), 113.9* (d, $^2J_{C\text{-}F}$ = 21.2 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.3 (C$_2$), 59.5* (C$_2$), 50.7* (C$_5$), 49.9 (C$_5$), 29.1 (C$_3$), 28.7* (C$_3$), 22.1 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$), -112.4 (CF); R$_f$: 0.52 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2930 (NH), 1600 (C=N), 1276 (C=S), 1172 (C-F st), 1128 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (24), 213 (22), 202 (10), 163 (11), 83 (33); HRMS: Calculated for [C$_{26}$H$_{22}$N$_4$SF$_7$]$^+$: 555.1453 [(M+H)$^+$]; found: 555.1453; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ$_{major}$ = 4.716 min, τ$_{minor}$ = 5.079 min (94% ee); [α]$_D^{20}$: +169.4 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 77-79 ºC.

(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((3-fluorophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3v). Following the general procedure F, **3v** (39.8 mg, 0.072 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 80% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(3-fluorobenzylidene)-2-phenylhydrazine **2p** (19.3 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.36* (s, 1H, NNH), 9.29 (s, 1H, NNH), 9.20* (s, 1H, CSNH), 8.47 (s, 1H, CSNH), 8.19 (s, 2H, C$_{Ar}$-H), 7.96* (s, 2H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 7.61-7.51 (m, 1H, C$_{Ar}$-H), 7.39-7.15 (m,

3H, C$_{Ar}$-H), 7.15-7.04 (m, 4H, C$_{Ar}$-H), 6.84-6.77* (m, 1H, C$_{Ar}$-H), 6.77-6.69 (m, 1H, C$_{Ar}$-H), 5.75-5.68* (m, 1H, C$_2$-H), 5.48-5.41 (m, 1H, C$_2$-H), 4.02-3.73 (m, 2H, C$_5$-H), 2.66-2.55* (m, 1H, C$_3$-H$_a$), 2.27-1.96 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.3* (CS), 178.0 (CS), 162.1 (d, $^1J_{C-F}$ = 245.6 Hz, CF), 145.3* (C$_{Ar}$-C), 145.2 (C$_{Ar}$-C), 142.4 (CN), 142.2* (CN), 134.8 (C$_{Ar}$-C), 130.7 (d, $^3J_{C-F}$ = 8.5 Hz, C$_{Ar}$-H), 129.4 (q, $^2J_{C-F}$ = 33.2 Hz, 2 × **C**CF$_3$), 128.3* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 123.8 (C$_{Ar}$-H), 123.6* (C$_{Ar}$-H), 122.5 (d, $^4J_{C-F}$ = 2.5 Hz, C$_{Ar}$-H), 122.9 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 119.6 (d, $^3J_{C-F}$ = 5.5 Hz, C$_{Ar}$-C), 119.1* (C$_{Ar}$-H), 118.7 (C$_{Ar}$-H), 116.0* (C$_{Ar}$-H), 115.9 (C$_{Ar}$-H), 115.4 (d, $^2J_{C-F}$ = 20.9 Hz, C$_{Ar}$-H), 114.7 (d, $^2J_{C-F}$ = 22.0 Hz, C$_{Ar}$-H), 113.5* (d, $^2J_{C-F}$ = 21.1 Hz, C$_{Ar}$-H), 113.2* (d, $^2J_{C-F}$ = 22.4 Hz, C$_{Ar}$-H), 112.8* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.2 (C$_2$), 59.5* (C$_2$), 50.7* (C$_5$), 49.9 (C$_5$), 29.2 (C$_3$), 28.7* (C$_3$), 23.8* (C$_4$), 22.1 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$), -112.0 (CF); R$_f$: 0.58 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3335 (NH), 2974 (NH), 1601 (C=N), 1275 (C=S), 1170 (C-F st), 1126 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (13), 83 (7); HRMS: Calculated for [C$_{26}$H$_{22}$N$_4$SF$_7$]$^+$: 555.1453 [(M+H)$^+$]; found: 555.1459; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 20.990 min, τ$_{minor}$ = 6.946 min (84% ee); [α]$_D^{20}$: +124.6 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 73-75 ºC.

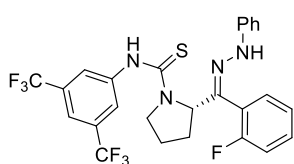**(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((2-fluorophenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3w).** Following the general procedure F, **3w** (47.2 mg, 0.085 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 94% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(2-fluorobenzylidene)-2-phenylhydrazine **2q** (19.3 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (8.4:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.28 (s, 1H, NNH), 8.48 (s ,1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 8.01* (s, 1H, CSNH), 7.64 (s, 1H, C$_{Ar}$-H), 7.59-7.47 (m, 2H, C$_{Ar}$-H), 7.35 (t, *J* = 7.5 Hz, 1H, C$_{Ar}$-H), 7.30 (t, *J* = 9.0 Hz, 1H, C$_{Ar}$-H), 7.17-7.05 (m, 4H, C$_{Ar}$-H), 6.80-6.76* (m, 1H, C$_{Ar}$-H), 6.76-6.71 (m, 1H, C$_{Ar}$-H), 5.88-5.77* (m, 1H, C$_2$-H), 5.52-5.45 (m, 1H, C$_2$-H), 3.99-3.77 (m, 2H, C$_5$-H), 3.58-3.51* (m, 1H, C$_5$-H$_a$), 3.42-3.35* (m, 1H, C$_5$-H$_b$), 2.67-

2.59* (m, 1H, C$_3$-H$_a$), 2.24-1.91 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.3* (CS), 178.1 (CS), 158.7 (d, $^1J_{C-F}$ = 246.6 Hz, CF), 145.0 (C$_{Ar}$-C), 142.4 (CN), 137.3 (C$_{Ar}$-C), 130.9 (d, $^3J_{C-F}$ = 8.1 Hz, C$_{Ar}$-H), 129.8 (d, $^3J_{C-F}$ = 4.3 Hz, C$_{Ar}$-H), 129.4 (q, $^2J_{C-F}$ = 33.1 Hz, 2 × CCF$_3$), 128.2* (C$_{Ar}$-H), 128.1 (C$_{Ar}$-H), 124.6 (d, $^4J_{C-F}$ = 2.5 Hz, C$_{Ar}$-H), 123.6 (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 272.3 Hz, 2 × CF$_3$), 119.9 (d, $^2J_{C-F}$ = 19.3 Hz, C$_{Ar}$-C), 119.0* (C$_{Ar}$-H), 118.7 (C$_{Ar}$-H), 115.8 (C$_{Ar}$-H), 115.7 (d, $^2J_{C-F}$ = 22.1 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.5 (C$_{Ar}$-H), 65.1 (C$_2$), 50.0 (C$_5$), 28.9 (C$_3$), 22.0 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$), -112.2 (CF); R$_f$: 0.54 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3331 (NH), 2963 (NH), 1601 (C=N), 1276 (C=S), 1172 (C-F st), 1128 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (8); HRMS: Calculated for [C$_{26}$H$_{22}$N$_4$SF$_7$]$^+$: 555.1453 [(M+H)$^+$]; found: 555.1467; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ$_{major}$ = 11.820 min, τ$_{minor}$ = 7.849 min (82% ee); [α]$_D^{20}$: +100.7 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 73-75 ºC.

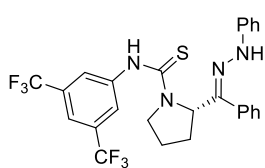**(S)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-(phenyl(2-phenylhydrazono)pyrrolidine-1-carbothipamide (3x).** Following the general procedure F, **3x** (45.6 mg, 0.085 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 94% yield as a white solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-benzylidene-2-phenylhydrazine **3r** (17.7 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (4.5:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.28 (s, 1H, NNH), 9.11* (s, 1H, NNH), 8.27 (s, 1H, C$_{Ar}$-H), 8.20 (s, 2H, C$_{Ar}$-H), 7.98-7.89* (m, 2H, C$_{Ar}$-H), 7.64 (s, 1H, CSNH), 7.63* (s, 1H, CSNH), 7.58-7.50 (m, 2H, C$_{Ar}$-H), 7.51-7.45 (m, 3H, C$_{Ar}$-H), 7.35-7.28* (m, 2H, C$_{Ar}$-H), 7.24-7.15* (m, 3H, C$_{Ar}$-H), 7.14-7.08 (m, 2H, C$_{Ar}$-H), 7.08-7.03 (m, 2H, C$_{Ar}$-H), 6.81-6.76* (m, 1H, C$_{Ar}$-H), 6.75-6.69 (m, 1H, C$_{Ar}$-H), 5.76-5.72* (m, 1H, C$_2$-H), 5.51-5.43 (m, 1H, C$_2$-H), 3.98-3.88 (m, 1H, C$_5$-H$_a$), 3.88-3.75 (m, 1H, C$_5$-H$_b$), 2.66-2.55* (C$_3$-H), 2.23-2.12 (m, 1H, C$_3$-H$_a$), 2.12-1.94 (m, 3H, C$_3$-H$_b$ + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.2* (CS), 178.0 (CS), 145.6* (CN), 145.2 (CN), 143.7 (C$_{Ar}$-C), 142.4 (C$_{Ar}$-C), 142.2* (C$_{Ar}$-C), 132.4 (C$_{Ar}$-C), 129.4 (q, $^2J_{C-F}$ = 32.9 Hz, 2 × CCF$_3$), 128.7 (C$_{Ar}$-H), 128.5* (C$_{Ar}$-H), 128.2* (C$_{Ar}$-H), 128.1 (C$_{Ar}$-H), 127.6 (C$_{Ar}$-H), 127.2*

(C$_{Ar}$-H), 126.8* (C$_{Ar}$-H), 126.7 (C$_{Ar}$-H), 123.7 (C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 118.8* (C$_{Ar}$-H), 118.6 (C$_{Ar}$-H), 116.1* (C$_{Ar}$-H), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.4 (C$_{Ar}$-H), 65.3 (C$_2$), 50.0 (C$_5$), 29.2 (C$_3$), 28.9* (C$_3$), 22.9* (C$_4$), 22.1 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.58 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3335 (NH), 2924 (NH), 2810 (C-H st), 1602 (C=N), 1275 (C=S), 1126 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (10), 163 (12), 83 (11); HRMS: Calculated for [C$_{26}$H$_{23}$N$_4$SF$_6$]$^+$: 537.1548 [(M+H)$^+$]; found: 537.1543; The ee was determined by HPLC using a Chiralpak IC column [*n*hexane/*i*PrOH (92:08)]; flow rate 1.00 mL/min; τ$_{major}$ = 4.825 min, τ$_{minor}$ = 5.576 min (90% ee); [α]$_D^{20}$: +158.0 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 56-58 ºC.

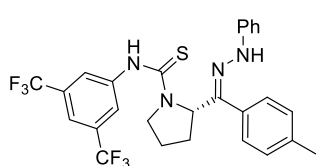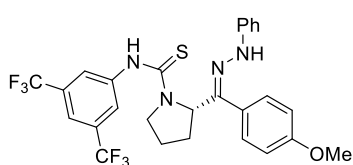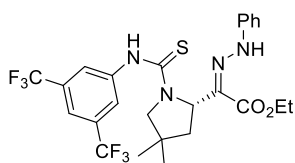**(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((2-phenylhydrazono)(*p*-tolyl)methyl)pyrrolidine-1-carbothioamide (3y).** Following the general procedure F, **3y** (41.2 mg, 0.075 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 83% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(4-methylbenzylidene)-2-phenylhydrazine **2s** (18.9 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (5.5:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.27 (s, 1H, CSNH), 9.06* (s, 1H, NNH), 8.24 (s, 1H, NNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.93* (s, 2H, C$_{Ar}$-H), 7.64 (s, 1H, C$_{Ar}$-H), 7.40-7.29 (m, 4H, C$_{Ar}$-H), 7.23-7.14* (m, 4H, C$_{Ar}$-H), 7.14-7.01 (m, 4H, C$_{Ar}$-H), 6.81-6.75* (m, 1H, C$_{Ar}$-H), 6.74-6.68 (m, 1H, C$_{Ar}$-H), 5.75-5.68* (m, 1H, C$_2$-H), 5.50-542 (m, 1H, C$_2$-H), 3.98-3.79 (m, 2H, C$_5$-H), 2.64-2.55* (m, 1H, C$_3$-H$_a$), 2.39 (s, 3H, CH$_3$), 2.32* (s, 3H, CH$_3$), 2.23-2.12 (m, 1H, C$_3$-H$_a$), 2.11-1.95 (m, 3H, C$_3$-H$_b$ + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.2* (CS), 178.0 (CS), 145.7* (C$_{Ar}$-C), 145.2 (C$_{Ar}$-C), 143.8 (C$_{Ar}$-C), 142.5 (CN), 142.2* (CN), 138.0 (C$_{Ar}$-C), 136.2 (C$_{Ar}$-C), 129.3 (q, $^2J_{C-F}$ = 33.2 Hz, 2 × **C**CF$_3$), 129.3 (C$_{Ar}$-H), 128.2* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 127.8* (C$_{Ar}$-H), 127.4 (C$_{Ar}$-H), 126.5* (C$_{Ar}$-H), 123.6 (C$_{Ar}$-H), 123.6* (C$_{Ar}$-H), 122.8 (q, $^1J_{C-F}$ = 272.9 Hz, 2 × CF$_3$), 118.7* (C$_{Ar}$-H), 118.5 (C$_{Ar}$-H), 115.8 (q, $^3J_{C-F}$ = 3.6 Hz, C$_{Ar}$-H), 112.7* (C$_{Ar}$-H), 112.4 (C$_{Ar}$-H), 65.2 (C$_2$), 59.4* (C$_2$), 50.9* (C$_5$), 50.0 (C$_5$), 29.2 (C$_3$), 28.9* (C$_3$), 23.7* (C$_4$), 22.0 (C$_4$), 20.3 (CH$_3$), 20.0* (CH$_3$); ^{19}F NMR (282

MHz, DMSO-d_6): δ -61.5 (2 × CF$_3$); R$_f$: 0.70 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3336 (NH), 2972 (NH), 2830 (C-H st), 1602 (C=N), 1275 (C=S), 1127 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (22), 202 (11), 163 (12), 83 (16); HRMS: Calculated for [C$_{27}$H$_{25}$N$_4$SF$_6$]$^+$: 551.1704 [(M+H)$^+$]; found: 551.1698; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (97:03)]; flow rate 1.00 mL/min; τ_{major} = 19.741 min, τ_{minor} = 22.974 min (91% ee). [α]$_D^{20}$: +163.7 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 68-70 °C.

(*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((4-methoxyphenyl)(2-phenylhydrazono)methyl)pyrrolidine-1-carbothioamide (3z). Following the general procedure F, **3z** (31.0 mg, 0.055 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 60% yield as a yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1e** (45.9 mg, 0.135 mmol) and (*E*)-1-(4-methoxybenzylidene)-2-phenylhydrazine **2t** (20.4 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d_6, 100°C): (6.2:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances, #overlapped signals) δ 9.26 (s, 1H, NNH), 9.01* (s, 1H, CSNH), 8.25 (s, 1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 7.97* (s, 2H, C$_{Ar}$-H), 7.64 (s, 1H, C$_{Ar}$-H), 7.47-7.35 (m, 2H, C$_{Ar}$-H), 7.23-7.14* (m, 4H, C$_{Ar}$-H), 7.14-7.02 (m, 6H, C$_{Ar}$-H), 6.89* (d, *J* = 8.7 Hz, 2H, C$_{Ar}$-H), 6.80-6.74* (m, 1H, C$_{Ar}$-H), 6.74-6.68 (m, 1H, C$_{Ar}$-H), 5.74-5.67* (m, 1H, C$_2$-H), 5.47-5.42 (m, 1H, C$_2$-H), 4.00-3.88 (m, 1H, C$_5$-H$_a$), 3.88-3.80# (m, 4H, C$_5$-H$_b$ + OCH$_3$), 3.79* (s, 4H, C$_5$-H$_b$ + OCH$_3$), 2.66-2.56* (m, 1H, C$_3$-H$_a$), 2.24-1.90 (m, 4H, C$_3$-H + C$_4$-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100°C): δ 178.2* (CS), 177.9 (CS), 159.4 (C$_{Ar}$-C), 158.6* (C$_{Ar}$-C), 145.8* (C$_{Ar}$-C), 145.2 (C$_{Ar}$-C), 143.7 (C$_{Ar}$-C), 142.4 (CN), 142.2* (CN), 129.4 (q, $^2J_{C-F}$ = 33.3 Hz, 2 × **C**CF$_3$), 129.0 (C$_{Ar}$-H), 128.2* (C$_{Ar}$-H), 128.0 (C$_{Ar}$-H), 127.9* (C$_{Ar}$-H), 124.4 (C$_{Ar}$-C), 123.7 (C$_{Ar}$-H), 123.5* (C$_{Ar}$-H), 122.9 (q, $^1J_{C-F}$ = 273.3 Hz, 2 × CF$_3$), 118.6* (C$_{Ar}$-H), 118.5 (C$_{Ar}$-H), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C$_{Ar}$-H), 114.4 (C$_{Ar}$-H), 112.9* (C$_{Ar}$-H), 112.6* (C$_{Ar}$-H), 112.4 (C$_{Ar}$-H), 65.3 (C$_2$), 58.9* (C$_2$), 54.8 (OCH$_3$), 54.7* (OCH$_3$), 50.8* (C$_5$), 50.1 (C$_5$), 29.2 (C$_3$), 28.8* (C$_3$), 22.0 (C$_4$); ^{19}F NMR (282 MHz, DMSO-d_6): δ -61.5 (2 × CF$_3$); R$_f$: 0.40 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3334 (NH), 2973 (NH), 2820 (C-H st), 1602 (C=N), 1278 (C=S), 1134 (C-N st); MS (EI)

m/z (%): 271 (100), 252 (23), 213 (22), 202 (11), 163 (12), 83 (6), 69 (7); HRMS: Calculated for $[C_{27}H_{25}N_4OSF_6]^+$: 567.1653 [(M+H)$^+$]; found: 567.1668; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 12.553 min, τ_{minor} = 9.783 min (83% ee); $[\alpha]_D^{20}$: +135.3 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 76-78 ºC.

(*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)-4,4-dimethylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate

(3aa). Following the general procedure F, **3aa** (45.0 mg, 0.080 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 20h in 89% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1f** (49.7 mg, 0.135 mmol) and ethyl (*E*)-2-(2-phenylhydrazono)acetate **2c** (17.2 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (3.4 mg, 0.0045 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.1:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.63 (s, 1H, NNH), 9.97* (s, 1H, NNH), 9.37* (s, 1H, CSNH), 9.27 (s, 1H, CSNH), 8.19* (s, 2H, C$_{Ar}$-H), 8.11 (s, 2H, C$_{Ar}$-H), 7.62* (s, 1H, C$_{Ar}$-H), 7.59 (s, 1H, C$_{Ar}$-H), 7.29-7.17 (m, 4H, C$_{Ar}$-H), 6.97-6.84 (m, 1H, C$_{Ar}$-H), 5.73-*5.62* (m, 1H, C$_2$-H), 5.50-5.40 (m, 1H, C$_2$-H), 4.34-4.26 (m, 2H, C**H**$_2$CH$_3$), 4.22-4.12* (m, 2H, C**H**$_2$CH$_3$), 3.93-3.82 (m, 1H, C$_5$-H$_a$), 3.74-3.62* (m, 2H, C$_5$-H), 3.62-3.54 (m, 1H, C$_5$-H$_b$), 2.27 (dd, *J* = 12.3, 8.2 Hz, 1H, C$_3$-H$_a$), 2.22-2.15* (m, 1H, C$_3$-H$_a$), 1.95 (dd, *J* = 12.5, 8.1 Hz, 1H, C$_3$-H$_b$), 1.91-1.84* (m, 1H, C$_3$-H$_b$), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.25* (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.21* (s, 3H, CH$_3$), 1.19 (s, 3H, CH$_3$), 1.15* (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 178.4 (CS), 161.3 (COO), 144.1 (C$_{Ar}$-C), 142.9 (C$_{Ar}$-C), 142.4 (CN), 129.4 (q, $^2J_{C-F}$ = 32.4 Hz, 2 × **C**CF$_3$), 128.6 (C$_{Ar}$-H), 128.3* (C$_{Ar}$-H), 123.0 (C$_{Ar}$-H), 122.7 (q, $^1J_{C-F}$ = 271.5 Hz, 2 × CF$_3$), 122.6* (C$_{Ar}$-H), 121.4 (C$_{Ar}$-H), 120.5* (C$_{Ar}$-H), 115.5 (C$_{Ar}$-H), 113.5* (C$_{Ar}$-H), 113.3 (C$_{Ar}$-H), 63.4 (C$_5$), 61.3 (C$_2$), 60.2 (**C**H$_2$CH$_3$), 59.3* (**C**H$_2$CH$_3$), 45.4 (C$_3$), 36.5 (C$_4$), 26.2 (CH$_3$), 25.8* (CH$_3$), 25.5 (CH$_3$), 25.0* (CH$_3$), 13.6* (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$); ^{19}F NMR (282MHz, DMSO-d$_6$): δ -61.6 (2 × CF$_3$); R$_f$: 0.67 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3248 (NH), 2962 (NH), 2820 (C-H st), 1681 (C=O), 1603 (C=N), 1276 (C=S), 1127 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (23), 202 (10), 163 (12), 83 (8); HRMS: Calculated

for $[C_{25}H_{27}N_4O_2SF_6]^+$: 561.1759 $[(M+H)^+]$; found: 561.1769; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 4.858 min, τ_{minor} = 10.813 min (>99% ee); $[\alpha]_D^{20}$: +258.3 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 110-112 ºC.
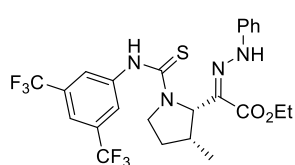
(2*S*/3*R*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)-3-methylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate (3ab). Following the general procedure F, **3ab** (29.8 mg, 0.054 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 72h in 60% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-4-methyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1g** (5 × 7.9 mg + 1 × 8.3 mg every 14 h, 0.135 mmol) added in portions and ethyl (*E*)-2-(2-phenylhydrazono)acetate **2c** (17.2 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.2:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.82 (s, 1H, NN**H**), 11.67* (s, 1H, NN**H**), 9.16 (bs, 1H, CSN**H**), 8.18 (s, 2H, C$_{Ar}$-**H**), 8.13* (s, 2H, C$_{Ar}$-**H**), 7.65* (s, 1H, C$_{Ar}$-**H**), 7.63 (s, 1H, C$_{Ar}$-**H**), 7.34-7.24 (m, 2H, C$_{Ar}$-**H**), 7.24-7.13 (m, 2H, C$_{Ar}$-**H**), 6.99-6.91 (m, 1H, C$_{Ar}$-**H**), 5.72-5.63 (m, 1H, C$_2$-**H**), 5.13-5.07* (m, 1H, C$_2$-**H**), 4.39-4.24 (m, 2H, C**H$_2$**CH$_3$), 4.07-3.99 (m, 1H, C$_5$-**H**$_a$), 3.97-3.92* (C$_5$-**H**), 3.85-3.70 (m, 1H, C$_5$-**H**$_b$), 2.72-2.54 (m, 1H, C$_3$-**H**), 2.30-2.13 (m, 1H, C$_4$-**H**$_a$), 2.13-1.90 (m, 1H, C$_4$-**H**$_b$), 1.34 (t, *J* = 7.0 Hz, 3H, CH$_2$C**H$_3$**), 1.19* (d, *J* = 6.8 Hz, 3H, CHC**H$_3$**), 0.98 (d, *J* = 6.8 Hz, CHC**H$_3$**); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ CS not detected 161.8 (CO), 161.4* (CO), 143.0 (CN), 142.4 (C$_{Ar}$-C), 129.3 (q, $^2J_{C-F}$ = 33.1 Hz, 2 × **C**CF$_3$), 128.7 (C$_{Ar}$-H), 128.6* (C$_{Ar}$-H), 128.4 (C$_{Ar}$-C), 122.8 (q, $^1J_{C-F}$ = 272.6 Hz, 2 × CF$_3$), 123.8 (C$_{Ar}$-H), 121.4 (C$_{Ar}$-H), 121.3* (C$_{Ar}$-H), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C$_{Ar}$-H), 113.2* (C$_{Ar}$-H), 113.2 (C$_{Ar}$-H), 68.4 (C$_2$), 64.0* (C$_2$), 60.1 (**C**H$_2$CH$_3$), 49.1 (C$_5$), 36.2 (C$_3$), 30.6 (C$_4$), 18.0* (CH**C**H$_3$), 13.6 (CH**C**H$_3$), 13.4 (CH$_2$**C**H$_3$), 13.4* (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.81 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 3253 (NH), 2966 (NH), 2830 (C-H st), 1681 (C=O), 1603 (C=N), 1277 (C=S), 1132 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (26), 213 (26), 202 (11), 163 (13), 83 (84), 69 (16); HRMS: Calculated for $[C_{24}H_{25}N_4O_2SF_6]^+$: 547.1602 $[(M+H)^+]$; found: 547.1613; The ee was determined by HPLC using a Chiralpak IA column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} =

11.179 min, τ_{minor} = 8.525 min (For the major diastereisomer: 97% ee); $[\alpha]_D^{20}$: -87.7 (c = 0.75, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 190-192 ºC.
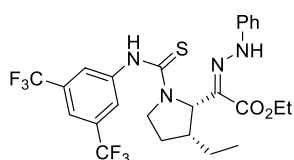
(2*S*/3*R*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)-3-ethylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate   (3ac). Following the general procedure F, **3ac** (44.8 mg, 0.080 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 68h in 89% yield as a light yellow solid starting from *N*-(3,5-bis(trifluoromethyl)phenyl)-4-ethyl-2,3-dihydro-1*H*-pyrrole-1-carbothioamide **1h** (49.7 mg, 0.135 mmol) and ethyl (*E*)-2-(2-phenylhydrazono)acetate **2c** (17.2 mg, 0.09 mmol) in the presence of catalyst (*R*)-TRIP (6.8 mg, 0.009 mmol), MS (4Å, 27 mg) and using dry toluene (0.18 mL) as solvent. ^{1}H NMR (500 MHz, DMSO-d$_6$, 100ºC): (3.4:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 11.81 (s, 1H, NNH), 11.70* (s, 1H, NNH), 9.20* (s, 1H, CSNH), 9.14 (s, 1H, CSNH), 8.20 (s, 2H, C$_{Ar}$-H), 8.13* (s, 2H, C$_{Ar}$-H), 7.65* (s, 1H, C$_{Ar}$-H), 7.63 (s, 1H, C$_{Ar}$-H), 7.32-7.23 (m, 2H, C$_{Ar}$-H), 7.22* (d, J = 7.9 Hz, 2H, C$_{Ar}$-H), 7.18 (d, J = 7.9 Hz, 2H, C$_{Ar}$-H), 6.98-6.92 (m, C$_{Ar}$-H), 5.76-5.68 (m, 1H, C$_2$-H), 5.30-5.22* (m, 1H, C$_2$-H), 4.33 (q, J = 7.3 Hz, 2H, OC**H$_2$**CH$_3$), 4.23-4.12* (m, 2H, OC**H$_2$**CH$_3$), 4.08-4.02 (m, 1H, C$_5$-H$_a$), 3.97-3.88* (m, 2H, C$_5$-H), 3.83-3.73 (m, 1H, C$_5$-H$_b$), 2.46-2.37 (m, 1H, C$_3$-H), 2.32-2.21 (m, 1H, C$_4$-H$_a$), 2.12-1.97 (m, 1H, C$_4$-H$_b$), 1.66-1.43 (m, 1H, CHC**H$_a$**H$_b$CH$_3$), 1.33 (t, J = 7.3 Hz, 3H, OCH$_2$**CH$_3$**), 1.21-1.07 (m, 1H, CHCH$_a$**H$_b$**CH$_3$), 1.03* (t, J = 7.3 Hz, 3H, CHCH$_2$**CH$_3$**), 0.95 (t, J = 7.3 Hz, 3H, CHCH$_2$**CH$_3$**); ^{13}C NMR (125 MHz, DMSO-d$_6$, 100ºC): δ 177.1 (CS), 161.8 (COO), 142.9 (C$_{Ar}$-C), 142.4 (CN), 129.3 (q, $^2J_{C-F}$ = 29.7 Hz, 2 × **C**CF$_3$), 128.7 (C$_{Ar}$-H), 128.6* (C$_{Ar}$-H), 128.4 (C$_{Ar}$-C), 122.7 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 123.8 (C$_{Ar}$-H), 121.4 (C$_{Ar}$-H), 121.3* (C$_{Ar}$-H), 115.8 (C$_{Ar}$-H), 113.2 (C$_{Ar}$-H), 66.3* (C$_2$), 63.3 (C$_2$), 60.1 (OCH$_2$CH$_3$), 59.3* (OCH$_2$CH$_3$), 49.0* (C$_5$), 48.5 (C$_5$), 45.2* (C$_3$), 44.0 (C$_3$), 28.3 (C$_4$), 21.7 (CHCH$_2$CH$_3$), 13.4 (OCH$_2$CH$_3$), 11.7 (CHCH$_2$CH$_3$), 11.1* (CHCH$_2$CH$_3$); ^{19}F NMR (282 MHz, DMSO-d$_6$): δ -61.5 (2 × CF$_3$); R$_f$: 0.59 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3257 (NH), 2966 (NH), 2872 (C-H st), 1682 (C=O), 1603 (C=N), 1276 (C=S), 1129 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (23), 213 (27), 163 (12), 83 (63), 69 (11); HRMS: Calculated for [C$_{25}$H$_{27}$N$_4$O$_2$SF$_6$]$^+$: 561.1759 [(M+H)$^+$]; found: 561.1769; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 20.686 min, τ_{minor} =
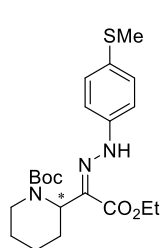
4.110 min (For the major diastereoisomer: >99% ee); $[\alpha]_D^{20}$: -254.2 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 185-187 ºC.

(*S*/*R*)-*tert*-butyl-(*E*/*Z*)-2-(2-ethoxy-1-(2-(4-(methylthio)phenyl)hydrazono)-2-oxoethyl)piperidine-1-carboxylate (3ae). Following the general procedure F, **3ae** (17.1 mg, 0.040 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) after 1 week in 31% yield as a yellow oil starting from *N*-Boc-3,4-dihydro-2*H*-pyridine **1j** (37.3 µL, 0.195 mmol) and ethyl-(*E*)-2-(2-(4-(methylthio)phenyl)hydrazono)acetate **2b** (31.0 mg, 0.13 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent at room temperature. ¹H NMR (300 MHz, CDCl$_3$): δ 12.05 (s, 1H, N**H**), 7.30-7.24 (m, 2H, C$_{Ar}$-H), 7.14-7.01 (m, 2H, C$_{Ar}$-H), 5.26 (bs, 1H, C$_2$-H), 4.28 (q, *J* = 7.2 Hz, 2H, C**H**$_2$CH$_3$), 4.04-3.88 (m, 1H, C$_6$-H$_a$), 3.37-3.23 (m, 1H, C$_6$-H$_b$), 2.46 (s, 3H, SC**H**$_3$), 2.10-1.93 (C$_3$-H$_a$), 1.84-1.38 (m, 14H, C$_3$-H$_b$ + C$_4$-H + C$_5$-H + C(C**H**$_3$)$_3$), 1.34 (t, *J* = 7.2 Hz, 3H, CH$_2$C**H**$_3$); ¹³C NMR (75 MHz, CDCl$_3$): δ 163.2 (COO), 156.1 (NCO), 142.0 (CN), 130.3 (C$_{Ar}$-C), 129.8 (C$_{Ar}$-H), 128.1 (C$_{Ar}$-C), 114.5 (C$_{Ar}$-H), 79.5 (**C**(CH$_3$)$_3$), 60.9 (**C**H$_2$CH$_3$), 51.6 (C$_2$), 41.9 (C$_6$), 28.6 (C(**C**H$_3$)$_3$), 27.8 (C$_3$), 25.4 (C$_5$), 19.4 (C$_4$), 17.8 (S**C**H$_3$), 14.3 (CH$_2$**C**H$_3$); R$_f$: 0.70 (hexanes/EtOAc 7:3); IR (ATR) cm⁻¹: 2963 (NH), 2858 (C-H st), 1692 (C=O), 1550 (C=N); MS (EI) *m/z* (%): 281 (28), 207 (100), 191 (10), 165 (20), 150 (12), 138 (10), 96 (17), 73 (18), 59 (10); HRMS: Calculated for [C$_{21}$H$_{32}$N$_3$O$_4$S]$^+$: 422.2114 [(M+H)$^+$]; found: 422.2108; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 9.448 min, τ$_{minor}$ = 8.151 min (37% ee).
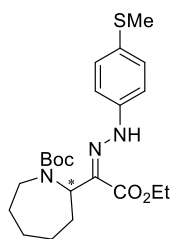
(*S*/*R*)-*tert*-butyl-(*E*/*Z*)-2-(2-ethoxy-1-(2-(4-(methylthio)phenyl)hydrazono)-2-oxoethyl)azepane-1-carboxylate (3af). Following the general procedure F, **3af** (43.3 mg, 0.099 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) after 72h in 76% yield as a yellow oil starting from *N*-Boc-2,3,4,5-tetrahydroazepine **1k** (6 × 6.4 µL every 14h, 0.195 mmol) added in portions and ethyl (*E*)-2-(2-(4-(methylthio)phenyl)hydrazono)acetate **2b** (31.0 mg, 0.13 mmol) in the presence of catalyst (*S*)-TRIP (9.8 mg, 0.013 mmol), MS (4Å, 38 mg) and using dry toluene (0.26 mL) as solvent

at room temperature. ^{1}H NMR (300 MHz, CDCl$_3$): (1.1:1 rotamer ratio, *denotes minor rotamer resonances) δ 12.06 (s, 1H, NH), 11.99* (s, 1H, NH), 7.25 (d, J = 8.7 Hz, 2H, C$_{Ar}$-H), 7.24* (d, J = 8.7 Hz, 2H, C$_{Ar}$-H), 7.07 (d, J = 8.7 Hz, 2H, C$_{Ar}$-H), 5.17 (dd, J = 11.5, 6.4 Hz, 1H, C$_2$-H), 4.88* (dd, J = 11.8, 5.5 Hz, 1H, C$_2$-H), 4.41-4.17 (m, 2H, C**H$_2$**CH$_3$), 4.10-4.00* (m, 1H, C$_7$-H$_a$), 3.91-3.81 (m, 1H, C$_7$-H$_a$), 3.31-3.16* (m, 1H, C$_7$-H$_b$), 3.16-3.01* (m, 1H, C$_7$-H$_b$), 2.44 (s, 3H, SCH$_3$), 2.36-2.08 (m, 1H, C$_3$-H$_a$), 1.95-1.48 (m, 7H, C$_3$-H$_b$ + C$_4$-H + C$_5$-H + C$_6$-H), 1.45* (s, 9H, C(CH$_3$)$_3$), 1.38-1.29 (m, 12H, CH$_2$C**H$_3$**+ C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.4 (COO), 163.1* (COO), 156.0 (NCO), 155.7* (NCO), 142.1* (C$_{Ar}$-C), 141.7 (C$_{Ar}$-C), 130.7 (C$_{Ar}$-C), 130.5* (CN), 130.2 (CN), 129.8 (C$_{Ar}$-H), 129.7* (C$_{Ar}$-H), 114.4* (C$_{Ar}$-H), 114.3 (C$_{Ar}$-H), 79.3* (**C**(CH$_3$)$_3$), 79.2 (**C**(CH$_3$)$_3$), 60.9 (**C**H$_2$CH$_3$), 60.8* (**C**H$_2$CH$_3$), 57.2* (C$_2$), 55.3 (C$_2$), 43.8 (C$_7$), 33.6 (C$_3$), 33.0* (C$_3$), 30.0* (C$_6$), 29.8 (C$_6$), 29.5 (C$_5$), 28.7* (C(**C**H$_3$)$_3$), 28.6 (C(**C**H$_3$)$_3$), 26.4* (C$_4$), 25.5 (C$_4$), 17.9* (SCH$_3$), 17.7 (SCH$_3$), 14.4* (CH$_2$**C**H$_3$), 14.2(CH$_2$**C**H$_3$); R$_f$: 0.33 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2926 (NH), 2810 (C-H st), 1686 (C=O), 1549 (C=N); MS (EI) *m/z* (%): 281 (37), 252 (54) 235 (32), 207 (100), 189 (26), 147 (21), 124 (50), 67 (11), 56 (36); HRMS: Calculated for [C$_{22}$H$_{34}$N$_3$O$_4$S]$^+$: 436.2270 [(M+H)$^+$]; found: 436.2267; The ee was determined by HPLC using a Chiralpak IA column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 8.345 min, τ$_{minor}$ = 9.261 min (51% ee).

2.4. Transformation of the adducts

2.4.1. Synthesis of compound **5a**
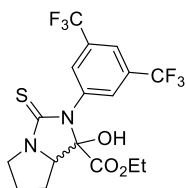
Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-1-hydroxy-3-thioxohexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1-carboxylate (5a). To a solution of **3k** (30.0 mg, 0.059 mmol) in THF (0.7 mL) oxalic acid (26.3 mg, 0.293 mmol) was added at room temperature. The reaction mixture was stirred at reflux for 4 days and then saturated NaHCO$_3$ solution was added. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 12.1 mg of **5a** (0.027 mmol, 47%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.86 (s, 2H, C$_{Ar}$-H), 7.83 (s, 1H, C$_{Ar}$-H), 4.60 (s, 1H, OH), 4.43 (t, J = 7.6 Hz, 1H, C$_{7a}$-H), 4.33-4.14 (m, 2H, C**H$_2$**CH$_3$), 4.02-3.89 (m, 1H, C$_5$-

H$_a$), 3.56 (ddd, J = 11.6, 8.3, 3.6 Hz, 1H, C$_5$-H$_b$), 2.34-1.85 (m, 4H, C$_6$-H + C$_7$-H), 1.20 (t, J = 7.1 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 183.1 (C$_3$), 170.5 (COO), 138.9 (C$_{Ar}$-C), 132.4 (q, $^2J_{C-F}$ = 34.1 Hz, 2 × **C**CF$_3$), 129.7 (C$_{Ar}$-H), 122.0 (q, $^3J_{C-F}$ = 3.9 Hz, C$_{Ar}$-H), 90.4 (C$_1$), 68.8 (C$_{7a}$), 64.7 (**C**H$_2$CH$_3$), 48.2 (C$_5$), 26.1 (C$_7$), 24.8 (C$_6$), 14.0 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.9 (2 × CF$_3$); R$_f$: 0.2 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 3518 (OH), 1745 (C=O), 1275 (C=S), 1122 (C-N st); MS (EI) *m/z* (%): 442 (61), 369 (47), 271 (100), 252 (33), 213 (34), 202 (10), 163 (16), 69 (47); HRMS: Calculated for [C$_{17}$H$_{17}$N$_2$O$_3$F$_6$]$^+$: 443.0864 [(M+H)$^+$]; found: 443.0861; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ$_{major}$ = 9.933 min, τ$_{minor}$ = 11.432 min (0% ee).

2.4.2. Synthesis of compounds **6a-b**

3 **6**
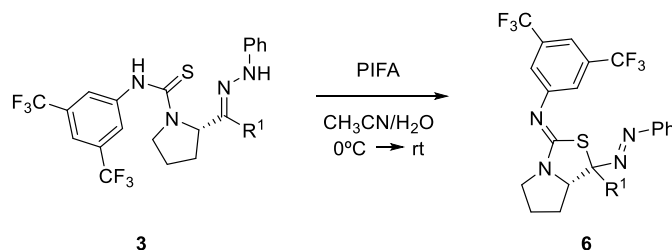
General Procedure G: To a stirred solution of hydrazone (0.43 mmol, 1.0 eq.) in CH$_3$CN/H$_2$O (1.4/0.25 mL) at 0°C, was added [bis(trifluoroacetoxy)iodo]benzene (0.86 mmol, 2.0 eq.). The reaction mixture was allowed to stir at room temperature for 15 min. Then, the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.
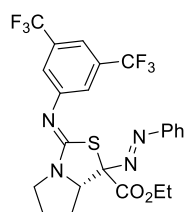
Ethyl (1*S*,7*aS*,*E*/*Z*)-3-((3,5-bis(trifluoromethyl)phenyl)imino)-1-((*E*)-phenyldiazenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-1-carboxylate (6a). Following the general procedure G, **6a** (72.8 mg, 0.137 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 15min in 73% yield as an orange solid starting from (*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-

phenylhydrazono)acetate **3i** (100 mg, 0.188 mmol) and PIFA (166.5 mg, 0.376 mmol) in CH$_3$CN/H$_2$O (0.7/0.12 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.82-7.69 (m, 2H, C$_{Ar}$-H), 7.60-7.50 (m, 4H, C$_{Ar}$-H), 7.46 (s, 2H, C$_{Ar}$-H), 5.04 (t, *J* = 6.8 Hz, 1H, C$_2$-H), 4.43-4.16 (m, 2H, C**H$_2$**CH$_3$), 3.77-3.58 (m, 1H, C$_5$-H$_a$), 3.56-3.36 (m, 1H, C$_5$-H$_b$), 2.26-1.88 (m, 4H, C$_3$-H + C$_4$-H), 1.28 (t, *J* = 7.1 Hz, 3H, CH$_2$**CH$_3$**); ^{13}C NMR (75 MHz, CDCl$_3$): δ 166.7 (COO), 155.1 (C$_{Ar}$-C), 152.5 (C$_{Ar}$-C), 150.8 (CN), 132.6 (C$_{Ar}$-H), 132.2 (q, $^2J_{C-F}$ = 33.0 Hz, 2 × **C**CF$_3$), 129.5 (C$_{Ar}$-H), 123.6 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 123.3 (C$_{Ar}$-H), 122.7 (q, $^3J_{C-F}$ = 3.4 Hz, 2 × C$_{Ar}$-H), 116.5 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 88.5 (**C**COO), 70.2 (C$_2$), 63.0 (**C**H$_2$CH$_3$), 46.1 (C$_5$), 27.6 (C$_4$), 24.5 (C$_3$), 14.2 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.9 (2 × CF$_3$); R$_f$: 0.7 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2887 (C-H st), 1737 (C=O), 1602 (C=N), 1125 (C-N st); MS (EI) *m/z* (%): 502 (29), 429 (58), 387 (10), 194 (26), 158 (17), 121 (100), 77 (6); HRMS: Calculated for [C$_{23}$H$_{21}$N$_4$O$_2$SF$_6$]$^+$: 531.1289 [(M+H)$^+$]; found: 531.1312; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ$_{major}$ = 5.707 min, τ$_{minor}$ = 5.306 min (>99% ee); [α]$_D$^{20}: -275.9 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 127-129 ºC.
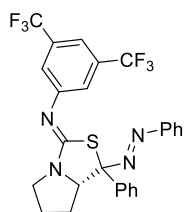
(1*R*,7a*S*,*E*/*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1-((*E*)-phenyldiazenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-3-imine (6b). Following the general procedure G, **6b** (37.6 mg, 0.07 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 19:1 to 7:3) after 15min in 90% yield as an orange solid starting from (*S*)-(*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-(phenyl(2-phenylhydrazono)pyrrolidine-1-carbothioamide **3x** (41.8 mg, 0.078 mmol) and PIFA (69.1 mg, 0.156 mmol) in CH$_3$CN/H$_2$O (1.2/0.24 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.82-7.69 (m, 2H, C$_{Ar}$-H), 7.60-7.50 (m, 4H, C$_{Ar}$-H), 7.46 (s, 2H, C$_{Ar}$-H), 5.04 (t, *J* = 6.8 Hz, 1H, C$_{7a}$-H), 4.43-4.16 (m, 2H, C**H$_2$**CH$_3$), 3.77-3.58 (m, 1H, C$_5$-H$_a$), 3.56-3.36 (m, 1H, C$_5$-H$_b$), 2.26-1.88 (m, 4H, C$_6$-H + C$_7$-H), 1.28 (t, *J* = 7.1 Hz, 3H, CH$_2$**CH$_3$**); ^{13}C NMR (75 MHz, CDCl$_3$): δ 166.7 (COO), 155.1 (C$_{Ar}$-C), 152.5 (C$_{Ar}$-C), 150.8 (C$_3$), 132.6 (C$_{Ar}$-H), 132.2 (q, $^2J_{C-F}$ = 33.0 Hz, 2 × **C**CF$_3$), 129.5 (C$_{Ar}$-H), 123.6 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 123.3 (C$_{Ar}$-H), 122.7 (q, $^3J_{C-F}$ = 3.4 Hz, 2 × C$_{Ar}$-H), 116.5 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 88.5 (C$_1$), 70.2 (C$_{7a}$), 63.0 (**C**H$_2$CH$_3$), 46.1 (C$_5$), 27.6 (C$_6$), 24.5 (C$_7$), 14.2 (CH$_2$**C**H$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.9 (2 × CF$_3$); R$_f$: 0.57 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2877 (C-H st), 1595 (C=N), 1125 (C-N st); MS (EI) *m/z* (%): 502 (73), 398 (24),

330 (100), 213 (12), 115 (24), 77 (85), 69 (24); HRMS: Calculated for $[C_{23}H_{21}N_4O_2SF_6]^+$: 531.1289 [(M+H)$^+$]; found: 531.1312; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 4.544 min, τ_{minor} = 5.694 min (90% ee); $[\alpha]_D^{20}$: -193.9 (*c* = 1.0, CH_2Cl_2); M.p. (CH_2Cl_2): 50-52 ºC.

2.4.3. Synthesis of compound **7a**
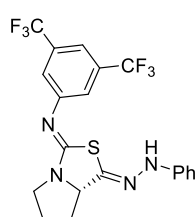
(*S*,1*E*/*Z*,3*E*/*Z*)-*N*-(3,5-bis(trofluoromethyl)phenyl)-1-(2-phenylhydrazono)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-imine (7a). K_2CO_3 (14.7 mg, 0.107 mmol) is added to a cooled solution (0ºC) of ethyl (1*S,7aS,E*/*Z*)-3-((3,5-bis(trifluoromethyl)phenyl)imino)-1-((*E*)-phenyldiazenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-1-carboxylate

6a (56.5 mg, 0.107 mmol) in ethanol (0.9 mL). The reaction was allowed to stir at room temperature for 6 hours and then quenched with NH$_4$Cl. The crude product was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel to afford 43.4 mg of **7a** (0.095 mmol, 88%) as an orange solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.60 (s, 1H, C$_{Ar}$-H), 7.41 (s, 2H, C$_{Ar}$-H), 7.31-7.19 (m, 2H, C$_{Ar}$-H), 6.99 (d, *J* = 7.7 Hz, 2H, C$_{Ar}$-H), 6.91 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H), 6.45 (bs, 1H, NH), 4.85 (dd, *J* = 9.9, 5.9 Hz, 1H, C$_{7a}$-H), 3.98-3.83 (m, 1H, C$_5$-H$_a$), 3.60-3.46 (m, 1H, C$_5$-H$_b$), 2.46-2.14 (m, 3H, C$_6$-H$_a$ + C$_7$-H), 1.98-1.80 (m, 1H, C$_6$-H$_b$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 154.8 (C$_3$), 152.2 (C$_1$), 144.7 (C$_{Ar}$-C), 137.6 (C$_{Ar}$-C), 132.5 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, 2 × **C**CF$_3$), 129.4 (C$_{Ar}$-H), 123.4 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 122.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C$_{Ar}$-H), 121.2 (C$_{Ar}$-H), 117.1 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C$_{Ar}$-H), 113.5 (C$_{Ar}$-H), 69.1 (C$_{7a}$), 47.9 (C$_5$), 30.4 (C$_7$), 26.4 (C$_6$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.9 (2 × CF$_3$); R$_f$: 0.81 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2989 (NH), 1601 (C=N), 1121 (C-N st); MS (EI) *m/z* (%): 458 (96), 353 (10), 271 (100), 252 (30), 213 (35), 202 (10), 163 (19), 143 (11), 93 (47), 77 (52), 69 (22); HRMS: Calculated for $[C_{20}H_{17}N_4SF_6]^+$: 459.1078 [(M+H)$^+$]; found: 459.1088; The ee was determined by HPLC using a Chiralpak ID-3 column [*n*hexane/*i*PrOH (98:02)]; flow rate 0.70 mL/min; τ_{major} = 8.310 min, τ_{minor} = 11.439 min (>99% ee); $[\alpha]_D^{20}$: +253.5 (*c* = 0.46, CH_2Cl_2); M.p. (CH_2Cl_2): 86-88 ºC.
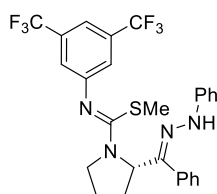
Methyl-(*S*,*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((*E*/*Z*)-phenyl(2-phenylhydrazono)methyl)pyrrolidine-1-carbimidothioate (8a). To a solution of **3x** (100 mg, 0.186 mmol) in CH_2Cl_2 (2.0 mL) at 0ºC, sodium hydride (9.0 mg, 0.224 mmol, 60% in mineral oil) was added. After being stirred for 30 min at 0ºC, methyl iodide (12.8 μL, 0.205 mmol) was added and the reaction was stirred 3 hours at room temperature. Then, the reaction mixture was washed with water and brine, and extracted with EtOAc (3 x 2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 76.3 mg of **8a** (0.139 mmol, 75%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.59-7.44 (m, 3H, C_{Ar}-H), 7.44-7.34 (m, 6H, C_{Ar}-H + NH), 7.32-7.20 (m, 2H, C_{Ar}-H), 7.05-6.99 (m, 2H, C_{Ar}-H), 6.86 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 5.18 (m, 1H, C_2-H), 3.97-3.85 (m, 1H, C_5-H_a), 3.81-3.67 (m, 1H, C_5-H_b), 2.25-1.98 (m, 4H, C_3-H + C_4-H), 1.89 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5 (NCN), 151.4 (C_{Ar}-C), 145.2 (C_{Ar}-C), 145.0 (CNN), 132.6 (C_{Ar}-C), 131.9 (q, $^2J_{C-F}$ = 32.7 Hz, 2 × **C**CF$_3$), 129.8 (C_{Ar}-H), 129.6 (C_{Ar}-H), 129.3 (C_{Ar}-H), 128.0 (C_{Ar}-H), 123.7 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 121.9 (C_{Ar}-H), 120.1 (C_{Ar}-H), 114.1 (q, $^3J_{C-F}$ = 4.0 Hz, C_{Ar}-H), 112.7 (C_{Ar}-H), 64.9 (C_2), 49.9 (C_5), 30.2 (C_3), 22.8 (C_4), 16.0 (SCH_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.9 (2 × CF$_3$); R_f: 0.89 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2976 (NH), 2875 (C-H st), 1601 (C=N), 1124 (C-N st); MS (EI) *m/z* (%): 502 (71), 398 (25), 330 (100), 207 (15), 215 (24), 77 (81), 69 (23); HRMS: Calculated for $[C_{27}H_{25}N_4SF_6]^+$: 551.1704 $[(M+H)^+]$; found: 551.1711; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (99:01)]; flow rate 0.70 mL/min; $τ_{major}$ = 10.461 min, $τ_{minor}$ = 11.362 min (88% ee); $[α]_D^{20}$: -93.3 (*c* = 1.0, CH_2Cl_2); M.p. (CH_2Cl_2): 82-84 ºC.

2.5.4. Synthesis of compounds **9a** and **10a**
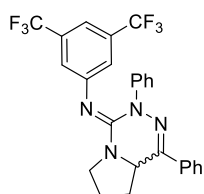
(*E*/*Z*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-1,3-diphenyl-6,7,8,8a-tetrahydropyrrolo[1,2-*c*][1,2,4]triazin-4(3*H*)-imine (9a). To a solution of **8a** (33.6 mg, 0.061 mmol) in THF-MeOH (0.5 mL-4 μL) mixture, TMSOK (45.9 μL, 0.092 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. Then, water was added and the crude product was extracted with CH_2Cl_2 (3 x 1 mL). The organic layer was dried over

Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 17.7 mg of **9a** (0.035 mmol, 57%) as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.66-7.54 (m, 2H, C$_{Ar}$-H), 7.49-7.38 (m, 3H, C$_{Ar}$-H), 7.33 (d, *J* = 7.4 Hz, 2H, C$_{Ar}$-H), 7.18-7.05 (m, 3H, C$_{Ar}$-H), 7.03 (s, 2H, C$_{Ar}$-H), 6.99-6.90 (m, 1H, C$_{Ar}$-H), 4.71 (t, *J* = 7.3 Hz, 1H, C$_{8a}$-H), 3.50 (dd, *J* = 7.6, 6.1 Hz, 2H, C$_6$-H), 2.61-2.47 (m, 1H, C$_8$-H$_a$), 2.16-1.78 (m, 3H, C$_7$-H + C$_8$-H$_b$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.2 (C$_4$), 150.7 (C$_{Ar}$-C), 144.7 (C$_1$), 142.3 (C$_{Ar}$-C), 134.2 (C$_{Ar}$-C), 131.2 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, 2 × **C**CF$_3$), 130.1 (C$_{Ar}$-H), 128.7 (C$_{Ar}$-H), 128.6 (C$_{Ar}$-H), 127.5 (C$_{Ar}$-H), 125.5 (C$_{Ar}$-H), 124.7 (q, $^1J_{C\text{-}F}$ = 272.5 Hz, 2 × CF$_3$), 123.8 (C$_{Ar}$-H), 121.8 (C$_{Ar}$-H), 113.0 (C$_{Ar}$-H), 56.1 (C$_{8a}$), 49.0 (C$_6$), 31.6 (C$_8$), 23.7 (C$_7$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.1 (2 × CF$_3$); R$_f$: 0.36 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 1577 (C=N), 1126 (C-N st); MS (EI) *m/z* (%): 502 (69), 398 (29), 369 (12), 330 (100), 213 (13), 115 (21), 77 (61); The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 5.040 min, τ$_{minor}$ = 4.295 min (9% ee).
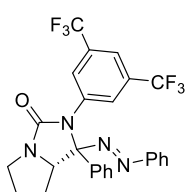
(1S,7aS,E/Z)-2-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1-(phenyldiazenyl)hexahydro-3H-pyrrolo[1,2-c]imidazol-3-one **(10a)**. Powered *N*-bromosuccinimide (52.3 mg, 0.291 mmol) was added at 0ºC to an stirred 50% acetone-MeOH (0.2 mL-0.2 mL) solution of **8a** (40.0 mg, 0.073 mmol). The reaction mixture was allowed to stir at room temperature for 30 min and water was added. The crude product was extracted with CH$_2$Cl$_2$ (3 x 1 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 18.2 mg of **10a** (0.035 mmol, 48%) as an orange oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.85-7.79 (m, 2H, C$_{Ar}$-H), 7.79-7.73 (m, 2H, C$_{Ar}$-H), 7.51 (dd, *J* = 5.1, 2.0 Hz, 3H, C$_{Ar}$-H), 7.48-7.38 (m, 3H, C$_{Ar}$-H), 7.35 (bs, 3H, C$_{Ar}$-H), 4.43 (t, *J* = 6.8 Hz, 1H, C$_{7a}$-H), 3.66 (ddd, *J* = 11.0, 7.8, 5.1 Hz, 1H, C$_5$-H$_a$), 3.17 (dt, *J* = 11.1, 6.9 Hz, 1H, C$_5$-H$_b$), 1.90-1.70 (m, 3H, C$_6$-H$_a$ + C$_7$-H), 1.59-1.47 (m, 1H, C$_6$-H$_b$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 159.2 (C$_3$), 151.0 (C$_{Ar}$-C), 139.2 (2 x C$_{Ar}$-C), 132.3 (C$_{Ar}$-H), 131.2 (q, $^2J_{C\text{-}F}$ = 33.3 Hz, 2 × **C**CF$_3$), 129.5 (C$_{Ar}$-H), 129.5 (C$_{Ar}$-H), 129.1 (C$_{Ar}$-H), 127.1 (C$_{Ar}$-H), 123.2 (q, $^1J_{C\text{-}F}$ = 273.2 Hz, 2 × CF$_3$), 123.1 (C$_{Ar}$-H), 122.5 (C$_{Ar}$-H), 116.4 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C$_{Ar}$-H), 91.2 (C$_1$), 71.0 (C$_{7a}$), 45.4 (C$_5$), 25.9 (C$_7$), 24.2 (C$_6$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -63.2 (2 × CF$_3$); R$_f$: 0.43 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 1722 (C=O),

1128 (C-N st); MS (EI) *m/z* (%): 412 (100), 316 (28), 253 (14); HRMS: Calculated for $[C_{26}H_{21}N_4OF_6]^+$: 519.1620 $[(M+H)^+]$; found: 519.1612; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/m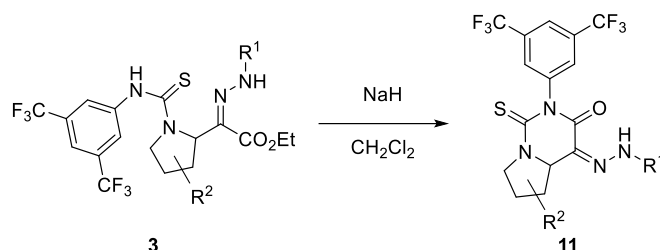in; τ_{major} = 7.107 min, τ_{minor} = 7.926 min (88% ee); $[\alpha]_D^{20}$: -113.7 (c = 0.66, CH$_2$Cl$_2$).

2.5.5. Synthesis of compounds **11a-e**

General Procedure H: Under inert atmosphere, to a stirred solution of hydrazone (0.38 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (4.2 mL), sodium hydride (0.46 mmol, 1.2 eq.) was added. The reaction mixture was allowed to stir at room temperature until completion of the reaction. Then, water was added and the mixture was extracted with CH$_2$Cl$_2$, washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo* and was used for the next step without further purification.
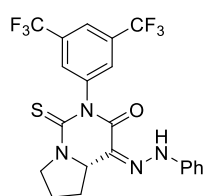
(*S*,*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (11a). Following the general procedure H, **11a** (116 mg, 0.238 mmol) was isolated after 30 min in >99% yield as a yellow solid starting from (*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate **3i** (129 mg, 0.24 mmol) and NaH (11.6 mg, 0.29 mmol, 60% in mineral oil) in CH$_2$Cl$_2$ (3.0 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.56 (s, 1H, NH), 7.94 (s, 1H, C$_{Ar}$-H), 7.73 (s, 2H, C$_{Ar}$-H), 7.34 (t, *J* = 7.7 Hz, 2H, C$_{Ar}$-H), 7.20 (d, *J* = 8.0 Hz, 2H, C$_{Ar}$-H), 7.07 (t, *J* = 7.2 Hz, 1H, C$_{Ar}$-H), 4.71 (dd, *J* = 9.8, 5.9 Hz, 1H, C$_{4a}$-H), 4.15-4.02 (m, 1H, C$_7$-H$_a$), 3.99-3.82 (m, 1H, C$_7$-H$_b$), 2.80-2.68 (m, 1H, C$_5$-H$_a$), 2.45-2.06 (m, 3H, C$_5$-H$_b$ + C$_6$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 175.5 (C$_1$), 158.5 (C$_3$), 142.3 (C$_4$), 139.5 (C$_{Ar}$-C), 132.3 (q, $^2J_{C-F}$ = 34.0 Hz, 2 × CCF$_3$), 131.0 (C$_{Ar}$-H), 129.7 (C$_{Ar}$-H), 124.0 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 272.6 Hz, 2 × CF$_3$), 122.7 (q, $^3J_{C-F}$ = 3.5 Hz, C$_{Ar}$-H), 120.8 (C$_{Ar}$-C), 114.6 (C$_{Ar}$-H), 61.1 (C$_{4a}$), 53.5

(C$_7$), 31.1 (C$_5$), 22.6 (C$_6$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.7 (2 × CF$_3$); R$_f$: 0.8 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2930 (NH), 1660 (C=O), 1548 (C=N), 1277 (C=S), 1122 (C-N st); MS (EI) *m/z* (%): 486 (100), 381 (19), 252 (11), 207 (16), 77 (45), 69 (11); HRMS: Calculated for [C$_{21}$H$_{17}$N$_4$OSF$_6$]$^+$: 487.1027 [(M+H)$^+$]; found: 487.1026; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (98:02)]; flow rate 1.00 mL/min; τ$_{major}$ = 6.439 min, τ$_{minor}$ = 7.654 min (>99% ee); [α]$_D^{20}$: -186.5 (*c* = 0.8, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 176-178 ºC.
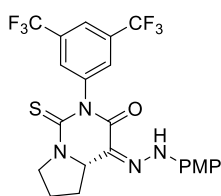
(*S*,*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-4-(2-(4-methoxyphenyl)hydrazono)-1-thioxohexahydropyrrolo[1,2-c]pyrimidin-3(4*H*)-one (11b). Following the general procedure H, **11b** (91.7 mg, 0.177 mmol) was isolated after 30 min in >99% yield as a yellow solid starting from (*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-(4-methoxyphenyl)hydrazono)acetate **3j** (100 mg, 0.177 mmol) and NaH (8.5 mg, 0.21 mmol, 60% in mineral oil) in CH$_2$Cl$_2$ (2.0 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.63 (s, 1H, NH), 7.93 (s, 1H, C$_{Ar}$-H), 7.73 (s, 2H, C$_{Ar}$-H), 7.15 (d, *J* = 9.0 Hz, 2H, C$_{Ar}$-H), 6.89 (d, *J* = 9.0 Hz, 2H, C$_{Ar}$-H), 4.70 (dd, *J* = 9.9, 5.9 Hz, 1H, C$_{4a}$-H), 4.14-4.02 (m, 1H, C$_7$-H$_a$), 3.98-3.78 (m, 4H, C$_7$-H$_b$ + OCH$_3$), 2.79-2.66 (m, 1H, C$_5$-H$_a$), 2.42-2.05 (m, 3H, C$_5$-H$_b$ + C$_6$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 175.5 (C$_1$), 158.6 (C$_3$), 156.6 (C$_{Ar}$-C), 139.6 (C$_4$), 136.1 (C$_{Ar}$-C), 132.3 (q, $^2J_{C-F}$ = 33.9 Hz, 2 × **C**CF$_3$), 131.0 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 271.9 Hz, 2 × CF$_3$), 122.6 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 119.5 (C$_{Ar}$-C), 115.9 (C$_{Ar}$-H), 115.0 (C$_{Ar}$-H), 61.0 (C$_{4a}$), 55.7 (OCH$_3$), 53.5 (C$_7$), 31.2 (C$_5$), 22.6 (C$_6$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.7 (2 × CF$_3$); R$_f$: 0.51 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2917 (NH), 2847 (C-H st), 1741 (C=O), 1514 (C=N), 1279 (C=S), 1124 (C-N st); MS (EI) *m/z* (%): 271 (100), 252 (31), 213 (27), 202 (14), 163 (16), 108 (10), 83 (100), 69 (15); HRMS: Calculated for [C$_{22}$H$_{19}$N$_4$O$_2$SF$_6$]$^+$: 517.1133 [(M+H)$^+$]; found: 517.1122; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 6.642 min, τ$_{minor}$ = 7.732 min (96% ee); [α]$_D^{20}$: -191.3 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 178-180 ºC.
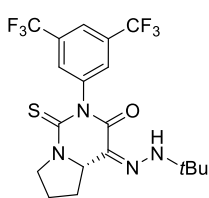
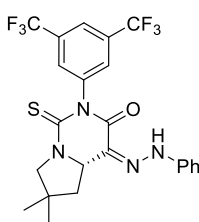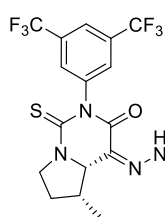**(*S*,*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-4-(2-(*tert*-butyl)hydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (11c).** Following the general procedure H, **11c** (121 mg, 0.261 mmol) was isolated after 30 min in 91% yield as a light yellow solid starting from (*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)pyrrolidin-2-yl)-2-(2-(*tert*-butyl)hydrazono)acetate **3k** (147 mg, 0.287 mmol) and NaH (13.8 mg, 0.43 mmol, 60% in mineral oil) in CH_2Cl_2 (1.8 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.88 (s, 1H, NH), 7.90 (s, 1H, C$_{Ar}$-H), 7.71 (s, 2H, C$_{Ar}$-H), 4.59 (dd, *J* = 9.2, 6.1 Hz, 1H, C$_{4a}$-H), 4.04 (ddd, *J* = 10.6, 8.7, 2.2 Hz, 1H, C$_7$-H$_a$), 3.94-3.78 (m, 1H, C$_7$-H$_b$), 2.66-2.52 (m, 1H, C$_5$-H$_a$), 2.29-1.97 (m, 3H, C$_5$-H$_b$ + C$_6$-H), 1.28 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 175.7 (C$_1$), 158.3 (C$_3$), 139.9 (C$_4$), 132.1 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2 × **C**CF$_3$), 131.2 (C$_{Ar}$-H), 123.1 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2 × CF$_3$), 122.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, C$_{Ar}$-H), 116.6 (C$_{Ar}$-C), 61.0 (C$_{4a}$), 56.0 (**C**(CH$_3$)$_3$), 53.3 (C$_7$), 31.1 (C$_5$), 28.7 (C(**C**H$_3$)$_3$), 22.6 (C$_6$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.7 (2 × CF$_3$); R$_f$: 0.68 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2925 (NH), 2883 (C-H st), 1658 (C=O), 1538 (C=N), 1274 (C=S), 1120 (C-N st); MS (EI) *m/z* (%): 466 (M$^+$, 100), 451 (45), 381 (22), 252 (12), 213 (12), 152 (16), 82 (17), 69 (12), 57 (35); HRMS: Calculated for [C$_{19}$H$_{21}$N$_4$OSF$_6$]$^+$: 467.1340 [(M+H)$^+$]; found: 467.1348; The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ$_{major}$ = 5.416 min, τ$_{minor}$ = 4.948 min (87% ee); [α]$_D^{20}$: -20.8 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 197-199 ºC.

(*S*,*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-6,6-dimethyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (11d). Following the general procedure H, **11d** (104 mg, 0.20 mmol) was isolated after 30 min in >99% yield as an orange solid starting from (*S*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)-4,4-dimethylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate **3aa** (114 mg, 0.20 mmol) and NaH (9.8 mg, 0.24 mmol, 60% in mineral oil) in CH$_2$Cl$_2$ (1.4 mL). ^{1}H NMR (300 MHz, CDCl$_3$): (8.9:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 12.52 (s, 1H, NH), 8.47* (s, 1H, NH), 7.95 (s, 1H, C$_{Ar}$-H), 7.92* (s, 1H, C$_{Ar}$-H), 7.76 (s, 2H, C$_{Ar}$-H), 7.72* (s, 1H, C$_{Ar}$-H), 7.40-7.30 (m, 2H, C$_{Ar}$-H), 7.24-7.17 (m, 2H, C$_{Ar}$-H), 7.07 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H), 4.92 (dd, *J* = 10.2,

6.1 Hz, 1H, C$_{4a}$-H), 3.86 (d, *J* = 12.9 Hz, 1H, C$_7$-H$_a$), 3.70 (d, *J* = 12.9 Hz, C$_7$-H$_b$), 2.46 (dd, *J* = 12.8, 6.1 Hz, C$_5$-H$_a$), 2.30 (dd, *J* = 12.8, 10.3 Hz, C$_5$-H$_b$), 1.31 (s, 6H, 2 × CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 175.5 (C$_1$), 158.5 (C$_3$), 142.3 (C$_{Ar}$-C), 139.4 (C$_4$), 132.3 (q, $^2J_{C-F}$ = 34.0 Hz, 2 × **C**CF$_3$), 131.0 (C$_{Ar}$-H), 129.6 (C$_{Ar}$-H), 123.9 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 272.9 Hz, 2 × CF$_3$), 122.6 (q, $^3J_{C-F}$ = 3.7 Hz, C$_{Ar}$-H), 120.9 (C$_{Ar}$-C), 114.5 (C$_{Ar}$-H), 66.1 (C$_7$), 60.0 (C$_{4a}$), 44.4 (C$_5$), 36.4 (C$_6$), 27.7 (CH$_3$), 27.5 (CH$_3$); ^{19}F NMR (282 MHz, CDCl$_3$): δ -62.7 (2 × CF$_3$); R$_f$: 0.67 (hexanes/EtOAc 8:2); IR (ATR) cm^{-1}: 2962 (NH), 2872 (C-H st), 1659 (C=O), 1543 (C=N), 1275 (C=S), 1127 (C-N st); MS (EI) *m/z* (%): 514 (M$^+$, 100), 409 (52), 252 (13), 207 (15), 135 (19), 123 (37), 92 (33), 77 (64), 65 (27); HRMS: Calculated for [C$_{23}$H$_{21}$N$_4$OSF$_6$]$^+$: 515.1340 [(M+H)$^+$]; found: 515.1348; The ee was determined by HPLC using a Chiralcel OD-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ$_{major}$ = 6.344 min, τ$_{minor}$ = 15.231 min (>99% ee); [α]$_D$^{20}: -63.6 (*c* = 1.0, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 184-186 ºC.

**(4a*S*,5*R*,*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one (11e).** Following the general procedure H, **11e** (46.7 mg, 0.093 mmol) was isolated after 30 min in >99% yield as an orange solid starting from (2*S*/3*R*)-ethyl-(*Z*)-2-(1-((3,5-bis(trifluoromethyl)phenyl)carbamothioyl)-3-methylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetate **3ab** (51.2 mg, 0.094 mmol) and NaH (5.6 mg, 0.14 mmol, 60% in mineral oil) in CH$_2$Cl$_2$ (0.6 mL). ^{1}H NMR (300 MHz, CDCl$_3$): (3.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 12.90 (s, 1H, NH), 7.94 (s, 1H, C$_{Ar}$-H), 7.73 (s, 2H, C$_{Ar}$-H), 7.34 (t, *J* = 7.8 Hz, 2H, C$_{Ar}$-H), 7.20 (d, *J* = 8.0 Hz, 2H, C$_{Ar}$-H), 7.08 (t, *J* = 7.3 Hz, 1H, C$_{Ar}$-H), 4.78 (d, *J* = 4.6 Hz, 1H, C$_{4a}$-H), 4.01 (dd, *J* = 10.5, 4.4 Hz, 1H, C$_7$-H), 3.10-2.98 (m, 1H, C$_5$-H), 2.34-2.17 (m, 1H, C$_6$-H$_a$), 2.01-1.90 (m, 1H, C$_6$-H$_b$), 1.13 (d, *J* = 6.9 Hz, 3H, CH$_3$), 1.02* (d, *J* = 6.9 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 175.8 (C$_1$), 158.7 (C$_3$), 142.3 (C$_4$), 139.7 (C$_{Ar}$-C), 132.4 (q, $^2J_{C-F}$ = 33.4 Hz, 2 × **C**CF$_3$), 130.9 (C$_{Ar}$-H), 129.7 (C$_{Ar}$-H), 124.1 (C$_{Ar}$-H), 123.1 (q, $^1J_{C-F}$ = 273.1 Hz, 2 × CF$_3$), 122.7 (q, $^3J_{C-F}$ = 3.7 Hz, C$_{Ar}$-H), 118.6 (C$_{Ar}$-C), 114.7 (C$_{Ar}$-H), 144.6* (C$_{Ar}$-H), 64.5 (C$_{4a}$), 51.8 (C$_7$), 36.4 (C$_5$), 29.8 (C$_6$), 14.3* (CH$_3$), 14.0 (CH$_3$); ^{19}F NMR (282MHz, CDCl$_3$): δ -62.8* (2 × CF$_3$), -62.7 (2 × CF$_3$); IR (ATR) cm^{-1}: 2973 (NH), 2876 (C-H st), 1665 (C=O), 1552 (C=N), 1275 (C=S), 1124 (C-N st); MS (EI) *m/z* (%): 500 (M$^+$, 100), 395 (10), 252 (15), 207 (31), 92 (22), 77 (39), 65 (17);

HRMS: Calculated for $[C_{22}H_{19}N_4OSF_6]^+$: 501.1184 [(M+H)$^+$]; found: 501.1186; The ee was determined by HPLC using a Chiralpak IE-3 column [*n*hexane/*i*PrOH (95:05)]; flow rate 0.70 mL/min; τ_{major} = 6.953 min, τ_{minor} = 7.400 min (For the major diastereisomer: 96% ee); $[\alpha]_D^{20}$: -55.7 (*c* = 1.0, CH$_2$Cl$_2$). M. p. (CH$_2$Cl$_2$): Decomposition before melting.

2.4.6. Synthesis of compounds **13a-c**
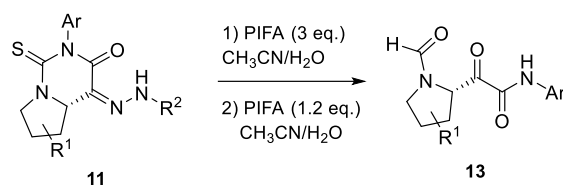
General Procedure I: PIFA (0.696 mmol, 3 eq.) was added to a cooled solution (0 ºC) of **11a-e** (0.232 mmol, 1 eq.) in CH$_3$CN/H$_2$O (5/1). The reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude product was used for the next step without further purification. The crude mixture was dissolved in CH$_3$CN/H$_2$O (5/1) and cooled to 0 ºC. PIFA (0.27 mmol, 1.2 eq.) was added and the reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatrography on silica gel.
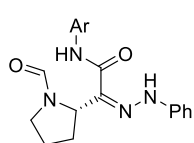
(*S*,*Z*)-*N*-(3,5-bis(trifluromethyl)phenyl)-2-(1-formylpyrrolidin-2-yl)-2-(2-phenylhydrazono)acetamide (12a). PIFA (309 mg, 0.696 mmol) was added to a cooled (0 ºC) solution of (*Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **11a** (113 mg, 0.232 mmol) in CH$_3$CN/H$_2$O (0.9/0.2 mL). The reaction was allowed to stir at room temperature for 10 min and then the mixture was diluted with CH$_2$Cl$_2$, washed with saturated NaHCO$_3$ solution and water, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude product was used for the next step without further purification, in this case affording 108 mg of **12a** (0.23 mmol, 99%) as an orange solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.84 (s, 1H, NNH), 11.74 (s, 1H, NHAr), 8.27

(s, 3H, C$_{Ar}$-H + CHO), 7.64 (s, 1H, C$_{Ar}$-H), 7.35 (t, *J* = 7.5 Hz, 2H, C$_{Ar}$-H), 7.20 (d, *J* = 7.5 Hz, 2H, C$_{Ar}$-H), 7.03 (t, *J* = 7.5 Hz, 1H, C$_{Ar}$-H), 5.23 (dd, *J* = 8.3, 2.7 Hz, 1H, C$_2$-H), 3.85-3.63 (m, 2H, C$_5$-H), 2.70-2.61 (m, 1H, C$_3$-H$_a$), 2.54-2.42 (m, 1H, C$_4$-H$_a$), 2.25-2.14 (m, 1H, C$_3$-H$_b$), 2.14-2.04 (m, 1H, C$_4$-H$_b$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.6 (CO), 162.7 (CHO), 143.3 (CN), 140.1 (C$_{Ar}$-C), 132.3 (q, $^2J_{C-F}$ = 33.4 Hz, 2 × **C**CF$_3$), 129.6 (C$_{Ar}$-H), 128.1 (C$_{Ar}$-C), 123.2 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 122.7 (C$_{Ar}$-H), 120.3 (C$_{Ar}$-H), 117.5 (C$_{Ar}$-H), 114.0 (C$_{Ar}$-H), 55.0 (C$_2$), 46.5 (C$_5$), 30.4 (C$_3$), 24.0 (C$_4$); ^{19}F NMR (282MHz, CDCl$_3$): δ -62.9 (2 × CF$_3$); IR (ATR) cm^{-1}: 2962 (NH), 1635 (C=O), 1534 (C=N), 1123 (C-N st); HRMS: Calculated for [C$_{21}$H$_{19}$N$_4$O$_2$F$_6$]$^+$: 473.1412 [(M+H)$^+$]; found: 473.1411; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ$_{major}$ = 5.106 min, τ$_{minor}$ = 5.663 min (>99% ee); [α]$_D^{20}$: -261.9 (*c* = 0.57, CH$_2$Cl$_2$); M.p. (CH$_2$Cl$_2$): 140-142 ºC.
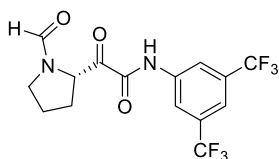
(*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-(1-formylpyrrolidin-2-yl)-2-oxoacetamide (13a). Following general procedure I, **13a** (43.2 mg, 0.11 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 67% yield as a white foam starting from (*S,Z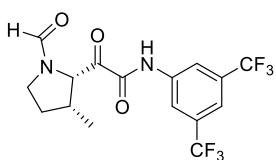*)-2-(3,5-bis(trifluoromethyl)phenyl)-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **11a** (80 mg, 0.164 mmol) and PIFA (218 mg, 0.492 mmol + 87.5 mg, 0.197 mmol) in CH$_3$CN/H$_2$O (0.7/0.2 mL).
^{1}H NMR (300 MHz, CDCl$_3$): (3.7:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.36* (bs,1H, NH), 9.21 (bs, 1H, NH), 8.28 (s, 1H, NCHO), 8.21* (s, 2H, C$_{Ar}$-H), 8.16 (s, 2H, C$_{Ar}$-H), 8.13* (s, 1H, NCHO), 7.69* (s, 1H, C$_{Ar}$-H), 7.65 (s, 1H, C$_{Ar}$-H), 5.42* (dd, *J* = 9.2, 4.2 Hz, 1H, C$_2$-H), 5.33-5.23 (m, 1H, C$_2$-H), 3.78-3.69 (m, 2H, C$_5$-H), 2.64-2.56* (m, 1H, C$_3$-H$_a$), 2.55-2.40 (m, 1H, C$_3$-H$_a$), 2.15-1.95 (m, 3H, C$_3$-H$_b$ + C$_4$-H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 194.8* (CO), 194.1 (CO), 161.9* (NCHO), 160.7 (NCHO), 157.8 (CONH), 157.3* (CONH), 138.0 (C$_{Ar}$-C), 137.8* (C$_{Ar}$-C), 133.6* (q, $^2J_{C-F}$ = 33.4 Hz, 2 × **C**CF$_3$), 132.7 (q, $^2J_{C-F}$ = 33.8 Hz, 2 × **C**CF$_3$), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz, 2 × CF$_3$), 119.9 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 118.7 (q, $^3J_{C-F}$ = 3.8 Hz, C$_{Ar}$-H), 61.0* (C$_2$), 58.5 (C$_2$), 46.7 (C$_5$), 44.4* (C$_5$), 29.3* (C$_3$), 28.9 (C$_3$), 24.7 (C$_4$), 22.8* (C$_4$); ^{19}F NMR (282MHz, CDCl$_3$): δ -63.1 (2 × CF$_3$); IR (ATR) cm^{-1}: 2961 (NH), 2886 (C-H st), 1653 (C=O), 1126 (C-N st); MS (EI) *m/z* (%): 255 (56), 207 (17), 98 (100), 83 (12), 69 (31); HRMS: Calculated for [C$_{15}$H$_{13}$N$_2$O$_3$F$_6$]$^+$: 383.0830 [(M+H)$^+$];

found: 383.0833; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 6.548 min, τ_{minor} = 5.993 min (99% ee); $[\alpha]_D^{20}$: -40.7 (*c* = 1.0, CH$_2$Cl$_2$).
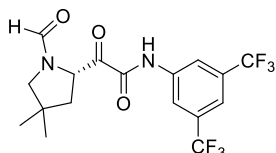
N-(3,5-bis(trifluoromethyl)phenyl)-2-(1-formyl-4,4-dimethylpyrrolidin-2-yl)-2-oxoacetamide (13b).

Following general procedure I, **13b** (50.1 mg, 0.122 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 63% yield as a yellow foam starting from (*S,Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-6,6-dimethyl-4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **11d** (100 mg, 0.194 mmol) and PIFA (258 mg, 0.582 mmol + 103 mg, 0.233 mmol) in CH$_3$CN/H$_2$O (0.8/0.2 mL). ^{1}H NMR (300 MHz, CDCl$_3$): (3.0:1 rotamer ratio, *denotes minor rotamer resonances) δ 9.21 (bs, 1H, NH), 9.11* (bs, 1H, NH), 8.27 (s, 1H, NCHO), 8.22* (s, 1H, NCHO), 8.21* (s, 1H, C$_{Ar}$-H), 8.17 (s, 2H, C$_{Ar}$-H), 7.70* (s, 1H, C$_{Ar}$-H), 7.66 (s, 1H, C$_{Ar}$-H), 5.46-5.38* (m, 1H, C$_2$-H), 5.33-5.24 (m, 1H, C$_2$-H), 3.78-3.68 (m, 2H, C$_5$-H), 2.52-2.41 (m, 1H, C$_3$-H$_a$), 2.07-2.04 (m, 1H, C$_3$-H$_b$), 1.91* (s, 6H, C(CH$_3$)$_2$), 1.34 (s, 6H, C(CH$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 194.8* (CO), 194.0 (CO), 169.9* (NCHO), 161.7* (CONH), 160.7 (NCHO), 157.7 (CONH), 138.0 (C$_{Ar}$-C), 137.7* (C$_{Ar}$-C), 132.7 (q, $^2J_{C-F}$ = 33.7 Hz, 2 × **C**CF$_3$), 123.1 (q, $^1J_{C-F}$ = 272.7 Hz, 2 × CF$_3$), 119.9 (q, $^3J_{C-F}$ = 3.3 Hz, C$_{Ar}$-H), 118.7 (q, $^3J_{C-F}$ = 4.0 Hz, C$_{Ar}$-H), 60.9* (C$_2$), 58.5 (C$_2$), 51.5 (C$_4$), 46.7 (C$_5$), 44.4* (C$_5$), 28.9 (C(CH$_3$)$_2$), 24.7 (C$_3$), 24.6* (C(CH$_3$)$_2$), 22.8* (C$_3$); ^{19}F NMR (282MHz, CDCl$_3$): δ -63.1 (2 × CF$_3$); IR (ATR) cm^{-1}: 2965 (NH), 2877 (C-H st), 1658 (C=O), 1128 (C-N st); MS (EI) *m/z* (%): 380 (17), 281 (16), 255 (72), 236 (41), 207 (31), 186 (15), 152 (57), 108 (100), 81 (23), 69 (25); The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; τ_{major} = 6.502 min, τ_{minor} = 5.960 min (90% ee); $[\alpha]_D^{20}$: -27.5 (*c* = 1.0, CH$_2$Cl$_2$).

**N-(3,5-bis(trifluoromethyl)phenyl)-2-((2S,3R)-1-formyl-3-methylpyrrolidin-2-yl)-2-oxoacetamide (13c).** Following general procedure I, **13c** (17.2 mg, 0.043 mmol) was isolated by FC (petroleum ether/EtOAc gradient from 8:2 to 1:1) in 60% yield as a yellow foam starting from (4a*S*,5*R,Z*)-2-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-

4-(2-phenylhydrazono)-1-thioxohexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **11e** (36.3 mg, 0.073 mmol) and PIFA (96.4 mg, 0.22 mmol + 38.6 mg, 0.087 mmol) in CH_3CN/H_2O (0.4/0.1 mL). ^1H NMR (300 MHz, $CDCl_3$): (7.0:1 diastereoisomer ratio, *denotes minor diastereoisomer resonances) δ 9.17 (bs, 1H, NH), 8.20 (s, 1H, NCHO), 8.15 (s, 2H, C_{Ar}-H), 7.64 (s, 1H, C_{Ar}-H), 4.75 (d, J = 7.0 Hz, 1H, C_2-H), 3.79 (dd, J = 8.3, 5.4 Hz, 2H, C_5-H), 2.50 (h, J = 7.0 Hz, 1H, C_3-H), 2.28-2.13 (m, 1H, C_4-H_a), 1.82-1.65 (m, 1H, C_4-H_b), 1.33* (d, J = 7.0 Hz, 3H, CH_3), 1.27 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (CO), 160.8 (NCHO), 158.1 (CONH), 138.1 (C_{Ar}-C), 137.7* (C_{Ar}-C), 132.7 (q, $^2J_{C-F}$ = 33.6 Hz, 2 × **C**CF_3), 123.0 (q, $^1J_{C-F}$ = 273.1 Hz, 2 × CF_3), 119.9 (C_{Ar}-H), 118.7 (q, $^3J_{C-F}$ = 3.6 Hz, C_{Ar}-H), 62.9* (C_2), 60.6 (C_2), 45.7 (C_5), 43.7* (C_5), 38.1* (C_3), 36.7 (C_3), 32.4 (C_4), 30.8* (C_4), 15.2* (CH_3), 14.9 (CH_3); ^{19}F NMR (282MHz, $CDCl_3$): δ -63.1 (2 × CF_3); IR (ATR) cm^{-1}: 2973 (NH), 2887 (C-H st), 1652 (C=O), 1126 (C-N st); MS (EI) *m*/*z* (%): 255 (68), 236 (30), 207 (29), 112 (100), 83 (39), 69 (37); HRMS: Calculated for $[C_{16}H_{15}N_2O_3F_6]^+$: 397.0987 $[(M+H)^+]$; found: 397.0988; The ee was determined by HPLC using a Chiralpak AD-H column [*n*hexane/*i*PrOH (95:05)]; flow rate 1.00 mL/min; τ_{major} = 10.119 min, τ_{minor} = 9.370 min (For the major diastereisomer: 96% ee); $[\alpha]_D^{20}$: -15.7 (*c* = 0.85, CH_2Cl_2).
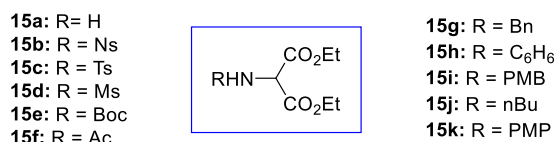
3. AMINOCATALYTIC VINYLOGOUS IMINIUM ION STRATEGY IN ORGANOCASCADE REACTIONS

3.1. General structures of cyclic dienones 14a-d

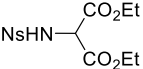**14a:** R = Me
14b: R = *n*Pr
14c: R = Ph

14d
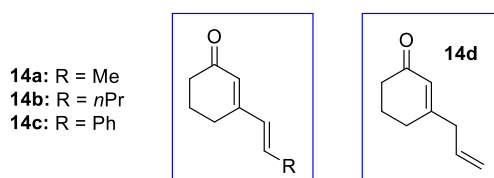
Cyclic ketones **14a-d**[17] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

3.2. General structures of *N*-substituted 2-aminomalonates 15a-k

15a: R= H
15b: R = Ns
15c: R = Ts
15d: R = Ms
15e: R = Boc
15f: R = Ac

15g: R = Bn
15h: R = C_6H_6
15i: R = PMB
15j: R = nBu
15k: R = PMP

2-Aminomalonate **15a** is commercially available. *N*-substituted 2-aminomalonates **15c**,[18] **15d**,[19] **15e**,[20] **15f**,[21] **15g-j**[22] and **15k**[23] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

3.2.1. Synthesis of 2-aminomalonate **15b**

4-((1,3-diethoxy-1,3-dioxopropan-2-yl)amino)-3-nitrobenzenesulfonic acid (15b). Nosyl chloride (0.66 g, 3.0 mmol) dissolved in tetrahydrofuran (15 mL) was added dropwise to a solution of diethyl aminomalonate hydrochloride (800 mg, 3.6 mmol) and Et₃N (0.84 mL, 6 mmol) in tetrahydrofuran (10 mL) at

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[19] Miao, C.-B.; Dong, C.-P.; Zhang, M.; Ren, W.-L.; Meng, Q.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2013**, *78*, 4329.

[20] Hung, A.; Pawar, S.; Borggraeve, W. *Tetrahedron Lett.* **2014**, *55*, 4664.

[21] Brun, P.; Dean, A.; Marco, V.; Surajit, P.; Castagliuolo, I.; Carta, D.; Ferlin, M. G. *Eur. J. Med. Chem.* **2013**, *62*, 486.

[22] Ugarriza, I.; Uria, U.; Carrillo, L.; Vicario, J. L.; Reyes, E. *Chem. Eur. J.* **2014**, *20*, 11650.

[23] Simig, G.; Doleschall, G.; Hornyák, G. *Tetrahedron* **1985**, *41*, 479.

-30 ºC. The reaction was stirred for 1h. After warming up to rt, the solution was washed with 1M HCl (2 x 10mL). The aqueous phase was extracted with THF (2 x 10mL) and the combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1 to 4:6) to afford 400 mg of **15b** (1.06 mmol, 35%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.34 (d, J = 8.7 Hz, 2H, C$_{Ar}$-H), 8.06 (d, J = 8.7 Hz, 2H, C$_{Ar}$-H), 5.98 (d, J = 6.9 Hz, 1H, NH), 4.75 (d, J = 6.9 Hz, 1H, CH), 4.16 (q, J = 7.2 Hz, 4H, 2 × C**H**$_2$CH$_3$), 1.22 (t, J = 7.2 Hz, 6H, 2 × CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.3 (COO), 150.4 (C$_{Ar}$-C), 145.7 (C$_{Ar}$-C), 128.7 (C$_{Ar}$-H), 124.4 (C$_{Ar}$-H), 63.4 (CH$_2$), 58.8 (CH), 14.1 (CH$_3$); R$_f$: 0.58 (hexanes/EtOAc 6:4); IR (ATR) cm^{-1}: 3253 (NH), 2984 (NH), 1741 (C=O); MS (EI) *m/z* (%): 360 (M$^+$, 11), 174 (22, M-[SO$_2$-*p*-NO$_2$(C$_6$H$_4$)]); 123 (59), 77 (100), 51 (42); M.p. (CH$_2$Cl$_2$): 128-130 ºC.

3.3. Synthesis of products 16
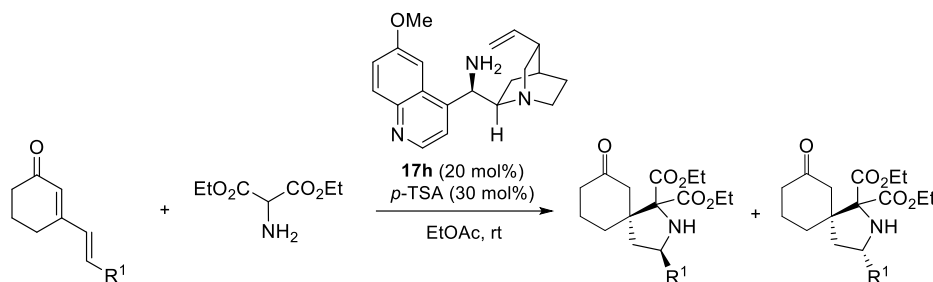
General Procedure J: In a vial the catalyst 18 (0.04 mmol, 0.2 eq.) and *p*-TSA (0.06 mmol, 0.3 eq.) were dissolved in EtOAc (0.8 mL) and the mixture was stirred at rt for 10 min. Then, the corresponding α,β,γ,δ-unsaturated cyclic ketone (0.2 mmol, 1.0 eq.) was added and was stirred for another 30 min. Afterwards, freshly liberated diethyl aminomalonate (0.3 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt. After 24 h, the crude was purified by flash column chromatography on silica gel to afford the pure compounds.
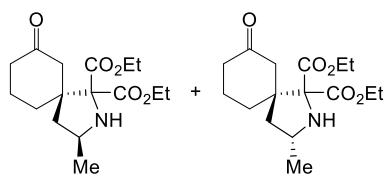
Diethyl (3*R*,5*R*)-3-methyl-7-oxo-2-azaspiro[4.5]decane-1,1-dicarboxylate (16a). Following the general procedure J, **16a** and **16a'** (43.0 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc

gradient from 7:3) in 69% yield as a yellow oil starting from catalyst **17h** (12.9 mg, 0.04 mmol), *p*-TSA (11.4 mg, 0.06 mmol), (*E*)-3-(prop-1-en-1-yl)cyclohex-2-en-1-one **14a** (27.2 mg, 0.2 mmol) and diethyl aminomalonate **15a** (52.6 mg, 0.3 mmol) in EtOAc (0.8 mL). ^{1}H NMR (300 MHz, CDCl$_3$): (1:1.2 diastereisomer ratio; *denotes minor diastereoisomer resonances) δ 4.31-4.13 (m, 4H, 2 × C**H**$_2$CH$_3$), 3.63-3.48 (m, 1H, C$_3$-H), 2.76* (d, *J* = 13.6 Hz, 1H, C$_6$-H$_a$), 2.59-2.49 (m, 1H, C$_6$-H$_a$ + C$_8$-H$_a$*), 2.40-2.20 (m, 3H, C$_6$-H$_b$ + C$_8$-H), 2.15-1.57 (m, 6H, C$_4$-H + C$_9$-H + C$_{10}$-H), 1.33-1.23 (m, 7H, 2 × CH$_2$C**H**$_3$ + NH), 1.17 (d, *J* = 6.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 210.3* (C$_7$), 210.1 (C$_7$), 170.8 (COO), 170.0* (COO), 169.9* (COO), 169.7 (COO), 78.9* (C$_1$), 78.7 (C$_1$), 61.8 (**C**H$_2$CH$_3$), 61.8* (**C**H$_2$CH$_3$), 61.7 (**C**H$_2$CH$_3$), 61.7* (**C**H$_2$CH$_3$), 53.2 (C$_5$), 52.3* (C$_5$), 50.7 (C$_3$), 50.6* (C$_3$), 48.9* (C$_6$), 48.1 (C$_6$), 42.3 (C$_8$), 41.3* (C$_8$), 41.1* (C$_4$), 41.1 (C$_4$), 31.1 (C$_{10}$), 30.2* (C$_{10}$), 23.2* (CH**C**H$_3$), 22.9 (C$_9$), 22.7 (CH**C**H$_3$), 22.2* (C$_9$), 14.2* (CH$_2$**C**H$_3$), 14.2 (CH$_2$**C**H$_3$), 14.2 (CH$_2$**C**H$_3$), 14.2* (CH$_2$**C**H$_3$); R$_f$: 0.35 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2984 (NH), 1741 (C=O); MS (EI) *m/z* (%): 312 (M$^+$ - CO$_2$Et, 57), 238 (100), 137 (12), 123 (12), 67 (10); HRMS: Calculated for [C$_{16}$H$_{26}$NO$_5$]$^+$: 312.1811 [(M+H)$^+$]; found: 312.1834; The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*hexane/*i*PrOH (90:10)]; flow rate 1.00 mL/min; **16a** diastereoisomer τ$_{major}$ = 16.415 min, τ$_{minor}$ = 14.470 min (54% ee); **16a'** diastereoisomer τ$_{major}$ = 18.498 min, τ$_{minor}$ = 23.421 min (63% ee).
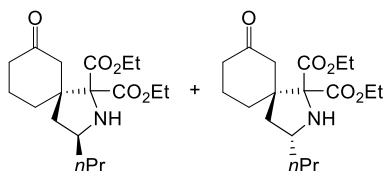
Diethyl (3*R*,5*R*)-7-oxo-3-propyl-2-azaspiro[4.5]decane-1,1-dicarboxylate (16b). Following the general procedure J, **16b** and **16b'** (20 mg, 0.059 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3) in 29% yield as a yellow oil starting from catalyst **17h** (12.9 mg, 0.04 mmol), *p*-TSA (11.4 mg, 0.06 mmol), (*E*)-3-(pent-1-en-1-yl)cyclohex-2-en-1-one **14b** (32.9 mg, 0.2 mmol) and diethyl aminomalonate **15a** (52.6 mg, 0.3 mmol) in EtOAc (0.8 mL). ^{1}H NMR (300 MHz, CDCl$_3$): (1:1.2 diastereisomer ratio; *denotes minor diastereoisomer resonances) δ 4.33-4.10 (m, 4H, 2 × C**H**$_2$CH$_3$), 3.47-3.30 (m, 1H, C$_3$-H), 2.85-2.65 (bs, 1H, NH), 2.75* (d, *J* = 13.6 Hz, 2H, C$_6$-H$_a$), 2.60-2.43 (m, 1H, C$_6$-H$_a$ + C$_8$-H$_a$*), 2.41-2.17 (m, 3H, C$_6$-H$_b$ + C$_8$-H), 2.14-1.58 (m, 6H, C$_4$-H + C$_9$-H + C$_{10}$-H), 1.57-1.17 (m, 10H, 2 × OCH$_2$C**H**$_3$ + C**H**$_2$C**H**$_2$CH$_3$), 0.88 (t, *J* = 7.0 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 210.4* (C$_7$), 210.1 (C$_7$), 170.6 (COO), 170.1* (COO), 169.8* (COO),

169.7 (COO), 78.4* (C$_1$), 78.3 (C$_1$), 61.8 (OCH$_2$CH$_3$), 61.7* (OCH$_2$CH$_3$), 61.6 (OCH$_2$CH$_3$), 61.6* (OCH$_2$CH$_3$), 55.2 (C$_3$), 55.2* (C$_3$), 52.7 (C$_5$), 51.7* (C$_5$), 48.7* (C$_6$), 48.1 (C$_6$), 41.1* (C$_8$), 41.1 (C$_8$), 40.6 (**C**H$_2$CH$_2$CH$_3$), 40.2* (**C**H$_2$CH$_2$CH$_3$), 40.0 (C$_4$), 39.6* (C$_4$), 30.9 (C$_{10}$), 30.2* (C$_{10}$), 22.9 (C$_9$), 22.1* (C$_9$), 20.4* (CH$_2$**C**H$_2$CH$_3$), 20.3 (CH$_2$**C**H$_2$CH$_3$), 14.3* (OCH$_2$**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$), 14.2* (OCH$_2$**C**H$_3$), 14.1 (CH$_3$), 14.1* (CH$_3$); R$_f$: 0.52 (hexanes/EtOAc 7:3); IR (ATR) cm^{-1}: 2985 (NH), 1740 (C=O); MS (EI) *m/z* (%): 340 (M$^+$ - CO$_2$Et, 57), 266 (100), 165 (10), 151 (10), 95 (9); HRMS: Calculated for [C$_{18}$H$_{30}$NO$_5$]$^+$: 340.2124 [(M+H)$^+$]; found: 340.2136; The ee was determined by HPLC using a Chiralpak AY-3 column [*n*hexane/*i*PrOH (80:20)]; flow rate 1.00 mL/min; **16b** diastereoisomer τ$_{major}$ = 7.269 min, τ$_{minor}$ = 8.341 min (14% ee); **16b'** diastereoisomer τ$_{major}$ = 10.500 min, τ$_{minor}$ = 12.897 min (43% ee).

4. SYNTHESIS OF ENANTIOENRICHED HINDERED TERTIARY BORONIC ESTERS THROUGH *IN SITU* LITHIATION-BORYLATION CONDITIONS

4.1. General structures of secondary carbamates 19a-g
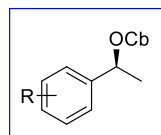
19a: R = 4-Cl
19b: R = 4-Br
19c: R = 4-I
19d: R = 3-CO$_2$*t*Bu
19e: R = 3-CF$_3$
19f: R = 3,5-(CF$_3$)$_2$
19g: R = 4-Ph

Secondary carbamates **19a-c**[24] **and 19g**[25] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature. Experimental data for compounds **19d-f**[26] are given in the literature.

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[24] Fandrick, K. R.; Patel, N. D.; Mulder, J. A.; Gao, J.; Konrad, M.; Archer, E.; Buono, F. G.; Duran, A.; Schmid, R.; Daeubler, J.; Fandrick, D. R.; Ma, S.; Grinberg, N.; Lee, H.; Busacca, C. A.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 4360.

[25] Watson, C.G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2014**, *136*, 17370.

[26] Blair, D. J.; Zhong, S.; Hesse, M. J.; Zabaleta, N.; Myers, E. L.; Aggarwal, V. K. *Chem. Commun.* **2016**, *52*, 5289.

4.2. General structures of boronic esters 20 and 22
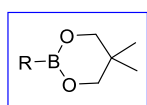
20a: R = *i*Pr
20b: R = *n*Bu
20c: R = allyl
20d: R = pentan-3-yl
20e: R = *t*Bu

22a: R = *n*Bu
22b: R = allyl
22c: R = pentan-3-yl
22d: R = 2-methylcyclopropane

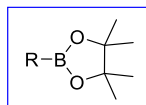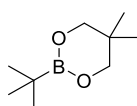Boronic esters **20a-b,**[27] **20d**[28], **20d**[29] and **22a,**[30] **22b,**[31] **22c**[29] and **22d**[32] were synthesized according to the literature procedures, and spectroscopic data were in agreement with those reported in the literature.

4.2.1. Synthesis of boronic ester **20e**

2-*tert*-butyl-5,5-dimethyl-1,3,2-dioxaborinane (20e). An oven dried round-bottomed flask was flushed with N_2. In the flask were placed $B(MeO)_3$ (3.34 mL, 30 mmol) in Et_2O (11 mL) and the flask was kept at 25ºC by using a water bath. Then, *t*BuMgCl (1.9 M in Et_2O, 7.9 mL, 15 mmol) was added drowise *via* cannula with vigorous stirring. Immediately a white precipitate formed. After completion of addition, the mixture was stirred for 3 hours at 25ºC. The reaction flask was brought to 0ºC and 2N HCl was added slowly and stirred for 2.5 hours at 25ºC. A clear separation of the water layer and the organic layer was apparent. The ^{11}B NMR spectrum of the organic layer showed only the presence of $B(OH)_3$ and tBuB$(OH)_2$. The organic layer, separated and washed with 2×50 mL of degassed water under N_2, showed the presence of tBuB$(OH)_2$ only. After evaporation of Et_2O, 50 mL of dry Et_2O, neopentyl glycol (1.05 g, 10 mmol) and $MgSO_4$ (3.6 g) were added and stirred for 30 min. The solid formed disappeared and the water separated out by $MgSO_4$. After completion of the reaction, filtrated and evaporated. The residue was purified by a short column chromatography (%2.5 Et_2O/pentane) to afford 830 mg of **20e** (4.88 mmol, 49%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (s, 4H, C_4-H + C_6-H), 0.93 (s, 6H, $C(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.1 (C_4), 72.1 (C_6), 27.4 ($C(\mathbf{CH_3})_3$),

27 Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054.
28 Heise, G. L., Myslinska, M. Patent US20120289733 A1.
29 Roesner, S.; Blair, D. J.; Aggarwal, V. K. *Chem. Sci.* **2015**, *6*, 3718.
30 Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890.
31 Roush, W. R.; Adam. M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.
32 Lin, H.; Tian, L.; Krauss, I. *J. Am. Chem. Soc.* **2015**, *137*, 13176.

21.9 (C(**CH₃**)₂), 31.7 (C₅), carbon attached to boron not observed; ^{11}B NMR (96 MHz, CDCl₃): δ 30.1; IR (neat) cm^{-1}: 2935, 1476 (B-O st), 1167.

4.3. Synthesis of tertiary alcohols from secondary benzylic carbamates

4.3.1. Synthesis of tertiary alcohols **21**
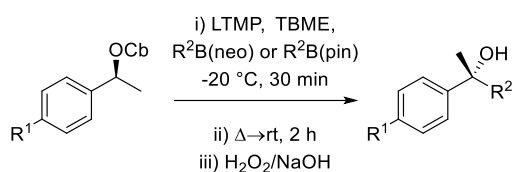
Preparation of LTMP

To a solution of 2,2,6,6-tetramethylpiperidine (0.11 mL, 0.65 mmol) in dry TBME (0.25 mL) cooled to 0 °C was added *n*BuLi (1.53 M in hexanes, 0.41 mL, 0.63 mmol) dropwise. The reaction was then warmed to rt and stirred for 30 min giving a clear colourless 1M solution of LTMP.

Note: Occasionally LTMP will precipitate out of solution, we have found that addition of the suspension does not negatively impact the lithiation-borylation reactions. However, addition of 1 mL of TBME rather than 0.25 mL is sufficient to redissolve LTMP.

General Procedure K: To a solution of benzylic carbamate (0.5 mmol, 1.0 eq.) and boronic ester (0.65 mmol, 1.3 eq.) in dry TBME (1 mL) cooled to −20 °C was added a solution of LTMP (*vide supra*) dropwise. The light yellow solution was then stirred at −20 °C for 30 min before warming to room temperature and stirring for a further 2 hours, at which point analysis of ^{11}B NMR data indicated no presence of an "ate" complex. A solution of 2:1 NaOH (2 M) and H₂O₂ (30% v/v) was added (1 mL/mmol) and the reaction mixture was stirred vigorously overnight. The reaction was diluted with H₂O (5 mL), the layers separated and the aqueous layer was extracted into Et₂O (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated *in vacuo* and purified by flash column chromatography to give

the product tertiary benzylic alcohol. Compounds **21a**[24] and **21i**[33] have been previously described in the literature.
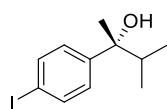
(R)-2-(4-Iodophenyl)-3-methylbutan-2-ol (21c). Prepared according to the general procedure K using carbamate **19c** (187 mg, 0.50 mmol, >98% ee), iPrB(neo) (101 mg, 0.65 mmol) and LTMP (0.65 mmol) to yield tertiary alcohol **21c** (134 mg, 92%) as a yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.64 (d, J = 8.5 Hz, 2H, C$_{Ar}$-H), 7.17 (d, J = 8.5 Hz, 2H, C$_{Ar}$-H), 1.97 (dt, J = 13.6, 6.8 Hz, 1H, C**H**(CH$_3$)$_2$), 1.66 (s, 1H, OH), 1.49 (s, 3H, CH$_3$), 0.89 (d, J = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.78 (d, J = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$); ^{13}C NMR (CDCl$_3$, 101 MHz): δ 147.6 (C$_{Ar}$-C), 137.0 (C$_{Ar}$-H), 127.6 (C$_{Ar}$-H), 92.0 (C$_{Ar}$-C), 76.7 (COH), 38.6 (CH), 26.9 (CH$_3$), 17.5 (CH(CH$_3$)$_2$), 17.1 (CH(CH$_3$)$_2$); R$_f$: 0.64 (pentane:Et$_2$O 8:2); IR (neat) cm^{-1} : 3459 (OH), 2968 (C$_{Ar}$-H), 1483 (C$_{Ar}$-H), 806 (C$_{Ar}$=C); HRMS (ESI) calc'd. for C$_{11}$H$_{15}$IONa [M+Na]$^+$ 313.0065; found: 313.0042; The ee was determined by HPLC using a Chiral SFC Whelk-01 column [$n$hexane/iPrOH (1:1), 5% co-solvent, 125 bar, 40ºC]; flow rate 4.0 mL/min; τ$_{major}$ = 3.9 min, τ$_{minor}$ = 3.4 min (99% ee); $[\alpha]_D^{20}$: +52.0 (c = 1.0, CH$_2$Cl$_2$).
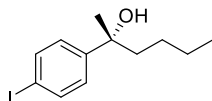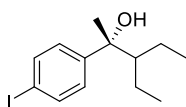
(R)-2-(4-iodophenyl)hexan-2-ol (21g). Prepared according to the general procedure K using carbamate **19c** (131 mg, 0.35 mmol, >98% ee), nBuB(neo) (77 mg, 0.45 mmol) and LTMP (0.45 mmol) to yield tertiary alcohol **21g** (101 mg, 95%) as a colourless oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.65 (d, J = 8.5 Hz, 2H, C$_{Ar}$-H), 7.17 (d, J = 8.5 Hz, 2H, C$_{Ar}$-H), 1.82 (s, 1H, OH), 1.80-1.73 (m, 2H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.52 (s, 3H, CC**H**$_3$), 1.35-1.16 (m, 3H, CH$_2$C**H**$_2$C**H**HCH$_3$), 1.16-0.99 (m, 1H, CH$_2$CH$_2$CH**H**CH$_3$), 0.84 (t, J = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 147.9 (C$_{Ar}$-C), 137.2 (C$_{Ar}$-H), 127.2 (C$_{Ar}$-H), 92.0 (C$_{Ar}$-C), 74.6 (COH), 43.9 (**C**H$_2$CH$_2$CH$_2$CH$_3$), 30.2 (C**C**H$_3$), 26.1 (CH$_2$**C**H$_2$CH$_2$CH$_3$), 23.1 (CH$_2$CH$_2$**C**H$_2$CH$_3$), 14.1 (CH$_2$**C**H$_3$); R$_f$: 0.73 (pentane:Et$_2$O 8:2); IR (neat) cm^{-1} : 3394 (OH), 2931 (C$_{Ar}$-H), 1483 (C$_{Ar}$-C); HRMS (ESI) calc'd. for C$_{12}$H$_{17}$INaO [M+Na]$^+$ 327.0216; found: 327.0219; The ee was determined by HPLC using a Chiralpak IC column with guard [$n$hexane/iPrOH (97:03)]; flow rate 1.0 mL/min; τ$_{major}$ = 5.6 min, τ$_{minor}$ = 6.4 min (99% ee); $[\alpha]_D^{20}$: +2.0 (c = 1.0, CH$_2$Cl$_2$).

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[33] Kamei, T.; Fujita, K.; Itami, K.; Yoshida, J-I. *Org. Lett.* **2005**, *7*, 4725.
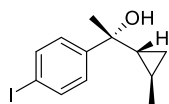
(*R*)-1-(4-iodophenyl)-1-((1*R*,2*R*)-2-methylcyclopropyl)ethan-1-ol (21h). Prepared according to the general procedure K using carbamate **19c** (79 mg, 0.21 mmol, >98% ee), 2-methylcyclopropaneB(pin) (50 mg, 0.27 mmol, 90% ee, >95:5 *dr*) and LTMP (0.27 mmol) to yield tertiary alcohol **21h** (44 mg, 68%) as a yellow oil. The product was obtained as a mixture of diastereomers (anti:syn 95:5 by ^{1}H NMR). Analytical data for the major anti diastereomer. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.64 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 7.24 (d, *J* = 8.5 Hz, 2H, C$_{Ar}$-H), 1.57 (s, 1H, OH), 1.42 (s, 3H, CC**H**$_3$), 1.01 (d, *J* = 5.9 Hz, 3H, CHC**H**$_3$), 0.96-0.83 (m, 1H, C**H**CH$_3$), 0.82-0.69 (m, 1H, CCH), 0.63-0.52 (m, 1H, CH**H**), 0.31-0.23 (m, 1H, C**H**H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 148.2 (C$_{Ar}$-C), 137.2 (C$_{Ar}$-H), 127.5 (C$_{Ar}$-H), 92.4 (C$_{Ar}$-C), 73.3 (COH), 31.5 (**C**HCH$_3$), 28.9 (C**C**H$_3$), 18.7 (CH**C**H$_3$), 10.4 (CH$_2$), 9.2 (C**C**H); R$_f$: 0.8 (pentane:Et$_2$O 8:2); IR (neat) cm^{-1} : 3418 (OH), 2949 (C$_{Ar}$-H), 1483 (C$_{Ar}$-H), 816 (C$_{Ar}$=C); HRMS (ESI) calc'd. for C$_{12}$H$_{15}$INaO [M+Na]$^+$ 325.0060; found: 325.0064; $[\alpha]_D^{20}$: +2.0 (*c* 1, CH$_2$Cl$_2$).

(*R*)-3-ethyl-2-(4-iodophenyl)pentan-2-ol (21j). Prepared according to the general procedure K using carbamate **19c** (78 mg, 0.21 mmol, >98% ee), (CH$_2$CH$_3$)$_2$CHB(neo) (50 mg, 0.27 mmol) and LTMP (0.27 mmol) to yield tertiary alcohol **21j** (64 mg, 97%) as a colourless oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.64 (d, *J* =8.4 Hz, 2H, C$_{Ar}$-H), 7.18 (d, *J* =8.4 Hz, 2H, C$_{Ar}$-H), 1.62 (br, 1H, OH), 1.60-1.52 (m, 1H, CH), 1.49 (s, 3H, CC**H**$_3$), 1.46-1.36 (m, 2H, CH$_2$), 1.31-1.18 (m, 1H, CH**H**), 1.18-1.06 (m, 1H, C**H**H), 0.88 (t, *J* = 7.5 Hz, 3H, CH$_2$C**H**$_3$), 0.83 (t, *J* = 7.5 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 148.4 (C$_{Ar}$-C), 137.0 (C$_{Ar}$-H), 127.5 (C$_{Ar}$-H), 91.9 (C$_{Ar}$-C), 77.7 (COH), 52.2 (CH), 27.4 (C**C**H$_3$), 22.5 (CH$_2$), 22.2 (CH$_2$), 13.6 (CH$_2$**C**H$_3$), 13.4 (CH$_2$**C**H$_3$); R$_f$: 0.60 (pentane:Et$_2$O 8:2); IR (neat) cm^{-1}: 3463 (OH), 2960 (C$_{Ar}$-H), 1483 (C$_{Ar}$-H), 818 (C$_{Ar}$=C); HRMS (ESI) calc'd. for C$_{13}$H$_{19}$INaO [M+Na]$^+$ 341.0373; found: 341.0371; The ee was determined by HPLC using a Chiralpak IA column with guard [*n*hexane/*i*PrOH (98:02)]; flow rate 1.0 mL/min; τ$_{major}$ = 10.5 min, τ$_{minor}$ = 11.6 min (84% ee); $[\alpha]_D^{20}$: +4.0 (*c* = 1.0, CH$_2$Cl$_2$).
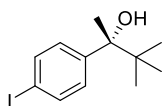
(*R*)-2-(4-iodophenyl)-3,3-dimethylbutan-2-ol (21k). Prepared according to the general procedure C using carbamate **19c** (131 mg, 0.35 mmol, >98% ee), *t*BuB(neo) (77 mg, 0.45 mmol) and LTMP (0.45 mmol) to yield tertiary alcohol **21k** (27 mg, 25%) as a yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.62 (d, *J* = 8.6 Hz,

2H, C_{Ar}-H), 7.19 (d, J = 8.6 Hz, 2H, C_{Ar}-H), 1.60-1.54 (m, 4H, OH + CH$_3$), 0.91 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 146.1 (C_{Ar}-C), 136.3 (C_{Ar}-H), 129.4 (C_{Ar}-H), 92.2 (C_{Ar}-C), 78.5 (COH), 38.1 (**C**(CH$_3$)$_3$), 25.8 (C(**C**H$_3$)$_3$), 25.2 (CH$_3$); R$_f$: 0.54 (pentane:Et$_2$O 8:2); IR (neat) cm^{-1} : 3467 (OH), 2964 (C_{Ar}-H), 1482 (C_{Ar}-C); HRMS (ESI) calc'd. for C$_{12}$H$_{17}$INaO [M+Na]$^+$ 327.0216; found: 327.0219; The ee was determined by HPLC using a Chiral SFC IC column [*n*hexane/*i*PrOH (1:1), 5% co-solvent, 125 bar, 41.6 ºC]; flow rate 4.0 mL/min; τ_{major} = 3.7 min, τ_{minor} = 6.1 min (4% ee).

Appendix

Abbreviations, acronyms and symbols[1]

Ac	Acetyl
acac	Acetylacetonate
ACDC	Asymmetric Counterion Directed Catalysis
Ac$_2$O	Acetic anhydride
AcOH	Acetic acid
aq.	Aqueous
Ar	Aryl
AU	Absorbance units
ATR	Atenuated total reflectance
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	Broad signal
***n*Bu**	*n*-Butyl
***t*Bu**	*tert*-Butyl
Bz	Benzoyl
c	Concentration (measured in g/100mL)
ºC	Degree Celsius
C$_{arom}$	Aromatic carbon
Cat.	Catalyst
Cbz	Benzyloxycarbonyl
CI	Chemical ionization
COSY	Correlation spectroscopy
***m*CPBA**	*meta*-Chloroperbenzoic acid

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

CPME	Cyclopentyl methyl ether
δ	Chemical shift
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabycyclo[5.4.0]undec-5-ene
DCE	1,2-dichloroethane
dd	Double of doublets
de	Diastereomeric excess
DEA	Diethylamine
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density functional theory
DIPEA	*N,N*-Di*iso*propylethylamine
DKR	Dynamic kinetic resolution
DMAP	*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPP	Diphenylphosphate
dr	Diastereomeric ratio
E	Electrophile or Energy
e.g.	*Exempli gratia* (for example)
ee	Enantiomeric excess
EI	Electron ionization
eq.	Equivalent
Et	Ethyl
et al.	*Et alii* (and others)
EtCN	Propionitrile

EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
FC	Flash column chromatography
Fmoc	Fluorenylmethyloxycarbonyl
GC	Gas chromatography
h	Hours
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i.e.	*Id est* (that is)
IR	Infrared
J	Coupling constant
kcal	kilocalorie
LDA	Lithium di*iso*popylamide
LG	Leaving group
LTMP	Lithium tetramethylpiperidine
LUMO	Lowest unoccupied molecular orbital
m	Multiplet or metres
m	*meta*
M	Molar concentration
M.p.	Melting point
m/z	Mass-to-charge ratio
M⁺	Molecular ion

Me	Methyl
MeCN	Acetonitrile
Mes	Mesityl
MeOH	Methanol
MS	Mass spectrometry or Molecular sieves
NCS	*N*-chlorosuccinimide
n.d.	Not determined
neo	Neopentyl
n.O.e.	Nuclear Overhauser effect
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
Nu	Nucleophile
o	*orto*
OAc	Acetate
OCb	Di*iso*propylcarbamate
OMe	Methoxy
OTIB	2,4,6-tri*iso*propyl benzoate
p	*para*
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	Parts per million
*i***Pr**	*iso*Propyl
*n***Pr**	*n*Propyl
*i***PrOH**	*iso*Propanol
pin	Pinacol
PTC	Phase-Transfer Catalysis

q	Quartet
R	Alkyl group
rt	Room temperature
rac	Racemic
s	Singlet
sat.	Aqueous saturated solution
SOMO	Single Occupied Molecular Orbital
t	Triplet or time
T	Temperature
TBAF	Tetrabutylammoniun fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butylmethyl ether
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
τ_{major}	Retention time of the major enantiomer
τ_{minor}	Retention time of the minor enantiomer
TMS	Trimethysilyl
Ts	Tosyl
*p***TSA**	*p*-Toluenesulfonic acid
vs.	Versus
X	Halogen
λ	Wavelength

Resumen extendido

En el trabajo de investigación recogido en la presente memoria se han implementado diversas metodologías para el desarrollo de nuevas reacciones enantioselectivas mediante el empleo de diferentes organocatalizadores quirales para la síntesis de compuestos orgánicos de interés.

En este sentido, la organocatálisis asimétrica ha contribuido al desarrollo de nuevos métodos de catálisis asimétrica, convirtiéndose en una de las herramientas sintéticas más importantes de la química orgánica, junto a la catálisis metálica y enzimática. Dentro de esta área, se han desarrollado diferentes tipos de activación mediante el empleo de organocatalizadores quirales. Uno de los métodos consiste en el empleo de organocatalizadores quirales que se unen mediante enlaces covalentes al sustrato para la activación del mismo, siendo la aminocatálisis una de las activaciones más empleadas. Otro método consiste en la catálisis no-covalente, en la cual la activación por enlaces de hidrógeno constituye la mayor parte de los ejemplos. En el presente trabajo de investigación se han utilizado estos dos métodos para el desarrollo de nuevas reacciones asimétricas de interés sintético, ya que el propio grupo de investigación ha desarrollado su actividad dentro de la organocatálisis asimétrica con éxito.

De este modo, en un primer capítulo se presenta una introducción al campo de la organocatálisis, haciendo mayor hincapié en los modos de activación que se emplearán para el desarrollo del manuscrito, la aminocatálisis y la catálisis por ácidos de Brønsted. En un segundo capítulo se ha demostrado la aplicabilidad de los catalizadores de ácidos de Brønsted para la activación de electrófilos. Mediante el empleo de catalizadores de ácidos fosfóricos quirales derivados del BINOL se ha llevado a cabo la reacción de adición de hidrazonas *N*-monosustituidas a dihidropirroles. El ácido fosfórico quiral derivado del BINOL es capaz de activar dihidropirroles para la creación del correspondiente ión *N*-acil iminio, que se une por contacto iónico al anión fosfato quiral del catalizador, creando un espacio quiral capaz de controlar la estereoquímica del producto final, tras el ataque de la hidrazona por el carbono

azometínico. De este modo se obtienen los correspondientes productos de hidrazona tras una transferencia *in situ* [1,3] de protón del compuesto azo intermedio (Esquema 1).
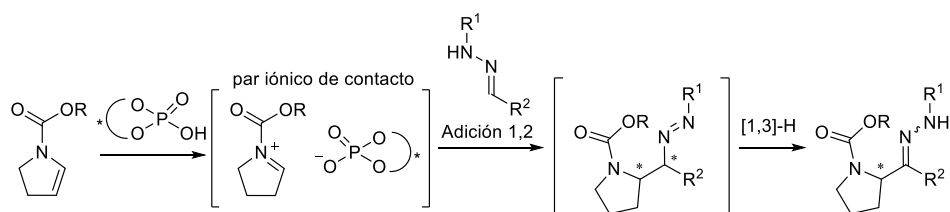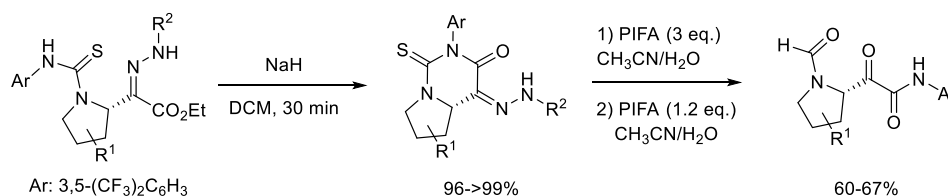

Esquema 1

Una vez demostrada la viabilidad de la reacción y tras un proceso exhaustivo de evaluación de parámetros experimentales, se consiguió determinar las mejores condiciones para llevar a cabo la reacción, las cuales consistían en el uso de un 5-10% mol de catalizador de ácido fosfórico quiral, a -5 ºC, en tolueno seco y en presencia de tamiz molecular, empleando enetioureas cíclicas e hidrazonas *N*-monosustituidas. La reacción se pudo extender de manera eficaz al empleo de dihidropirroles con diferente sustitución en el anillo, así como a hidrazonas con sustituyentes variables en la posición del nitrógeno, como en la posición azometínica, pudiendo emplear en este último caso tanto grupos electroatractores como electrodadores, obteniendo los productos finales con muy buenos rendimientos y enantioselectividades (Esquema 2).
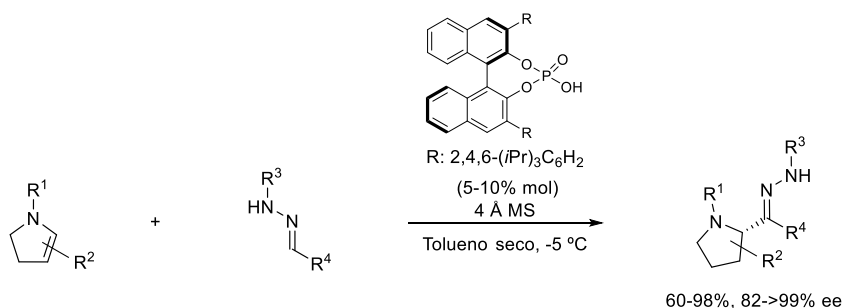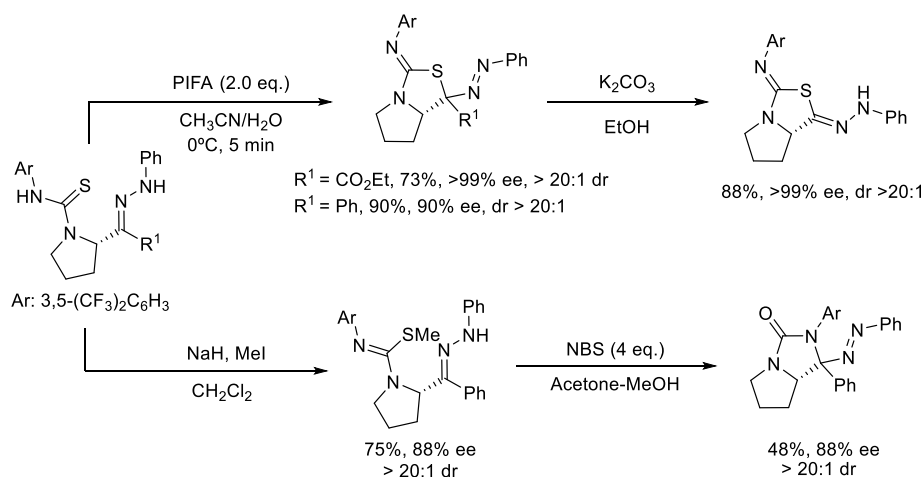

Esquema 2

Adicionalmente, se estudió la derivatización de los productos de hidrazona obtenidos para demostrar la aplicabilidad de las hidrazonas como equivalentes de aniones acilo. De esta forma, se consiguió desenmascarar el grupo carbonilo mediante el empleo de reacciones simples en tres pasos para la síntesis de derivados de prolina quirales con buenos

rendimientos y manteniendo el exceso enantiomérico para una variedad de compuestos (Esquema 3).

Esquema 3

Asimismo, se pudieron derivatizar los productos a otras estructuras bicíclicas quirales tras procedimientos sencillos manteniendo el alto grado de enantioselectividad en los productos finales (Esquema 4).
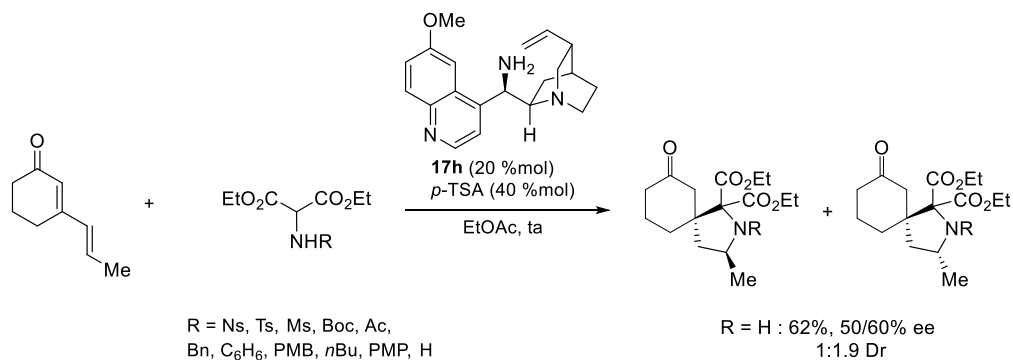

Esquema 4

Por otro lado, en el tercer capítulo de la tesis se ha estudiado la funcionalización remota de cetonas cíclicas poliinsaturadas mediante el empleo de la aminocatálisis. En este sentido, se decidió emplear catalizadores de amina primaria derivados de la cinchona para la activación de dienonas cíclicas $\alpha,\beta,\gamma,\delta$-insaturadas y 2-aminomalonatos como doble nucleófilos, para promover una reacción en cascada 1,6-aza-Michael/1,4-Michael mediante la activación ión iminio viníloga/ión iminio, obteniendo los correspondientes productos espirocíclicos por funcionalización en las posiciones β y δ de la dienona (Esquema 5).
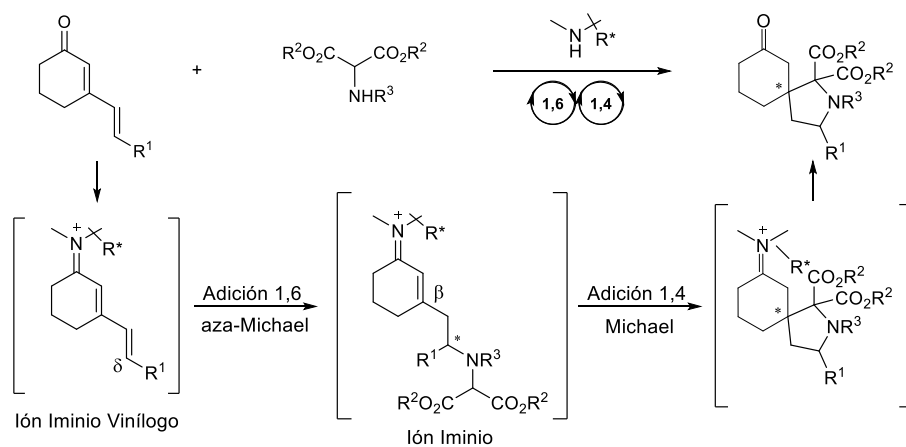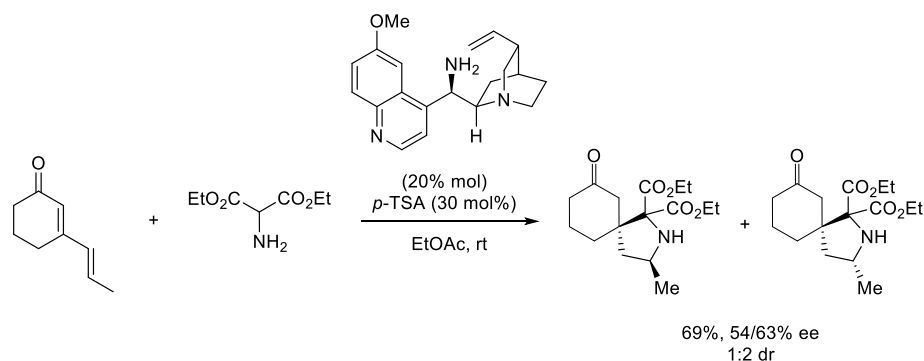
Esquema 5

Para determinar la viabilidad de la reacción, se emplearon diversos aminomalonatos *N*-sustituidos, así como el correspondiente a la amina primaria. Tal y como se muestra en el esquema 6, la reacción únicamente tuvo lugar al emplear 2-aminomalonato de dietilo, obteniendo el producto derivado de la adición 1,6-aza-Michael/1,4-Michael exclusivamente con buen rendimiento, moderada enantioselectividad, aunque como mezcla de diastereoisómeros.
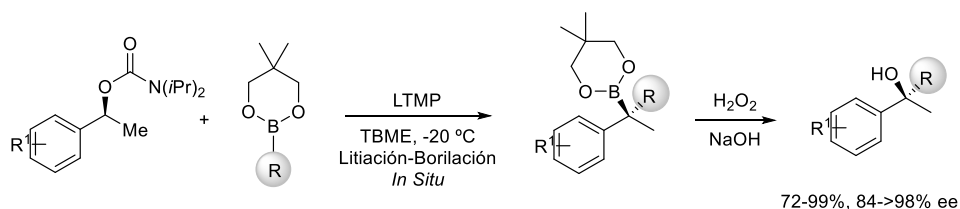

Esquema 6

Sin embargo, después de evaluar diferentes parámetros experimentales, tales como catalizadores, temperatura, aditivos, etc. los mejores resultados obtenidos fueron 69% de rendimiento, con una mezcla de diastereoisómeros 1:2 y con moderadas enantioselectividades, lo que deja abierta todavía la investigación de la reacción para la mejora de las condiciones e intentar obtener el producto de forma enantiopura (Esquema 6).

Esquema 6

Finalmente, se recoge el proyecto realizado en una estancia de tres meses en el grupo de investigación del profesor Varinder K. Aggarwal en la Universidad de Brístol. Durante ese periodo se desarrolló la síntesis de ésteres borónicos terciarios enantiopuros de gran impedimento estérico empleando el método de la litiación-borilación *in situ* de carbamatos bencílicos secundarios, haciendo uso de ésteres borónicos menos voluminosos. De esta forma, se pudo acceder a una gran variedad de ésteres borónicos con alto rendimiento y conservando la alta enantioselectividad de los sustratos iniciales (Esquema 7).

Esquema 7

Parte del trabajo recogido en la presente memoria ha dado lugar a las siguientes publicaciones:

1.   *"Full Chirality Transfer in the Synthesis of Hindered Tertiary Boronic Esters under In Situ Lithiation-Borylation Conditions"*

Daniel Blair, Siying Zhong, Matthew Hesse, Nagore Zabaleta, Eddie Myers, Varinder K. Aggarwal.

Chem. Commun. **2016***, 52*, 5289.

2.   *"Hydrazones as Acyl Anion Equivalents in the Enantioselective Addition to Dihydropyrroles under Chiral Phosphoric Acid Catalysis"*

Nagore Zabaleta, Uxue Uria, Efraím Reyes, Luisa Carrillo, José Luis Vicario.

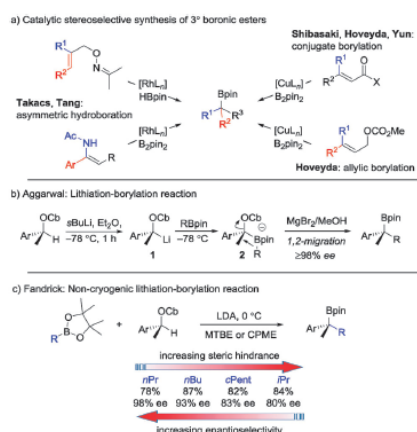*Manuscrito en preparación*

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Full chirality transfer in the synthesis of hindered tertiary boronic esters under *in situ* lithiation–borylation conditions†

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Hindered tertiary neopentyl glycol boronic esters can be prepared by using *in situ* lithiation–borylation of enantiopure secondary benzylic carbamates at −20 °C with full chirality transfer.

Boronic esters are versatile intermediates in synthesis and there are now numerous methods for their preparation in enantio-enriched form.[1] In the case of tertiary boronic esters, which are more difficult to prepare, a number of stereoselective and stereospecific methods have emerged over recent years (Scheme 1a (ref. 2) and Scheme 1b (ref. 3)). The stereospecific lithiation–borylation of enantiopure secondary carbamates (Scheme 1b), which has been developed in our research group,[3] has been employed by others[4] and indeed has even been scaled up to 24 kg.[5] For this scale-up, the cryogenic conditions commonly employed (sBuLi, −78 °C)[6] presented challenges. However, Fandrick[5] discovered that the carbamate could be deprotonated by a weaker base (LDA) and that this deprotonation could be conducted in the presence of pinacol boronic esters (*in situ* conditions) at elevated temperatures (0 °C), to give the corresponding tertiary boronic esters with high levels of enantiospecificity (Scheme 1c). At such an elevated temperature, having the boronic ester present in the reaction mixture during the deprotonation prevents epimerisation and/or decomposition of lithiated carbamate 1.

With more hindered secondary boronic esters, such as iPrBpin, lower levels of enantiospecificity were observed, presumably due to reversible formation of boronate complex 2. Such a process would return the sensitive lithiated carbamate 1, which would undergo racemisation and recombination with the boronic ester, thus leading to reduced stereoselectivity ∼80% es (Scheme 1b). We have previously found that the addition of MgBr₂/methanol following boronate complex formation enhances the rate of 1,2-migration and quenches any lithiated carbamate generated

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Scheme 1 State of the art: synthesis of tertiary boronic esters.

by the reverse process thereby leading to high yields and high stereoselectivity.[3a] Unfortunately, the addition of MgBr₂ in methanol is not compatible with an *in situ* lithiation–borylation reaction. Herein, we address the issue of low selectivity with hindered boronic esters and show that by using neopentyl glycol boronic esters[7] and LTMP (lithium 2,2,6,6-tetramethylpiperidine) as a base, high levels of enantiospecificity can now be achieved even with some of the most hindered boronic esters under non-cryogenic conditions.

During our investigations of lithiation–borylation methodology we found that the nature of the ligand on boron sometimes affected the enantioselectivity of the process.[3b,8] This is most dramatically illustrated in the case of the propargylic carbamate 3 where upon moving from the pinacol to the ethylene glycol based isopropyl boronic ester, enantiospecificity increased

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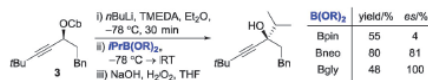
Scheme 2 Influence of the boron ligand on the stereochemical outcome of the lithiation–borylation of **3**; these results are taken from ref. 8a and are shown for comparison to results below (see Scheme 7).

from 4% to 100% (Scheme 2).[8a] Presumably, as the steric hindrance around boron was reduced, the boronate complex became less prone to reversibility and consequently the intermediate lithiated carbamate suffered less racemisation.

We therefore explored Fandrick's *in situ* conditions[5] with iPrBneo in place of iPrBpin. These conditions gave tertiary alcohol **5** from **4** with full stereospecificity (100% es, Scheme 3), a substantial improvement on that obtained using the pinacol boronate (80% es).[5] Other bases were tested and LTMP led to a higher yield (74%). Further improvement in the yield was realised by reducing the temperature from 0 °C to −20 °C, resulting in **5** being isolated in 90% yield and 100% es.

Our optimised conditions were applied to a range of otherwise challenging carbamates (Scheme 4). As noted by Fandrick, the *in situ* conditions involving an amide base in place of an organolithium base enables aryl bromides and iodides to be employed, and so these were initially tested. Using our conditions, these substrates gave the corresponding tertiary alcohols **6** and **7** in high yields and
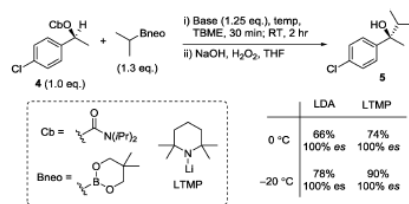
Scheme 3 Conditions for the homologation of neopentyl glycol boronic esters.
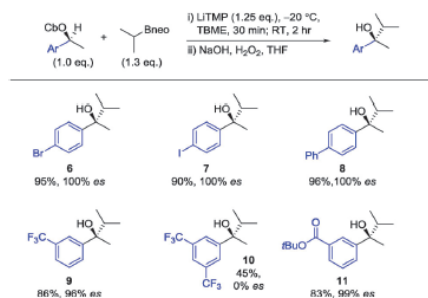

Scheme 4 Carbamate scope for the *in situ* lithiation–borylation of iPrBneo.

complete enantiospecificity. The *para*-phenyl-substituted carbamate is especially prone to racemisation and using iPrBpin gave **8** in low enantiospecificity (83% es). However, using the neopentyl glycol boronic ester, **8** was again obtained in high yield and enantio-specificity. Electron-withdrawing groups on the aromatic ring engenders reversibility in the formation of the boronate complex, thus rendering the lithiated carbamate more prone to racemisation. We found that although a single *meta*-CF_3 group was tolerated, enabling formation of **9** with excellent enantiospecificity, two *meta*-CF_3 groups was a step too far and led to essentially racemic product (**10**).[9] A hindered ester was compatible with our conditions and gave tertiary alcohol **11** with complete enantiospecificity. This functional group would not have been compatible with the preformed lithiated carbamate. Unfortunately, the use of *ortho*-substituted benzylic carbamates did not lead to the expected products. In contrast, we have previously shown these carbamates do give the expected products in good yield and near-complete enantiospecificity when subjected to our cryogenic lithiation–borylation conditions.[3a,10]

Because the stereoselectivity of the *in situ* lithiation–borylation reaction is affected by the steric bulk of the boronic ester substituent (R group), we tested a range of boronic esters of varying steric demand and compared both the pinacol (**A**) and neopentyl glycol (**B**) derivatives (Scheme 5). For unhindered nBu (**13**) and cyclopropyl (**14**) boronic esters high enantiospecificity was observed by using pinacol boronic esters (98% es), with neopentyl glycol boronic esters behaving similarly. Surprisingly, with unhindered allyl boronic esters (**15**) the pinacol derivative gave low es (82%) whilst the neopentyl glycol ester provided essentially complete enantiospecificity.

To explore the limits in steric bulk that could be tolerated we turned to 3-pentyl boronic esters.[11] Reaction of 3-pentyl-Bpin with **12** under our *in situ* conditions gave only traces of **16** with poor enantioselectivity. Simply switching to the corresponding neopentyl glycol ester significantly increased both the yield and selectivity, thus highlighting the advantages associated with neopentyl glycol derivatives, particularly in their application to hindered systems.

We have previously shown that secondary benzylic pinacol boronic esters form reversible boronate complexes with secondary benzylic carbamates leading to loss of both diastereo- and enantio-selectivity.[8c] The application of *in situ* conditions to the reaction of (*R*)-1-phenylethyl pinacol boronic ester with **12** gave **17** in high yield (90%, Scheme 6), high enantiospecificity (100% es) with respect to
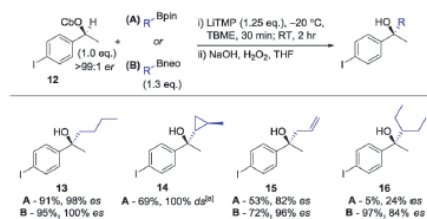
Scheme 5 Influence of boronic ester substituent on the *in situ* lithiation–borylation reaction of **12**. [a] Because the use of the pinacol boronic ester gave tertiary alcohol **14** with complete diastereospecificity, the corresponding experiment with the neopentyl glycol boronic ester was not carried out.

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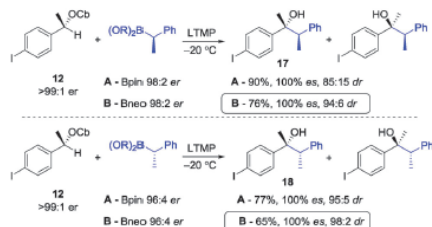
Scheme 6 The influence of boronic ester diol on the stereochemical outcome of homologation of (*R*)- and (*S*)-1-phenylethyl boronic esters with **12** under *in situ* conditions using pinacol (**A**) and neopentyl glycol (**B**) boronic esters.

the boronic ester starting material, but low diastereoselectivity (85 : 15 dr).[12] Simply switching to the corresponding neopentyl glycol boronic ester gave **17** in 94 : 6 dr, 100% es and high yield. In contrast, reaction of **12** with both pinacol and neopentyl glycol (*S*)-1-phenylethyl boronic esters gave **18** in high yield and selectivity (≥95 : 5 dr, 100% es).[13] Evidently, there is a significant matched/mis-matched effect operating under the reversible conditions with the pinacol boronic esters that can be minimised by using the neopentyl glycol boronic esters.

As noted above, for substrates that are especially prone to reversibility in boronate formation and therefore racemisation (*e.g.* **8**), the *in situ* conditions using neopentyl glycol boronic esters can lead to considerably higher levels of enantiospecificity. We therefore tested our *in situ* conditions with the secondary propargylic carbamate **19**, a substrate that only gave 81% es under conditions where the lithiated carbamate was preformed[8a] (Scheme 7). Under the new *in situ* conditions the tertiary propargylic alcohol **20** was obtained in high yield and excellent enantiospecificity (98% es).[14] This highlights the broad applicability of the new *in situ* lithiation–borylation protocol.[15]

In summary, we have found that almost complete enantiospecificity can be achieved in the lithiation–borylation reactions of secondary benzylic carbamates under *in situ* conditions when neopentyl glycol boronic esters are used in place of pinacol boronic esters. These conditions expand the range of tertiary boronic esters that can be prepared with very high selectivity with both increased functional-group and steric tolerance. The improved stereoselectivity results from reduced reversibility in boronate complex formation, a process that otherwise causes racemisation of the sensitive lithiated carbamate.
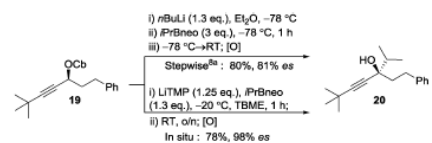
Scheme 7 Enhanced stereospecificity using *in situ* conditions in the lithiation–borylation reaction of secondary propargylic carbamates.

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9 Reducing the steric bulk of the boronic ester reaction partner from iPr to Et had no effect on the stereochemical outcome.

10 The *ortho*-bromo isomer of **6** and an *ortho*-methyl substrate (not depicted), did not lead to the expected products. The former substrate did not react whereas the latter gave a mixture of isomeric species derived from its fragmentation into the corresponding *ortho*-quinodimethane followed by (4+2) cycloaddition. See the ESI,† for further details on this side reaction.

11 *t*Bu boronic esters were also tested but both pinacol and neopentyl glycol esters failed to react under the *in situ* conditions.

12 Enantiospecificity was determined for the major diastereoisomer.

13 No epimerisation of the secondary boronic ester stereocentre was observed in either **17** or **18** with pinacol or neopentyl glycol esters. The presence of an electron-withdrawing group in **12** must bias the corresponding boronate complex towards fragmentation to Li-**12** rather than fragmentation of the C–B bond of the secondary boronic ester substrate to form a benzylic anion.

14 For the propargylic carbamates, unfortunately the use of a trialkyl-silyl substituent in place of a *t*-butyl group led to desilylated products not incorporating the boronic ester organic group.

15 We have previously shown that when substituted allylic carbamates are subjected to lithiation–borylation reactions under cryogenic conditions with neopentyl glycol boronic esters as partners, a mixture of products derived from α- and γ-borylation are obtained: (*a*) A. P. Pulis, PhD thesis, University of Bristol, 2012. However, the use of pinacol boronic esters lead to predominantly the required α-borylation: (*b*) A. P. Pulis and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2012, **134**, 7570.