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Hydrazides and Hydrazones as Versatile Michael-Donors for Iminium-Catalyzed Conjugate Addition Reactions

MEMORIA PRESENTADA POR

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To James

A mi familia

A mis amigas

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Abstract

In the work compiled in this thesis is presented a series of strategies that have been studied and have lead to the asymmetric synthesis of useful building blocks in high yields and stereochemical control. These are reliant on the use of chiral secondary amines as the element that induces stereocontrol, where the activation of the substrate is based on the formation of an iminium ion intermediate within the catalytic cycle. In this sense, it has been demonstrated that, under this type of activation, hydrazides and hydrazones are efficient and versatile reagents that can be used as Michael donors in conjugate addition reactions.

Thus, the performance of these hydrazide and hydrazone reagents as *N*-donors has been initially tested. In this context, two different aza-Michael initiated cascade reactions have been studied, using either *N*,*N*'-disubstituted hydrazides or hydrazones derived from pyruvaldehyde in the reaction with α,β-unsaturated aldehydes. Furthermore, the synthetic versatility of the products obtained has allowed a series of transformations to be performed, which is highlighted in the synthesis of valuable adducts (*e.g.* pyrazolines, pyrazolidinones or 1,3-diamines).

On the other hand, the ability of hydrazones to act *C*-pro-nucleophiles for the same type of reaction has also been demonstrated. In this sense, the conjugate addition reaction between *N*-monosubstituted hydrazones and various enals *via* iminium activation has been studied, confirming that hydrazones containing an electron-withdrawing group at the azomethine position undergo this process in a highly efficient manner. Moreover, the importance of this methodology has been highlighted by the synthesis of a series of 1,4-dicarbonyl compounds, verifying that hydrazones can behave as acyl anion equivalents.

Resumen

En el trabajo de investigación recogido en la presente memoria se han estudiado una serie de estrategias que tienen como finalidad la síntesis asimétrica de compuestos de interés con elevado rendimiento y control estereoquímico. Éstas están enmarcadas en el uso de aminas secundarias quirales a modo de elementos estereocontroladores, donde el tipo de activación del sustrato de partida se basa en la formación de iones iminio. En este sentido, se ha demostrado que las hidrazidas e hidrazonas son dadores de Michael versátiles y eficientes, que pueden ser aplicados a reacciones de adición conjugada bajo este tipo de activación.

Así, en un primer lugar se ha evaluado la aplicabilidad de estas hidrazidas e hidrazonas como nucleófilos nitrogenados. En este contexto, se han estudiado dos reacciones en cascada iniciadas por reacciones aza-Michael, empleando hidrazidas *N,N*'-disustituidas o hidrazonas derivadas del piruvaldehído con aldehídos α,β-insaturados. Además, la versatilidad sintética de los aductos obtenidos ha permitido llevar a cabo su posterior derivatización, pudiéndose destacar la síntesis de pirazolinas, pirazolidinonas y 1,3-diaminas.

Por otro lado, también se ha demostrado la capacidad de las hidrazonas para actuar como nucleófilos carbonados en reacciones de adición conjugada. En este sentido, se ha estudiado la reacción de adición conjugada de hidrazonas *N*-monosustituidas a diferentes enales bajo activación *via* iminio, observando que las hidrazonas que contienen un grupo electrón atractor en la posición azometínica son las más adecuadas para llevar a cabo este proceso. Además, la actuación de estas hidrazonas como equivalentes sintéticos de aniones acilo se ha resaltado mediante la síntesis de compuestos 1,4-dicarbonílicos.

Laburpena

Doktorego tesi honetan, interes handiko zenbait konposatuen sintesi asimetrikoa aurrera eramateko estrategiak bildu dira. Etekin eta kontrol estereokimiko altuko prozesuak lortzeko, aminokatalizatzaileetan oinarritutako katalisia aukeratu da, sustratua iminio ioi kirala bihurtuz. Zentzu honetan, hidrazida eta hidrazonak adizio konjokatuetan, eta aktibazio mota honekin, erabil daitezken konposatuak direla frogatu da.

Lehenik, hidrazida eta hidrazonen erabilera aztertu da nitrogenodun nukleozale gisa. Horretarako, bi aza-Michael erreakzio ikertu dira hidrazida *N,N'*-diordezkatuak edo pirubaldehidotik deribatutako hidrazonak eta aldehido α,β-asegabetuk erabiliz. Era berean, lortutako aduktuen aldakortasun sintetikoak zenbait eraldaketa kimiko aurrera eramatea ahalbidetu du, garrantzi handiko zenbait konposatuen sintesia lortuz, hala nola, pirazolinak, pirazolidinonak edo 1,3-diaminak.

Bestale, hidrazonen erabilera karbonodun nukleozale gisa ere frogatu da, erreakzio mota berdinerako. Horretarako, hidrazona *N*-monoordezkatuen adizio konjokatua enalekin aztertu da, azometino posizioan talde elektroi erakarle bat duten hidrazonek prozesu honetarako hoberenak direla ikuziz. Gainera, metodologia honetan hidrazonek azil anioien ekibalente sintetiko gisa jokatzen dutela erakutsi da konposatu 1,4-dikarbonilikoak lortuz.

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Chapter 1

INTRODUCTION

Chapter 2

HYDRAZIDES AND HYDRAZONES AS *N*-DONORS FOR AMINOCATALYTIC AZA-MICHAEL INITIATED REACTIONS

1

1

Introduction

1. ORGANOCATALYSIS

Synthetic chemistry is one of the key technologies for the discovery and development of new therapeutic compounds. Also, it should be highlighted that many of the drugs that are commercialized nowadays, as well as the ones in pre-clinical phase, are chiral compounds and therefore their biological activity and pharmacological properties depend on their spatial arrangement.[1] In this sense, and considering the ability of living beings to distinguish between the different enantiomeric forms of a given compound, each enantiomer of a drug might behave very differently *in vivo*. This is mainly the reason why over the last decades diverse regulatory agencies dedicated to the approval of new drugs[2] have been clearly toughening the requirements to commercialize drugs that may present enantioisomery.[3] Therefore, before marketing a racemic product, activities corresponding to each of the possible stereoisomers have to be evaluated, in order to make sure that none of them have harmful secondary effects. Even in the cases where this has been confirmed, commercialization of the single desired stereoisomer is highly recommended,[4] especially since 1992, when the commercialization of racemates was forbidden in those cases where both enantiomers are able to enter the life cycle or when the pure enantiomer is more effective than the racemate.

This legislation forced a significant increase in the number of enantiopure chiral drugs on the market over the last twenty years. Thus, both the relevance of

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[1] a) *Chirality and the Biological Activity of Drugs* (Ed.: Crossley, R.), CRS-Press, **1995**; b) Crossley, R. *Tetrahedron*, **1992**, *48*, 8155.

[2] Is the case of the American agency "Food and Drugs Administration" (FDA) and the "European Committee for Proprietary Medicinal Products" (CPMP).

[3] *Asymmetric Synthesis of Natural Products* (Ed.: Koskinen, A.), John Wiley and Sons, New York, **1993**.

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

asymmetric synthesis as a fundamental tool for the stereoselective preparation of chiral compounds, as well as the development of new technologies for an easier separation of enantiomers from a racemic mixture have also been increased. Some of the techniques employed in asymmetric synthesis, *e.g.* chiral auxiliaries or the chiral pool strategy, have been firmly established in industrial processes.[5] Referring to asymmetric catalysis, enzymatic transformations[6] and metal catalysts[7] have been shown to be useful tools for the synthetic organic chemists and the pharmacological industry. In addition, recent advances in the area of asymmetric catalysis have generated a third field, *organocatalysis*, where small chiral organic molecules, which do not contain any metal element in their active site, are able to act as catalytic species in diverse organic transformations.

The first work describing an enantioselective C-C bond formation using a small chiral organic molecule for induction of stereoselectivity dates back to 1913. Bredig and Fiske showed that addition of HCN to benzaldehyde was accelerated in the presence of quinine or quinidine (Scheme 1.1).[8] The resulting cyanohydrins were optically active, and moreover, they presented opposite chirality. Even though the

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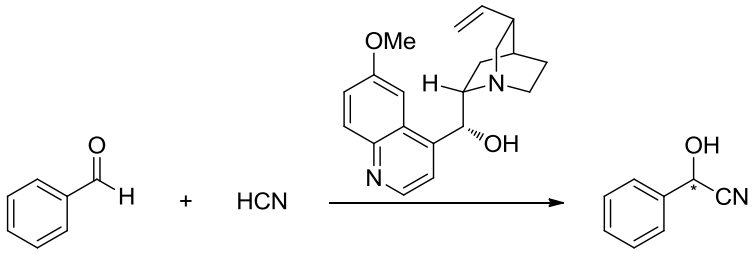
[5] a) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006,** *106*, 2734; b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3224; c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788; d) Beck, G. *Synlett* **2002**, *6*, 837; e) Kotha, S. *Tetrahedron* **1994**, *50*, 3639; f) Crosby, J. *Tetrahedron* **1991**, *47*, 4789.

[6] Enzymatic catalysis: a) Muhammad, M.; Noriho, K.; Masahiro, G. *Org. Biomol. Chem.* **2010**, *8*, 2887; b) Junhua, T.; Zhao, L.; Ran, N. *Org. Process Res. Dev.* **2007**, *11*, 259; b) *Enzyme Catalysis in Organic Chemistry*, 2nd ed. (Eds.: Drauz, K.; Waldmann, H.), Wiley-VCH, Weinheim, **2002**; c) *Biocatalysis for Fine Chemicals Synthesis* (Ed.: Roberts, S. M.), Wiley-VCH, New York, **1999**.

[7] Metal catalysis: a) *Transition Metals for Organic Synthesis*, 2nd ed. (Eds.: Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **2004**; b) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: Ojima, I.), Wiley-VCH, New York, **2000**; c) *Comprehensive Asymmetric Catalysis* (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**; d) *Asymmetric Catalysis in Organic Synthesis* (Ed.: Noyori, R.), Wiley, New York, **1994**.

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

enantiomeric excess shown by this reaction was very poor, the work is still considered as the proof of principle for the future investigations in this field.



Scheme 1.1

After a series of important contributions to the field between the 20's and the 40's, Langebeck introduced the term "organic catalysis" to define every reaction promoted by organic compounds. In his book entitled "*Organic Catalysts and their Relations with Enzymes*",[9] he established relations between the mechanisms of enzymatic reactions and those of reactions promoted by certain organic catalysts. In a different context, Pracejus published in 1960 what can be considered as the first organocatalyzed reaction with a remarkable level of enantioselectivity. Methanol was added to methylphenylketene, also employing an alkaloid derivative (*O*-acetylquinine) as a promoter, obtaining a 74% ee in the final product, which was determined by comparison of optical rotation data (Scheme 1.2).[10]

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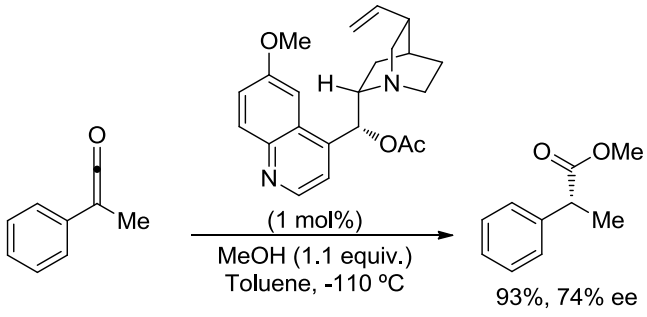
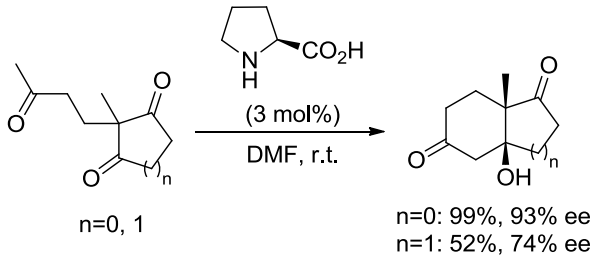
[9] *Die Organiche Katalysatoren und ihre Beziehungen zu den Fermenten* (Ed.: Langebeck, W.), Springer-Verlag, Berlin, **1949**.

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



Scheme 1.2

One of the most important landmarks for the development of organocatalysis was published in 1971 independently by two industry groups working at Hoffman-LaRoche[11] and Schering.[12] The reaction (now termed the Hajos-Parrish-Eder-Sauer-Wiecher reaction) consisted of a proline-catalyzed intramolecular aldol reaction, directed to the synthesis of chiral intermediates necessary for the preparation of steroids (Scheme 1.3).



Scheme 1.3

[11] a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; b) Hajos, Z. G.; Parrish, D. R. *Ger. Offen.* DE 2102623, **1971**.

[12] a) Eder, U.; Sauer, U.; Wiechert, U. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; b) Eder, U.; Sauer, G.; Wiechert, R. *Ger. Offen.* DE 2014757, **1971**.

Other important contributions to the field took place from the 80's to the late 90's. For example, the enantioselective alkylation of enolates was carried out employing quaternary ammonium salts based on cinchona alkaloids as catalysts, under phase-transfer conditions.[13] Also, the use of chiral Brønsted acids for the asymmetric hydrocyanation of aldehydes and imines was presented by Inoue[14] and Jacobsen.[15] However, the organocatalysis concept as we know it nowadays was not recognized and incorporated to the organic chemists toolbox until the year 2000, when two seminal papers studying the potential of aminocatalysis were published; one by List and Barbas III and the other by MacMillan. In the first one, List and Barbas III described the first proline-catalyzed intermolecular enantioselective aldol reaction, employing the activation method today widely known as enamine catalysis (Scheme 1.4).[16] Actually, this reaction is the culmination of a research that started with the use of aldolase antibodies as catalysts for aldol reactions.[17] Mechanistic studies were carried out to determine the exact role played by the antibody during the catalytic process, which demonstrated that enamine intermediates were present in the reaction. Thus, in a trial to mimic the behaviour of those antibodies, they observed that a simple aminoacid (*i.e.* proline) was able to catalyze these intermolecular aldol reactions.[18] The promising results obtained by List and Barbas III provided an exponential increase in the application of the concept to the proline-catalyzed α-functionalization of aldehydes and ketones, where enamine

[13] a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; b) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710; c) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

[14] Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229.

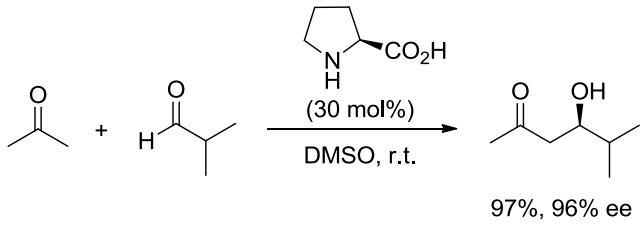
[15] a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; b) Sigman, M. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

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

[17] For the pioneering report, see: Von der Osten, C. H.; Sinskey, A. J.; Barbas III, C. F.; Pederson, R. L.; Wang, Y. F.; Wong, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 3924.

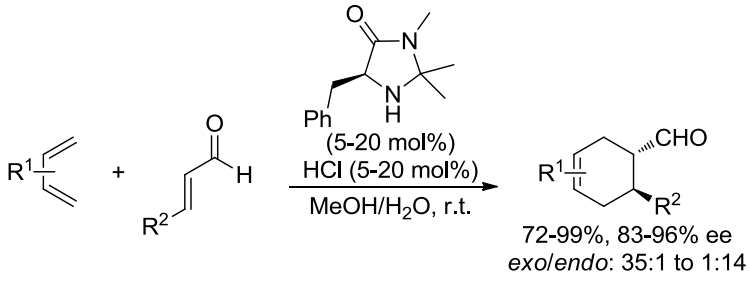
[18] For a full account regarding the evolution of the reseach made by Barbas III and co-workers from aldolase antibodies to proline, see: Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42.

intermediates would be able to act as potential nucleophiles reacting with a variety of electrophiles (*e.g.* Mannich, Michael, α-functionalization, etc.).



Scheme 1.4

On the other hand, the contribution by MacMillan described the first organocatalytic Diels-Alder reaction catalyzed by a secondary amine derived from phenylalanine, an imidazolidin-2-one, thus introducing a new concept: iminium catalysis (Scheme 1.5).[19] Multiple applications for this catalyst, and other related secondary amines working under this activation manifold, followed this work, demonstrating the power and efficiency of this approach to a platform of organic reactions.



Scheme 1.5

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

These two publications brought a considerable growth to the field of organocatalysis and, specifically, to asymmetric catalysis mediated by secondary amines. Today, organocatalysis is considered, together with the previously mentioned metal catalysis and enzymatic catalysis, as one of the most important branches for the enantioselective synthesis of chiral compounds, and it is widely utilized in the preparation of chiral molecules.[20] The major reason for this exponential development in the field falls on the fact that this methodology presents numerous advantages with respect to the use of biocatalysis or transition metal catalysis. Organocatalysts are normally inherently stable molecules, relatively inexpensive and easier to synthesize than the corresponding metal complexes that catalyze the same process. Also, they can be employed under milder and less rigorous conditions, since generally they allow presence of atmospheric moisture and oxygen in the reaction. Additionally, the absence of metals in the reaction environment turns the organocatalysis into an extremely attractive method for the preparation of products in which the final formulation does not allow the presence of metals even in trace amounts, such as pharmaceutical drugs. Referring to the advantages with respect to biocatalysis we could highlight the necessity of a specific catalyst for each substrate or particular reaction, due to the extremely high specificity of enzymatic catalysts, which is not the case when using organocatalysis. In addition, reactions catalyzed by enzymes need to be carried out in an aqueous buffered media, which is often problematic due to the low solubility of organic

[20] For some general reviews on organocatalysis, see: a) Jacobsen, E. N.; MacMillan, D. W. C *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618; b) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138; c) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) *Enantioselective Organocatalysis* (Ed.: Dalko, P. I.), Wiley-VCH, Weinheim, **2007**; e) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267; f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2006**, *12*, 8; g) List, B. *Chem. Commun.* **2006**, 819; h) *Asymmetric Organocatalysis* (Eds.: Berkessel, A.; Gröger, H.), Wiley-VCH, Weinheim, **2005**; For a review on mechanistic aspects of organocatalysis, see: i) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Celebi-Olcum, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042.

compounds in water. In this sense, the advantages offered by the use of organocatalysis seem evident, foregoing many of the inconveniences of utilizing transition metal complexes or biocatalysis.

However, this is still a relatively recent research area with several aspects that can be improved upon. First of all, we should mention that the amounts of catalyst required for organocatalytic processes are normally high when comparing to the typical catalyst loadings required with metal catalysts. Moreover, reaction times are usually rather long, with many reactions requiring a run length of several days in order to attain completion. The issue of catalyst loading has been addressed by promoting catalyst recycling. However, whereas this might be important for those cases where the catalysts are expensive (*e.g.* phosphoric acids), normally most catalysts (*i.e.* proline derivatives) are not recovered from the reactions since this process would result in similar cost to that of their initial purchase/synthesis. Another important drawback of organocatalysis to be considered is that the catalytic activity is generally highly dependant on the functionalities of the substrates used and actual reactions performed. It would be very interesting to design a catalyst that could be applied to a large diversity of substrates and reaction types. Finally, we should also highlight the necessity to further promote the effectiveness and relevance of organocatalytic reactions (*i.e.* trying to apply the new methodologies reported to the synthesis of natural products or compounds of high importance). In the same context, the feasability of reaction scale-up is an area that requires further investigation, in order to increase their applicability in the industrial area. The number of examples of this type is still limited; but it should be pointed out that this issue has received noticeable interest in recent years.

2. ORGANOCATALYTIC ACTIVATION MECHANISMS

Despite the numerous advantages mentioned above, possibly the most important point for the success of the methodology was the identification of the different generic modes for activation, asymmetric induction and reactivity that organocatalysts can display within the catalytic cycle. These were obtained based on the rationalization of the experimental results from a mechanistic perspective. The value of these generic models relies on the fact that once they had been established it is relatively easy to apply them as a template towards the development of future reactions. In fact, when evaluating the vast number of publications describing organocatalytic transformations it is noteworthy that only a few distinct activation methods have been identified.

In an effort to classify the most widely used reaction mechanisms, convention dictates a differentiation between the processes involving the formation of covalent adducts between the substrate and the catalyst during the catalytic cycle, and those based on substrate-catalyst non-covalent interactions, such as hydrogen bonds or ion pairs. The former mode is known as covalent catalysis, while the latter is defined as non-covalent catalysis. Figure 1.1 shows some examples of organic catalysts employed in different activation mechanisms.

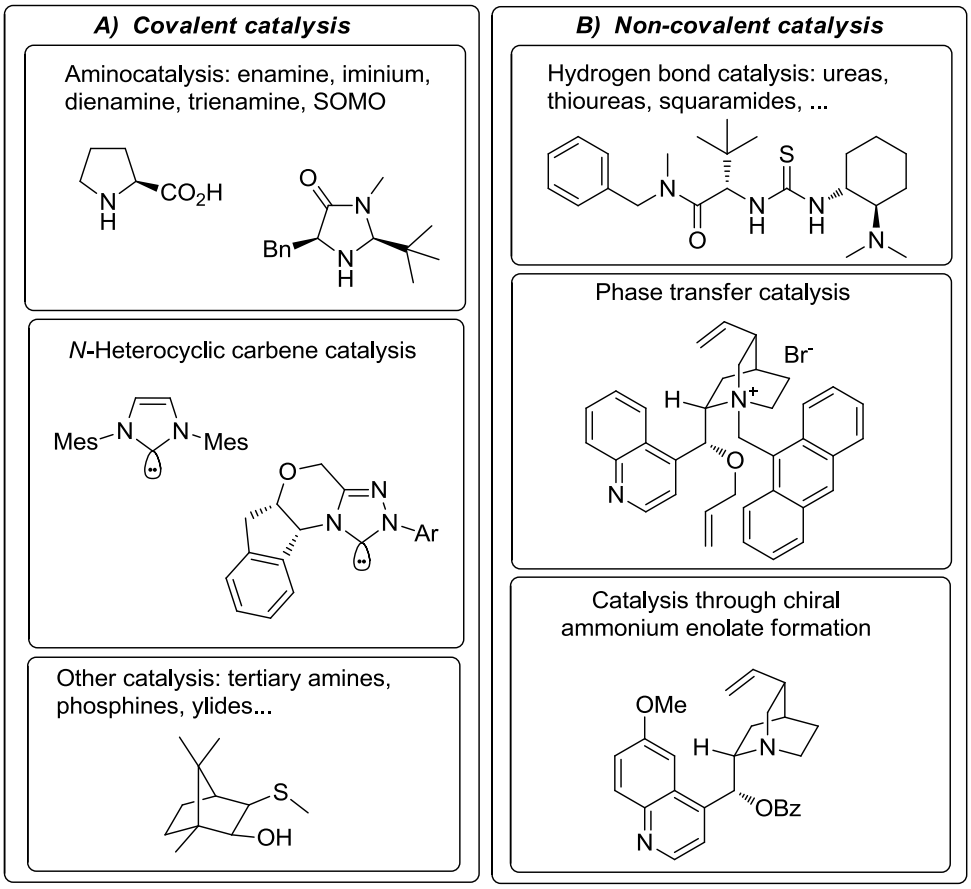


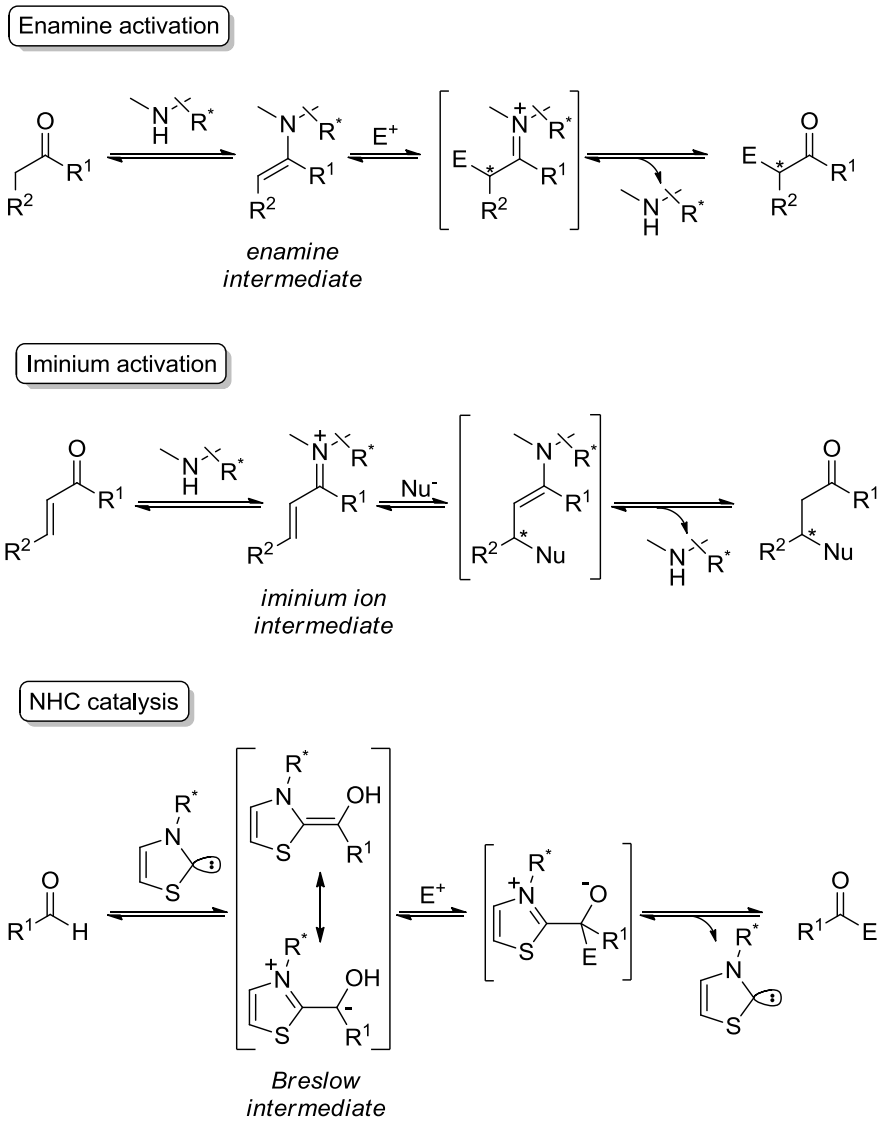
Figure 1.1

Covalent catalysis relies on the existence of a reversible reaction that will initially allow formation of the activated catalyst-substrate linked adduct, followed by formation of the desired chemical bond(s), and final cleavage of the catalyst-product covalent bond, thus regenerating the catalyst and releasing the product. Representative examples of this type of catalysis utilize primary/secondary amine catalysts (*i.e.* aminocatalysis) and catalysis employing *N*-heterocyclic carbenes.

We find a particularly relevant situation in the use of *chiral amines* as organocatalysts for multiple transformations that occur through the formation of enamine/iminium intermediate species (Scheme 1.6).[21] Reversibility of the formation of the azomethine species allows the possibility to use these amines in catalytic amounts. Also, the presence of covalent binding helps in providing effective stereoinduction to the process. However, this covalent nature of the catalyst-substrate interaction may at the same time be responsible for low catalytic turnover and high catalyst loading requirements. Since this is an important activation mode for the work to be presented in this thesis, it will be discussed in more detail later. *N-heterocyclic carbenes* (NHCs) are also included within this category.[22] In this context, an aldehyde, after covalently binding to an NHC, generates a nucleophilic intermediate (known as *Breslow intermediate*, shown in Scheme 1.6) that will be able to attack an electrophilic species. The unique activation mode portrayed by NHCs has created a large amount of interest within the organocatalysis field due to their capacity to invert the classic reactivity of aldehydes; from being typically electrophilic to behave as nucleophiles (*umpolung*).

[21] For recent reviews on aminocatalysis, see: a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen K. A. *Chem. Commun.* **2011**, *47*, 632; b) Kano, T.; Marouka, K. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1421; c) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.*, **2009**, *38*, 2178.

[22] For some reviews on *N*-heterocyclic carbenes, see: a) Bugaut, X.; Glorious, F. *Chem. Soc. Rev.* **2012**, *41*, 3511; b) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182; c) Grossman, A.; Enders, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 2; d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606; e) Marion, N.; Diéz-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; f) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534.


Enamine activation
enamine intermediate
Iminium activation
iminium ion intermediate
NHC catalysis
Breslow intermediate

Scheme 1.6

On the other hand, the category of non-covalent catalysis compiles all the organocatalytic processes based on weaker, non-covalent interactions between catalyst and substrate. In general, non-covalent catalysis requires lower catalyst loading and reaction times. This might be considered as a significant advantage compared to covalent catalysis, especially since organocatalysis has been sometimes criticized due to the relatively high catalyst loadings and extended reaction times required. However, the weaker nature of the substrate-catalyst interaction provides intermediates with higher conformational freedom, thus making it inherently more difficult for the catalysts to provide high levels of stereoinduction.

One of the most studied non-covalent organocatalytic activation methods relies on activating the substrate by forming *hydrogen bonds*.[23] Small molecules, with substructures possessing functionalities that are able to hydrogen bond with the reagents participating in the reaction, are able to catalyze a series of C-C or C-heteroatom bond forming reactions. Within this group we can find that chiral ureas, thioureas,[24] guanidines,[25] phosphoric acids,[26] squaramides,[27] and others, have been employed in many transformations due to their ability to be involved in the selective

[23] For recent reviews on hydrogen-bonding catalysis, see: a) *Hydrogen Bonding in Organic Synthesis* (Ed.: Pihko, P. M.), Wiley-VCH, Weinheim, **2009**; b) Connon, S. J. *Synlett* **2009**, 354; c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*. **2007**, *107*, 5713; d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 1520; e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal*. **2006**, *348*, 999.

[24] For specific reviews on ureas and thioureas as catalysts, see: a) Takemoto, Y. *Chem. Pharm. Bull*. **2010**, *58*, 593; b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev*. **2009**, *384*, 1187.

[25] For a specific review on guanidines as catalysts, see: Taylor, J. E.; Bull, S. D.; Williams, J. M. *J. Chem. Soc. Rev*. **2012**, *41*, 2109.

[26] For reviews on phosphoric acids as catalysts, see: a) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res*. **2011**, *44*, 1156; b) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227; c) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262; d) Terada, M. *Synthesis* **2010**, *12*, 1929; e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395.

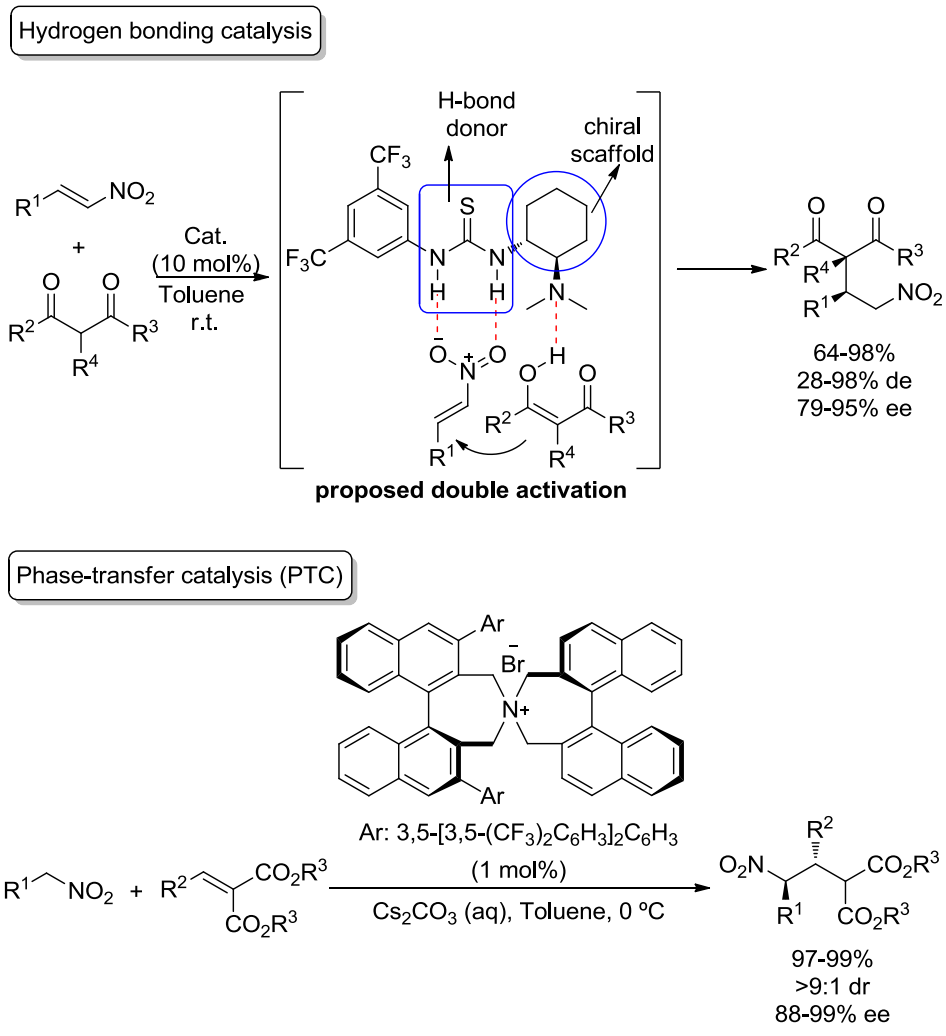
[27] For a specific review on squaramides as catalysts, see: Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 6890.

formation of hydrogen bonds with a variety of functional groups present on the substrate molecule (*e.g.* nitro, carbonyl, dicarbonyl or imine groups). These catalysts are particularly effective for the activation of the electrophilic counterpart of a polar reaction (*e.g.* electron deficient olefins in conjugate additions). These interactions release electronic density from the substrate and at the same time provide a defined spacial arrangement during the bond formation process, allowing for the high stereochemical control (for a representative example see Scheme 1.7).[28] *Phase-transfer catalysis* (PTC) is another activation method based on non-covalent substrate-catalyst interactions that could be highlighted.[29] These catalysts are typically chiral quaternary ammonium or phosphonium salts, which interact with the substrate forming substrate-catalyst chiral ion pairs. Apart from enhancing the reactivity by changing the chemical properties of the reagents, these catalysts are also able to induce a selective transfer phenomenon between two different phases. Asymmetric phase-transfer catalysis, based on the use of structurally well-defined chiral catalysts, is now a commonly employed method for a wide range of reactions. An example can also be found in the Scheme 1.7.[30]

[28] Okino, T.; Hoashi, Y.; Furukaya, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

[29] For some reviews on chiral phase-transfer catalysis, see: a) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090; b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656; b) Ooi, T.; Maruoka, K. *Aldrichim. Acta*, **2007**, *40*, 77.

[30] Takashi, O.; Shingo, F.; Keiji, M. *J. Am. Chem. Soc.* **2004**, *126*, 11790.


Hydrogen bonding catalysis
H-bond donor
chiral scaffold
Cat.
(10 mol%)
Toluene
r.t.
64-98%
28-98% de
79-95% ee
proposed double activation
Phase-transfer catalysis (PTC)
Ar: 3,5-[3,5-(CF3)2C6H3]2C6H3
(1 mol%)
Cs2CO3 (aq), Toluene, 0 ºC
97-99%
>9:1 dr
88-99% ee

Scheme 1.7

3. AMINOCATALYSIS

As it has been briefly mentioned before, aminocatalysis is that area where a primary or a secondary amine is used to activate a carbonyl compound through the formation of an azomethine intermediate, in order to facilitate a specific transformation. The two different azomethine intermediates formed in these processes allow the classification of aminocatalysis in two different activation modes: *enamine*[31] or *iminium catalysis*.[32] Also some variants of these activations have been described, such as the *SOMO catalysis*[31a,33] and the vinylogous versions (*i.e. dienamine*[34] and *vinilogous iminium*[35]), in which enamine or iminium-type intermediates are also generated. These activation methods enable the possibility to perform α-, β-, γ- and δ-functionalizations of carbonyl compounds. Specifically, when the substrate activated is a carbonyl compound, α-functionalizations can be achieved (*via* enamine and SOMO catalysis). Additionally, functionalization of α,β-unsaturated carbonyls can be performed with nucleophiles allowing substitution at

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

[32] For recent reviews on iminium catalysis, see: a) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. *Catalytic Asymmetric Conjugate Reactions* p. 219-294 (Ed.: Córdova, A.), Wiley-VCH, **2010**; b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416; c) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

[33] For some examples on SOMO catalysis, see: a) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494; b) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582; c) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004; For a highlight, see: Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356.

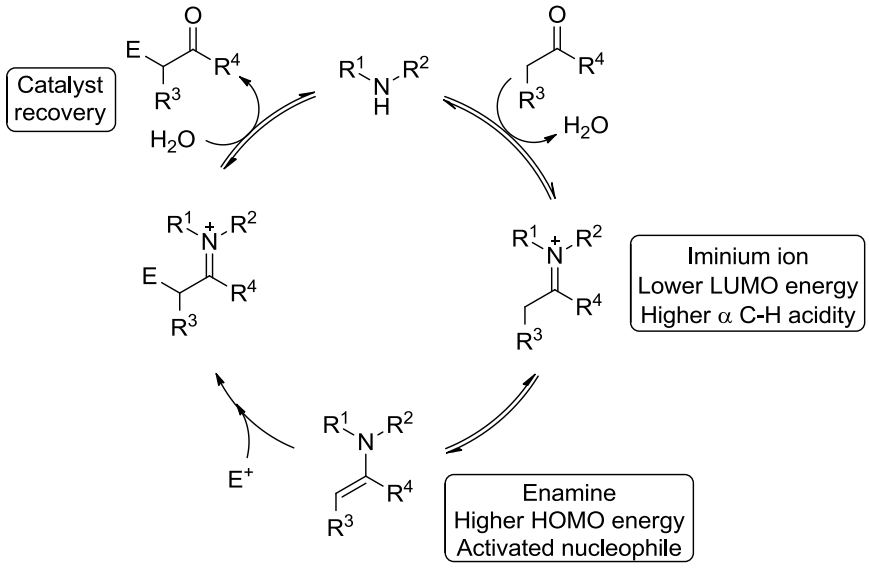
[34] For a review in diemamine catalysis, see: a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865; For pioneering work, see c) Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[35] For a pioneering example in vinilogous iminium catalysis, see: Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 6439.

the β- and δ-positions (using iminium catalysis) or with electrophiles granting γ-functionalization (using dienamine catalysis). Both enamine and iminium activation methods will be explained next, giving special interest to the iminium activation, since this is directly related to the studies carried out in the presented research work.

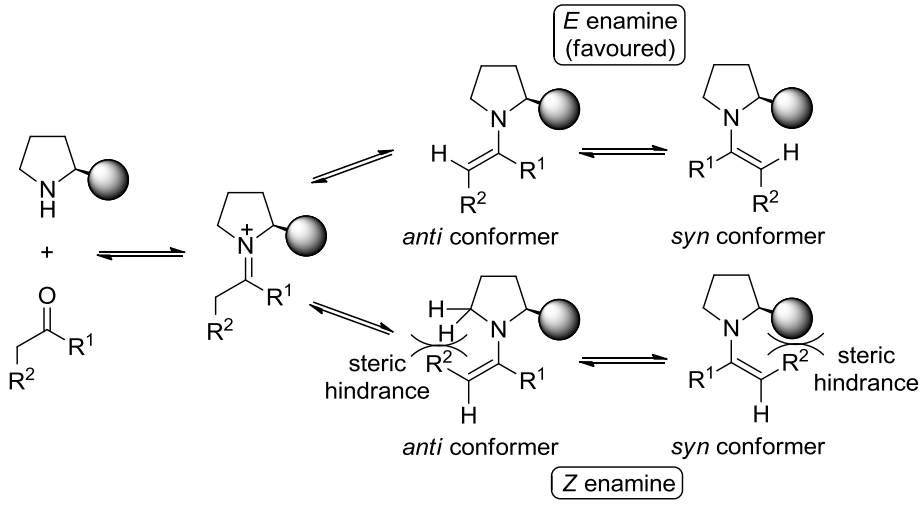
3.1. Enamine catalysis

Enamine catalysis[31] is described as the catalytic reaction that proceeds though enamine intermediates, thus, requiring a primary or secondary amine to condense with a ketone or aldehyde substrate. The basis of this activation method relies on the activation of an enolizable aldehyde or ketone by means of the reversible formation of an enamine intermediate. The key point is the initial reduction in energy of the LUMO by formation of the iminium ion (compared to the parent aldehyde/ketone) and the consequent increase in acidity of the C-H at the α-position. This will result in the formation of an enamine intermediate, where the energy of the HOMO is now higher, which in turn transforms the substrate into a much better nucleophile than the corresponding aldehyde or ketone substrate (Scheme 1.8). In the final step, as shown in the catalytic cycle, the iminium ion intermediate formed after the nucleophilic addition needs to be hydrolysed, in order to release the product and leave the catalyst ready to restart the catalytic cycle.



Scheme 1.8

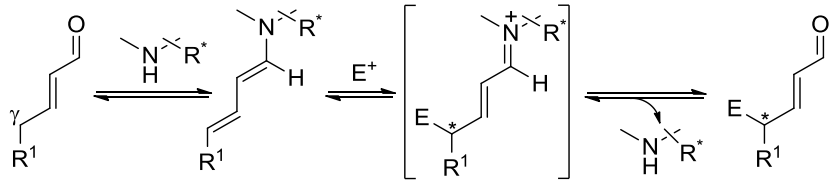
Chiral information present on the amine catalyst is responsible for the differentiation of the two faces of the enamine nucleophile, allowing the synthesis of enantioenriched compounds. In this sense, the ability of the catalyst to control the geometry of the enamine intermediate is a highly important issue, since mixtures of *Z* and *E* stereoisomers would lead to the formation of both possible enantiomers of the final product. Thus, same applies to the conformational aspects of the enamine moiety. The formation of only one of the possible conformers is essential for avoiding mixtures of stereoisomers. In this sense, the discrimination between the different possible enamine intermediate isomers can be achieved by imposing large steric constraints on the system *via* the amine catalyst (see Scheme 1.9). Alternatively, when stereodirecting elements such as hydrogen bonds are introduced to the catalyst, these interactions will be responsible for the preferential formation of the most reactive intermediate.



Scheme 1.9

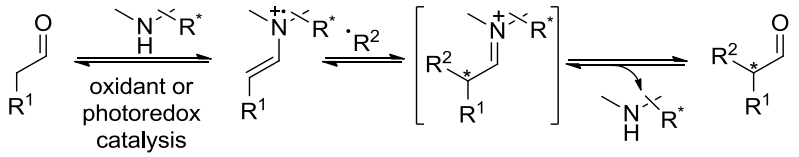
Jørgensen and co-workers first reported the vinylogous variant of enamine activation after observing a dienamine intermediate by NMR spectroscopy while performing mechanistic studies investigating the intermediates present in the organocatalytic β-functionalization of α,β-unsaturated aldehydes.[34c] The formation of this dienamine intermediate occurs if the initially formed α,β-unsaturated iminium ion undergoes deprotonation at the γ-position. This electron-rich dienamine intermediate now possesses nucleophilic character and is thus able to react with electrophiles, enabling a γ-functionalization. This discovery opened up a new activation protocol in aminocatalysis (Scheme 1.10). Enals and enones, traditionally considered as electrophiles, were now able to behave as nucleophiles. The asymmetric γ-functionalization of α,β-unsaturated aldehydes has proven to be an emerging area of interest and further applications of this activation method are

expected.[34] This concept can also be applied to extended systems, as demonstrated with some examples of reactions proceeding through trienamine intermediates.[36]



Scheme 1.10

Another variant of the enamine activation manifold arose from the development of SOMO catalysis. This method has been one of the latest activation protocols to be introduced into the field of organocatalysis.[33c] This concept shares some of the principles with the rest of the amine activation modes, while exhibiting some differences due to the involvement of radical cation intermediates. These radical species generated from enamine intermediates by oxidation are usually the ones with the lowest ionization potentials of all starting materials present. Importantly, this oxidation changes the normal electronic properties of the enamine into those of an electrophilic radical species, enabling the attack of a somophile at the α-position (see Scheme 1.11).

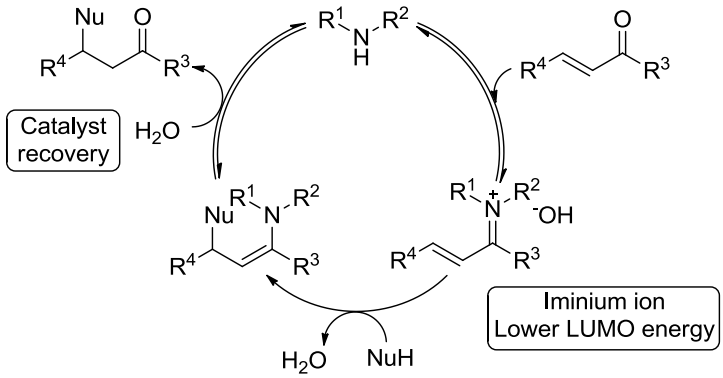


Scheme 1.11

[36] For pioneering work in trienamine activation, see: a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, 133, 5053; For other examples, see: b) Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2012**, *51*, 4401; c) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638; d) Jiang, H.; Gschwend, B.; Albrecht, L.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032.

3.2. Iminium catalysis

Iminium catalysis[32] is the second main aminocatalytic activation mode. This manifold opens the way to the activation of α,β-unsaturated aldehydes or ketones towards their participation as the electrophilic counterpart in a reaction, typically in conjugate additions. Many examples of the applicability of this activation method have been shown using different nucleophiles.[37] The catalytic cycle involved in this type of catalysis consists of the initial formation of an iminium ion, by condensation between the amine catalyst and the α,β-unsaturated aldehyde or ketone. This is the key point of the reaction, resulting in a reduction in the energy of the LUMO of the substrate, thus making these intermediates more electrophilic than the parent enal or enone. After the nucleophilic attack to the β-carbon atom of the iminium intermediate, a β-functionalized enamine intermediate is formed, in tautomeric equilibrium with the corresponding iminium ion. As in the case of enamine catalysis, the final hydrolysis step will render the expected product and release the catalyst to continue the catalytic cycle (Scheme 1.12).



Scheme 1.12

[37] *Organocatalytic Enantioslective Conjugate Addition Reactions* p. 62-111 (Eds.: Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.), RSC, **2010**.

Typically these reactions incorporate a Brønsted acid as a co-catalyst in order to obtain formation of the iminium salt more effectively. Moreover, the nature of the counterion associated with the iminium cation is an additional factor that might be considered when employing iminium activation as strategic approach. This anion might sometimes play the role of a base, assisting the deprotonation of the Michael donor, or may act as a simple spectator in the catalytic cycle. However, additional chiral information can be introduced into the reaction when taking advantage of the tight interaction existing between the iminium cation and its counterion. *Asymmetric Counterion Directed Catalysis* (ACDC) described by List in 2006,[38] relies on introducing a chiral Brønsted acid as an additive, which interacts strongly with the corresponding iminium counterion in organic non-polar solvents. This allows the use of non-chiral amines as catalysts (*e.g.* pyrrolidine or morpholine) since the chiral acid dictates the stereochemical outcome of the reaction.

In the same way as was commented for other activation methods, the role of the catalyst is not only limited to the activation of the reagents (in this case the Michael acceptor), but it should also have the ablity to provide high stereoselectivity to the process. In this sense, according to the presented catalytic cycle, the conjugate addition should be the step in which the catalyst has to play a crucial role in differentiating both diastereotopic faces of the Michael acceptor (*i.e.* the iminium ion). This way, the nucleophilic addition would occur selectively from only one of the two possible faces of the acceptor. The stereodiscrimination might be caused by two possible reasons. On the one hand, the catalyst may contain a strategically introduced large substituent that disfavours the approach of the nucleophile from the side of the molecule possessing the large steric presence. Alternatively, a substituent able to play a stereodirecting role might be introduced to the catalyst, resulting in

[38] a) Wang, X.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 1119; b) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; c) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

the nucleophile adding to same face of the molecule assisted by secondary interactions – *e.g.* hydrogen bonds (see Figure 1.2). Importantly, we also need to consider that all the steps in the catalytic cycle might be reversible, which would result in the epimerization of the newly formed stereogenic center, even if it had been selectively generated initially. For most of the cases this will not be a problem, since the addition process will be an irreversible process and the rate-determining step. However, some reactions such as the hetero-Michael reaction, where the conjugate addition step can be reversible, will present an additional complication when trying to obtain an efficient stereochemical control.

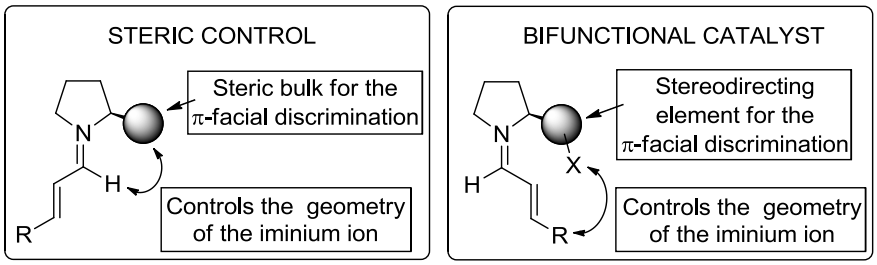


Figure 1.2

Another important factor to be taken into consideration is that the catalyst has to be able to generate a single iminium ion out of the possible geometries (*i.e. Z* and *E*). This is not an important factor when bifunctional catalysts are employed, where the directing group will determine the configuration of the reactive iminium ion. However, it is crucial when catalysts are designed based on facial differentiation by steric effects, since the volume of the bulky substituent present on the catalyst has to be large enough to provide good π-facial discrimination, as well as to determine the geometry of the iminium ion. In the case of enals, iminium geometry control is relatively easy due to the disparagy between the volume of both substituents at either side of the carbonyl group (*i.e.* H *vs.* alkenyl).

Many different catalysts have been strategically designed in order to avoid these problems and obtain high stereocontrol. Catalysts derived from α,α-diarylprolinols, such as the ones shown in Figure 1.3,[39] have been shown to promote a wide range of reactions involving iminium activation of enals very efficiently.[40] α,β-Unsaturated aldehydes undergo rapid condensation with these secondary amines, ensuring a high activity of the electrophiles. In terms of stereocontrol, their success is explained mainly due to the incorporation of a bulky group in the C-2 position of the pyrrolidine ring. These groups are able to efficiently control the *Z*/*E* geometry of the iminium ion and sterically block the access to one of the faces from attack by the nucleophile.

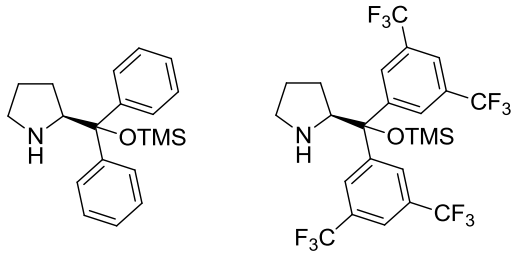


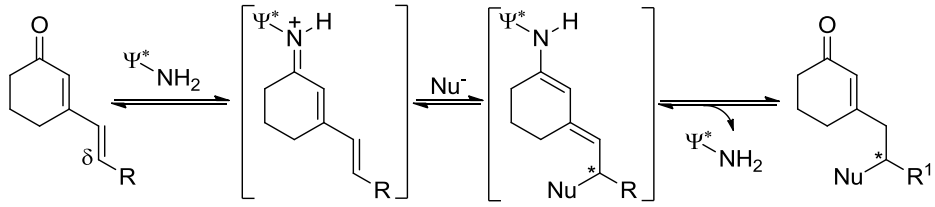
Figure 1.3

Recently, the vinylogous concept has also been applied to this activation manifold. In this context, the LUMO-lowering activation effect associated with iminium ion formation can be transmitted through the conjugated π-system of 2,4-dienones upon selective condensation with a primary amine catalyst.[35] The resulting activated vinylogous iminium ion provided the first example of an asymmetric

[39] These catalysts were developed by the groups of Jørgensen and Hayashi, see: a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[40] For some reviews covering general aspects and uses of these catalysts, see: a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248; b) Lattanzi, A. *Chem. Commun.* **2009**, 1452; c) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922; d) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, 45, 7876.

organocatalytic 1,6-addition proceeding with high stereocontrol and good selectivity (see Scheme 1.13).



Scheme 1.13

4. PRECEDENTS AND OBJECTIVES

4.1. Prior work of the group

Historically, our reasearch group has focussed on the development of new methodologies in asymmetric synthesis and their application to the synthesis of chiral building blocks and natural products. Initially the group chose the chiral auxiliary strategy to obtain stereocontrol. In this sense, the aminoalcohol (*S*,*S*)-(+)-pseudoephedrine was successfully applied to the development of methodologies that allowed us to conduct standard enolate chemistry in a stereoselective manner – *i.e.* aldol,[41] Mannich,[42] electrophilic amination[43] or aziridine ring opening[44] reactions. The excellent stereocontrol was a result of the auxiliary binding to the nucleophilic component of the corresponding reactions. Moreover, the same auxiliary was proven to be very effective for diverse conjugate addition reactions, now incorporated into the electrophilic α,β-unsaturated carbonyl substrate. In this case,

[41] a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460; b) Rodríguez, M.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Biomol. Chem.* **2005**, *10*, 2026; c) Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171; d) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754; e) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron Lett.* **1998**, *39*, 9267.

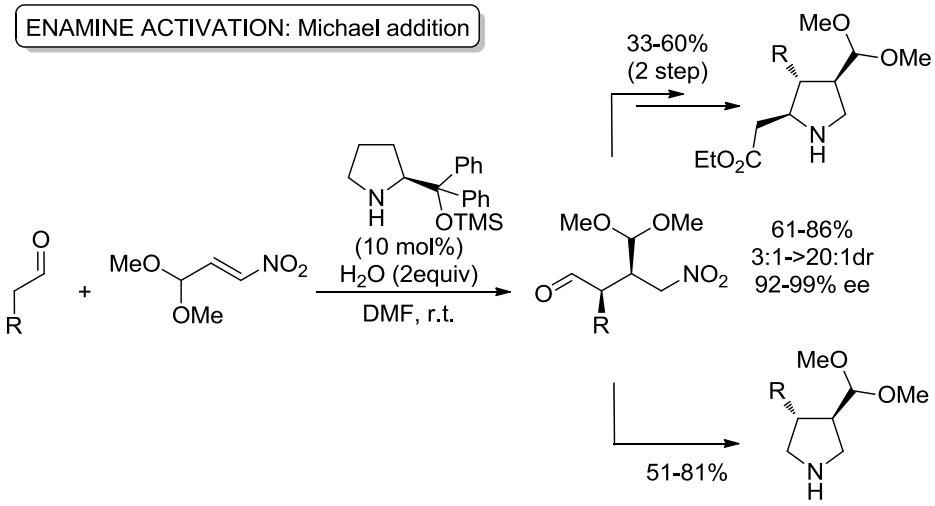
[42] a) Iza, A.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2006**, 4065; b) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773; c) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030.

[43] a) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745; b) Anakabe, E.; Vicario, J. L; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343; c) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron Lett.* **1999**, *40*, 7123.

[44] Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

conjugate addition of organolithium compounds,[45] 1,4-addition/α-alkylation tandem reactions[46] or aza-Michael reactions[47] were developed with very good results.

However, more recently we moved to the field of asymmetric catalysis and more specifically, to the organocatalysis. In this sense, the group made the first steps in the area using the *enamine activation* manifold for the development of a Michael reaction between aldehydes and β-nitroacrolein dimethyl acetal (see Scheme 1.14).[48] Also, a simple protocol for the synthesis of highly functionalized enantiopure pyrrolidines was designed, starting from the Michael adducts obtained from this method.



Scheme 1.14

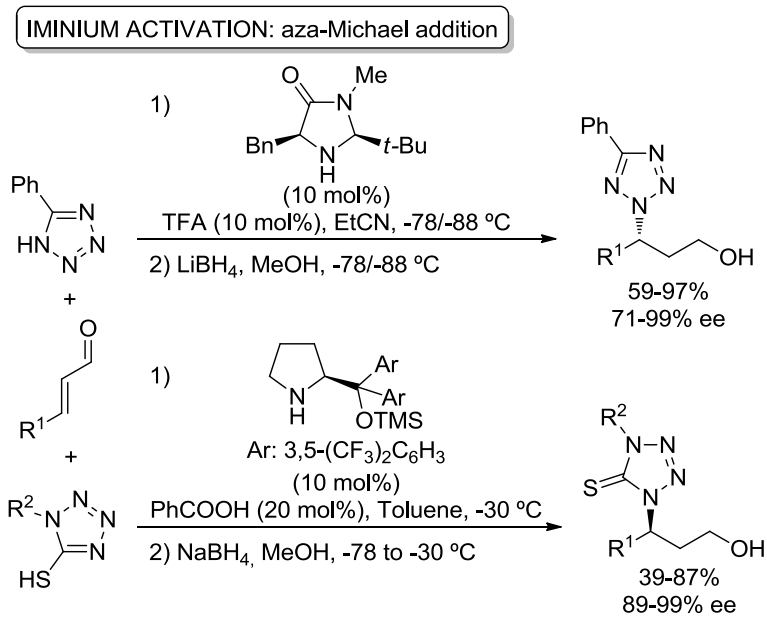
[45] a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404; b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763.

[46] Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535.

[47] a) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790; b) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588.

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

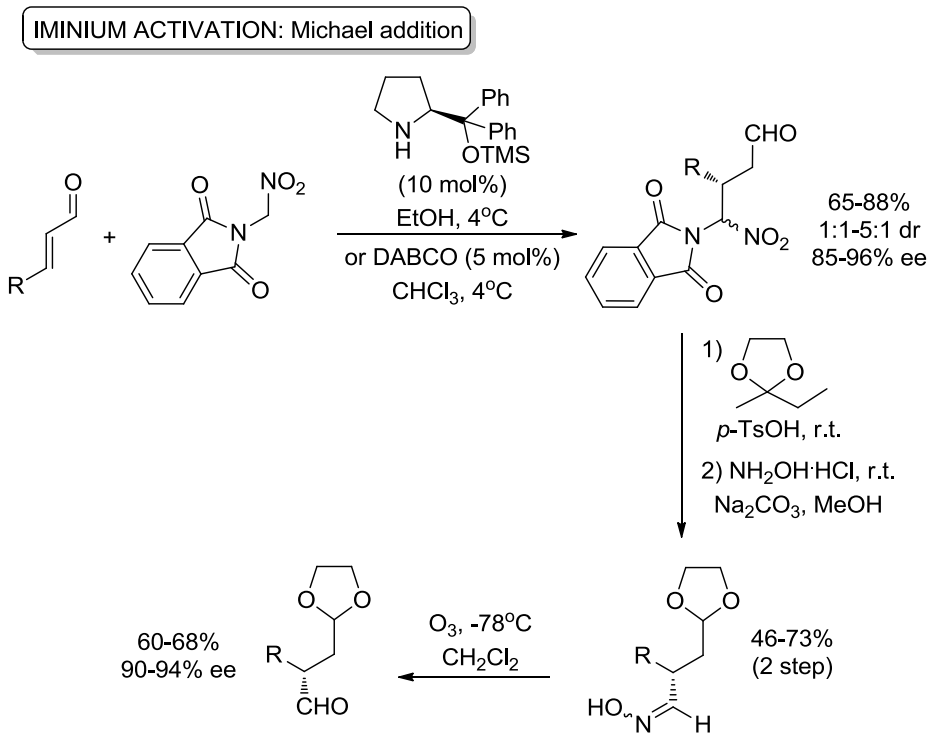
The *iminium activation* approach has also been widely explored in the group. In this sense, procedures for performing Michael and aza-Michael reactions have been developed. In the case of the aza-Michael reaction, different nitrogen heterocycles were used as pro-nucleophiles in conjuction with α,β-unsaturated aldehydes (see Scheme 1.15). During these investigations, MacMillan's catalyst was shown to promote the conjugate addition of 5-phenyl-1*H*-tetrazol to enals,[49] whereas an *O*-trimethylsilyl diarylprolinol catalyst was required when differently substituted 1*H*-tetrazol-5-(4*H*)-thiones were employed as Michael donors in the same reaction. In addition, the products obtained when using these types of heterocycles were shown to be excellent precursors for the synthesis of molecules of high synthetic interest.[50]



Scheme 1.15

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

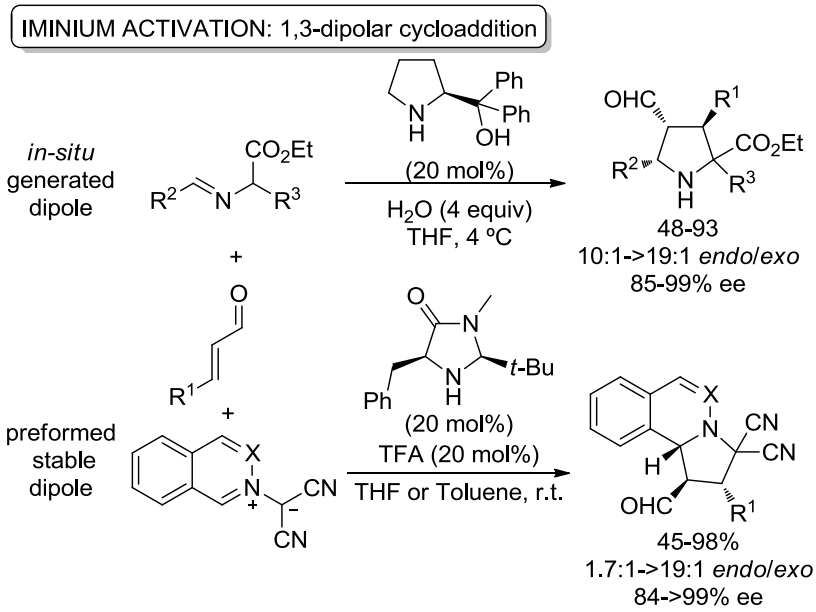
In reference to the Michael addition, a protocol for the formal conjugate addition of a hydroxymoyl anion to α,β-unsaturated aldehydes has been recently developed. Specifically, *N*-nitromethylphthalamide was employed as a synthetic equivalent of the *N*-hydroxyiminomethyl group (Scheme 1.16).[51] This reaction allowed access to chiral functionalized oximes that could subsequently be transformed in order to reveal the masked formyl group, leading to the generation of chiral butanedials in which both formyl groups were chemically differentiated.



Scheme 1.16

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

The iminium activation concept has also been effective in the development of 1,3-dipolar cycloaddition reactions (shown on Scheme 1.17). In this sense, our group has reported a highly efficient diphenylprolinol-catalyzed [3+2] cycloaddition with α,β-unsaturated aldehydes and azomethine ylides, which are generated *in situ* from aminomalonate imines.[52] Alternatively, stable azomethine ylides, such as isoquinolinium and phthalizinium methylides, have also been employed with success in the same reaction; this case required the use of MacMillan's second-generation catalyst.[53]



Scheme 1.17

[52] a) Reboredo, S.; Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Cat.* **2011**, *353*, 3307; b) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[53] Fernández, N.; Carrillo, L.; Vicario, J. L.; Badia, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313.

The potential of these reactions encouraged the group to look into the mechanistic insights of the aminocatalytic dipolar cycloaddition, taking the reaction of the azomethine ylides as a model.[54] DFT calculations suggested that the reaction should actually be understood as a Michael-initiated domino process in which iminium and enamine activations were combined in a typical cascade process. This increased our enthusiam on the study of new cascade reactions by combining the different activation methods of the aminocatalysis. This strategy allows the synthesis of complex molecules starting from very simple precursors, by processes where several bonds and stereogenic centers will be formed concomitantly and selectively.

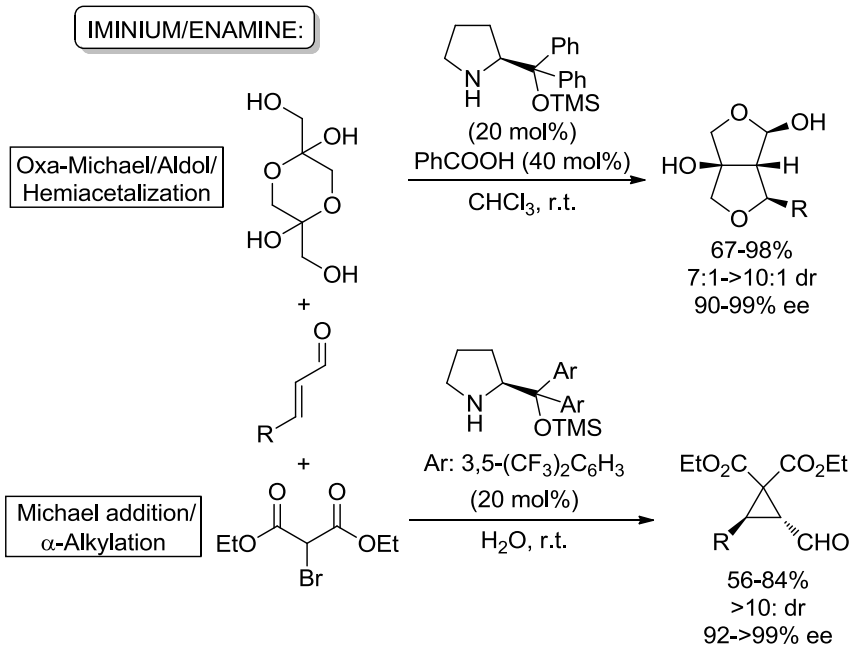
In this sense, several cascade processes have been developed in our group, with the *iminium/enamine manifold* successfully applied to the enantioselective synthesis of complex furofuranes from the reaction of dihydroxyacetone with α,β-unsaturated aldehydes (see Scheme 1.18).[55] In this transformation, the iminium-catalyzed initial oxa-Michael step was followed by an intramolecular enamine-promoted aldol reaction and a final hemiacetalization process. In this single reaction step two new C-O bonds, a C-C bond, and four stereogenic centers were simultaneously created. The same activation strategy was applied to the synthesis of enantiomerically enriched polyfunctionalized cyclopropanes.[56] This time, the reaction can be rationalized by means of an initial iminium ion-assisted conjugate addition of bromomalonate to the enal, followed by intramolecular α-alkylation of

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

[55] Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701. Highlighted in *Synfacts* **2009**, *9*, 1032.

[56] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701.

the resulting enamine intermediate. In this case, a single reaction step provides two new C-C bonds and two stereogenic centers (Scheme 1.18).

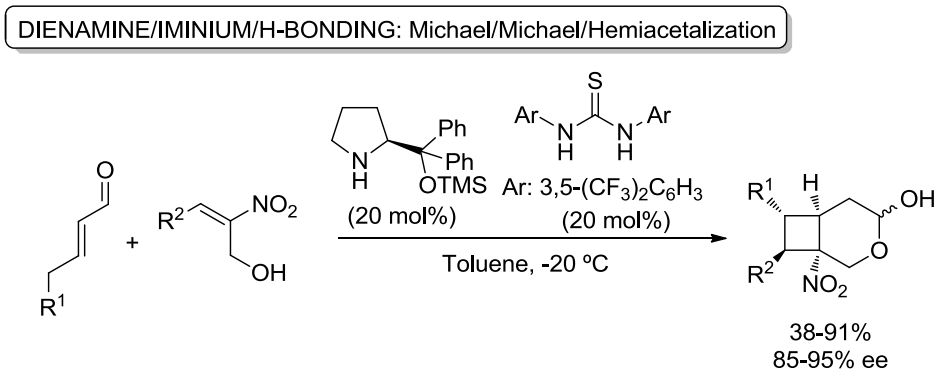


Scheme 1.18

Finally, the group has also succeded in the combined application of a *dienamine/iminium manifold*. In this case, a reaction between enals and α-hydroxymethylnitrostyrenes, in essence a formal [2+2] cycloaddition, led to the synthesis of enantioenriched cyclobutanes (Scheme 1.19).[57] Specifically, the reaction consists of an initial Michael addition of the enal to the nitroalkene (*i.e.* γ-functionalization of α,β-unsaturated aldehydes) followed by the intramolecular

[57] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104. Highlighted in *Synfacts* **2012**, *8*, 674.

addition of the nitronate to the iminium intermediate. Finally, the hydroxy group reacts in an intramolecular fashion with the formyl moiety in a hemiacetalization process.



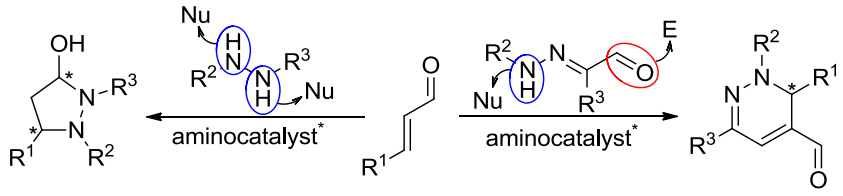
Scheme 1.19

4.2. General objectives of the present work

The work summarized in this thesis has been carried out in line with the recent research activity of the group. Therefore, we will focus on the development of new asymmetric methodologies, employing asymmetric organocatalysis as the main tool. More specifically, given the experience of the group with conjugate addition reactions and the synthetic potential that the transformation provides, the work will approach the use of hydrazides and hydrazones as pro-nucleophiles for conjugate addition reactions to α,β-unsaturated aldehydes, using the iminium activation catalytic strategy. Specifically, the thesis will be divided into two different parts:

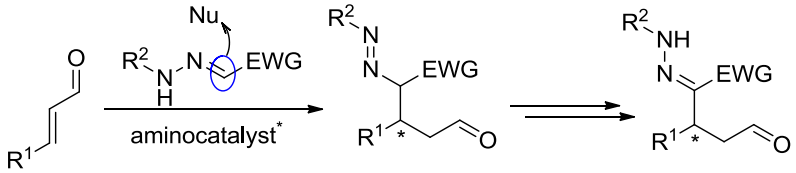
The **first general objective** will be to develop new methodologies to carry out aminocatalyzed aza-Michael initiated domino processes with enals, using

hydrazides and hydrazones as nitrogen pro-nucleophiles. In this sense, hydrazides will play the role of a double nitrogen pro-nucleophile, enabling a conjugate addition/intramolecular 1,2-addition sequence under iminium activation, whereas the hydrazones will incorporate an electrophilic carbonyl moiety in their structure that will allow an aza-Michael/aldol reaction cascade process under iminium/enamine manifold.



Scheme 1.20

For the **second** part of this work, the **general objective** will be to design a new methodology for the conjugate addition of acyl anion equivalents to enals under iminium activation, employing *hydrazones as umpolung carbon nucleophiles*. We have discovered that hydrazones containing an electron-withdrawing group at the azomethine carbon present enhanced nucleophilicity at this position, favouring their performance as Michael donors.



Scheme 1.21

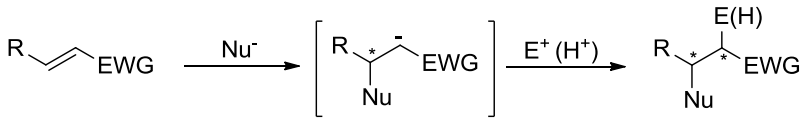
2

2

Hydrazides and hydrazones as *N*-donors for aminocatalytic aza-Michael initiated reactions

1. INTRODUCTION: AMINOCATALYTIC AZA-MICHAEL REACTIONS

The conjugate addition reaction of nucleophiles to α,β-unsaturated carbonyl compounds is one the most prevalent methods for the formation of carbon-carbon or carbon-heteroatom bonds.[1] This transformation consists of the addition of a nucleophile to an electron deficient C-C double bond that is attached to an electron-withdrawing group. During the addition process an anionic species is formed, which subsequently reacts with an electrophile; a proton in the simplest case (see Scheme 2.1). Considering the great potential that the reaction offers, together with the large variety of donor and acceptor substrates that may be employed, this methodology has been applied to the synthesis of numerous biologically active molecules. The nucleophile can be a simple hydride or can be centered at a carbon or heteroatom (*i.e.* N, O, S, Si, P, Se, Sn, I). However, the diversity of the acceptor species relies on the electron-withdrawing ability of the group attached to the double bond that promotes the electrophilic nature of the olefinic system (*e.g.* carbonyl, nitrile, nitro, sulfonate, sulfoxide, phosphate, phosphonate, etc.).



EWG = -CHO, -COR, -COOR, -$CONR_2$, -NO_2, ...
Nu^-= H^-, ROH, RNH_2, RSH, ...

Scheme 2.1

[1] For reviews on conjugate addition reactions, see: a) Nguyen, B. N.; Hii, K. K.; Szymanski, W.; Janssen, D. B. *Science of Synthesis, Stereoselective Synthesis* vol. 1, p. 571-688 (Eds.: De Vries, J. G.; Molander, G. A.; Evans, P. A.), **2011**; b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933; c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; d) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis* (Eds.: Baldwin, J. E.; Magnus, P. D.), Pergamon Press, Oxford, **1992**.

Amongst the variety of conjugate addition reactions, we will focus on the addition of nitrogen nucleophiles to the β-carbon of an olefin attached to an electron-withdrawing group, which is also known as the aza-Michael reaction.[2] This methodology has proven to be very convenient for the direct introduction of nitrogen containing functional groups, due to its simplicity and atom economy. In fact, this reaction presents a very attractive method for the synthesis of β-amino carbonyl compounds (*e.g.* β-amino acids and their derivatives), which are compounds with high synthetic and pharmacological interest, being well represented in both natural products and drug molecules.[3]

In this context, we could say that the use of organocatalysts for promoting the aza-Michael reaction in an enantioselective fashion presents an important alternative to the previously reported methodologies.[4] Encouraged by the interesting pioneering precedents, mild reaction conditions, improved operational simplicity and the robustness of organocatalysts, many researchers have focused their efforts to the exploration of new organocatalytic versions of the aza-Michael reaction. This is translated into a growing number of examples describing new synthetic

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[2] For some reviews on aza-Michael reactions, see: a) Rulev, A. Y. *Russ. Chem. Rev.* **2011**, *80*, 197; b) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657; c) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proc. Int.* **2005**, *37*, 513; d) Xu, L. -W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633.

[3] For some reviews on the synthesis of β-amino carbonyl compounds, see: a) Ma, J. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290; b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1; d) *Enantioselective Synthesis of β-Amino Acids* (Ed.: Juaristi, E.), Wiley-VCH, New York, **1997**; e) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117; f) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517; g) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.

[4] For reviews on organocatalytic conjugate additions, see: a) *Organocatalytic Enantioslective Conjugate Addition Reactions* p. 62-111 (Eds.: Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.), RSC, **2010**; b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065; c) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

methodologies for carrying out organocatalytic aza-Michael reactions. [5] Also, very interesting applications of this new methodological approach have been reported, directed to the synthesis of valuable compounds.

As have been mentioned in the previous chapter, different organocatalytic activation methods can be employed for increasing the reactivity of the substrates participating in a given reaction. In the particular case of the enantioselective aza-Michael reaction, a variety of organocatalytic activation methods have been applied to activate the reagents through both non-covalent and covalent interactions.

Considering that iminium activation is the most relevant activation mode for the present work, and due to the large amount of examples of organocatalytic asymmetric aza-Michael reactions described to date, the next section will cover the methodologies reported for the aminocatalytic aza-Michael reaction exclusively. The literature examples presented will be classified considering the aminocatalysts employed (*i.e.* primary or secondary amines).

1.1. Chiral secondary amines as catalysts: aza-Michael reaction with α,β-unsaturated aldehydes

The first enantioselective aza-Michael reaction catalyzed by a secondary amine was developed much later than other related aminocatalyzed conjugate addition reactions. The primary reason for this is a chemoselectivity issue arising from this specific conjugate addition approach, since both the nucleophile and the catalyst are amines. In order to carry out the reaction efficiently, the chiral amine chosen as catalyst has to be able to form an iminium ion and avoid its participation

[5] For some reviews on organocatalytic aza-Michael reactions, see: a) Reyes, E.; Fernández, M.; Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Curr. Org. Chem.* **2012**, *16*, 521; b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058.

as a nucleophile in an 1,4-addition process, since this would lead to catalyst consumption. Additionally, the amine that will act as a nucleophile has to provide the conjugate addition selectively without taking part in the iminium ion formation, in order to avoid the formation of an achiral intermediate that would deliver a racemic product (see Figure 2.1).

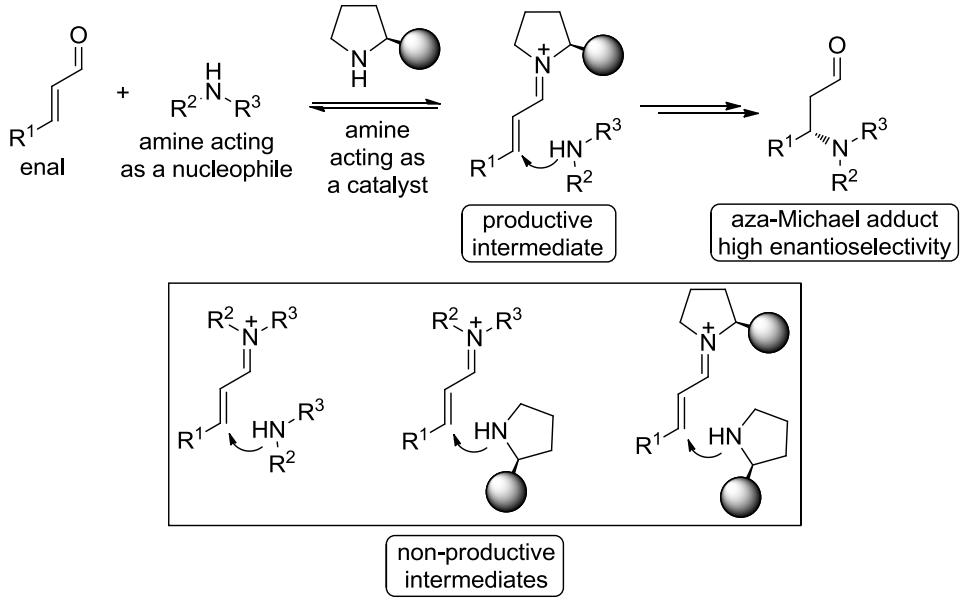

Figure 2.1

Another important problem of this transformation is the inherent reversibility of the aza-Michael reaction, which may lead to configurationally unstable conjugate adducts due to the high tendency towards racemization *via* a competitive uncatalyzed retro-aza-Michael/aza-Michael pathway. This racemization can be avoided by carefully selecting the nucleophile and/or by carrying out a subsequent reaction on the conjugate addition product either in a one-pot manner or by using

polyfunctionalized reagents that have the capability to engage in a multi-step cascade sequence.

Nevertheless, despite the highly challenging nature of the application of the iminium activation concept to aza-Michael reactions, many important and very successful examples have been reported.

1.1.1. Intermolecular reactions

MacMillan and co-workers described the first aminocatalytic enantioselective aza-Michael reaction in 2006.[6] This pioneering report addressed the addition of *N*-trialkylsilyloxycarbamates to α,β-unsaturated aldehydes using a chiral imidazolidinone as the catalyst. The nucleophile was rationally designed in order to avoid the chemoselectivity issues described above. First of all, the electron-donating $OSiR_3$ functionality at nitrogen provided an enhanced nucleophilic character to the nitrogen (*via* the α-effect) that also increased the tendency of the nucleophile to undergo 1,4- rather than 1,2-addition. Moreover, an alkoxycarbonyl motif was also incorporated to the nitrogen atom, which produced a non-basic *N*-protected carbamate addition product that minimized the reversibility of the reaction. As shown in Scheme 2.2, an imidazolidinone-type organocatalyst proved to be a very efficient promoter for the addition of these nucleophiles to β-alkyl substituted α,β-unsaturated aldehydes, yielding the corresponding β-amino aldehydes in good yields and high levels of enantiocontrol.

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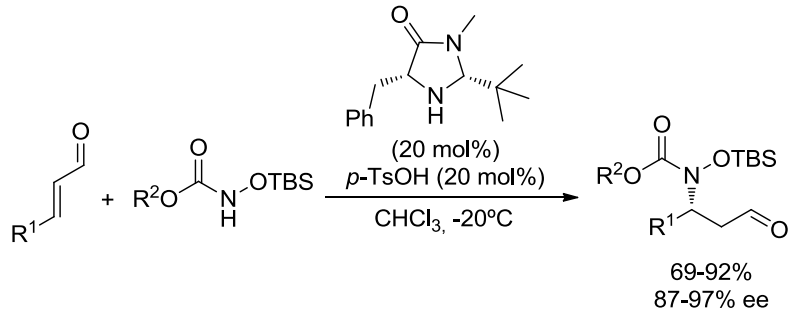
[6] Chen, K. Y.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

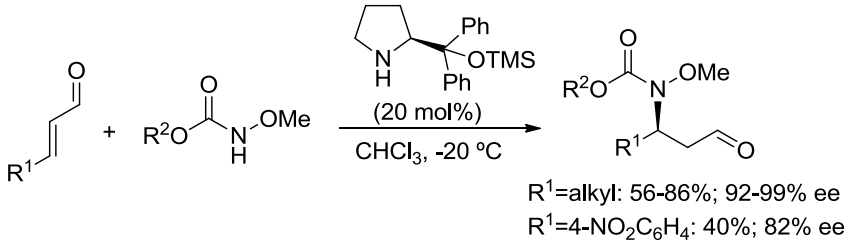


Scheme 2.2

However, this work did not describe the behaviour of the reaction with β-aryl substituted Michael acceptors, which normally show lower reactivity in conjugate addition reactions and also display a higher tendency for retro-aza-Michael and racemization processes. The relevance of the reaction was highlighted by the transformation of the obtained adducts into enantiomerically enriched β-amino acids or 1,3-amino alcohols.

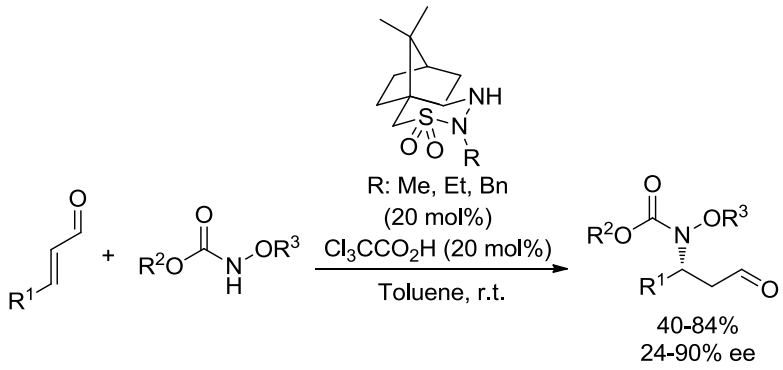
Soon after, Córdova demonstrated that the same reaction proceeded efficiently using *N*-methoxycarbamates as nucleophiles and a diphenylprolinol derivative as catalyst (Scheme 2.3).[7] In this case some β-aryl substituted α,β-unsaturated aldehydes were examined under these conditions. However, these particularly challenging Michael acceptors afforded the products in lower yields and enantioselectivities than the corresponding aliphatic aldehydes.

[7] Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G. -L.; Xu, Y.; Córdova, A. *Tetrahedron Lett*. **2007**, *48*, 2193.



Scheme 2.3

Also in this context, Lee and co-workers described the use of sulfonyl hydrazines as a new class of catalysts to be employed in the aza-Michael reaction of carbamates with α,β-unsaturated aldehydes (Scheme 2.4).[8] Camphorsulfonyl hydrazine aminocatalysts (synthesized in good yields from camphorsulfonic acid) afforded the corresponding aza-Michael adducts in enantioselectivities up to 90% ee and yields that varied depending on the substitution pattern of the Michael acceptor.

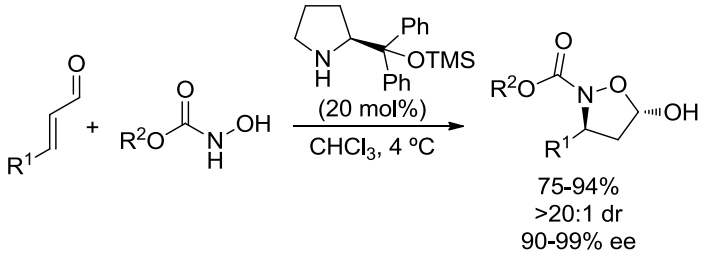


Scheme 2.4

In a different approach, Córdova and co-workers studied the possibility of employing a structurally related carbamate as a pro-nucleophile containing an

[8] Chen, L.-Y.; He, H.; Pei, B.-J.; Chan, W.-H.; Lee, A. W. *Synthesis* **2009**, 1573.

additional functionality that was able to react intramolecularly with the formyl group present at the final aza-Michael adducts (shown in Scheme 2.5).[9] The *N*-hydroxy group had a crucial influence, trapping the aza-Michael adduct, thus driving the reaction equilibria towards the final hemiacetal product. The reaction presented excellent enantioselectivities and the products were obtained in high yields as a single diastereoisomer when both β-alkyl and β-aryl substituted α,β-unsaturated aldehydes were employed. The relevance of the obtained adducts was highlighted through transformation into β-amino acids and γ-amino alcohols, and was later applied to the synthesis of a chemochine receptor 5 (CCR-5) antagonist, Maraviroc (UK-427,857).[10]



Scheme 2.5

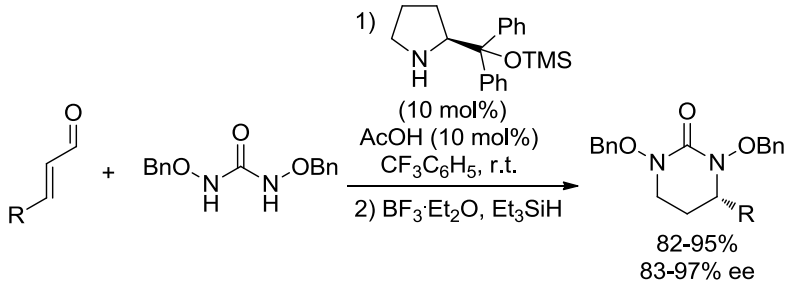
In a related example, Chen and co-workers described the addition of ureas to α,β-unsaturated aldehydes.[11] These species contain two nucleophilic nitrogen sources, which allowed an initial conjugate addition followed by intramolecular 1,2-addition to the formyl group. Thus, the authors proposed a facile method to the synthesis of chiral pyrimidinone derivatives based on an aza-Michael/hemiaminal formation/dehydroxylation reaction sequence. The desired compounds were obtained

[9] Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G. -L.; Córdova, A. *Chem. Commun.* **2007**, 849.

[10] Zhao, G.-L.; Lin, S.; Korotvička, A.; Deiana, L.; Kullberg, M.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 2291.

[11] He, Z.-Q.; Zhou, Q.; Wu, L.; Chen, Y.-C. *Adv. Synth. Catal.* **2010**, *352*, 1904.

in high yields and excellent enantioselectivities when an *O*-trimethylsilyl α,α-diphenylprolinol derivative was used as a catalyst (Scheme 2.6).

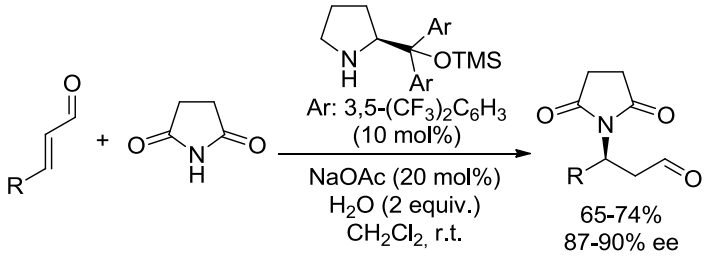


Scheme 2.6

Jørgensen also described the conjugate addition of succinimide to enals using a related *O*-trimethylsilyl diarylprolinol catalyst.[12] Once again, the results showed that the β-amination reaction proceeded in an efficient manner for aliphatic enals under the optimized condition reactions, in terms of yield and enantioselectivities (Scheme 2.7). The importance of the methodology was exemplified after reduction of the formyl group and subsequent hydrolysis of the succinimide moiety under basic conditions, allowing isolation of the corresponding *δ*-amino alcohols. The moderate yields obtained were explained based on the ability of the succinimide moiety to act as a good leaving group, enabling a facile retro-Michael process, which prevented the reaction from achieving full conversion. In fact, the yields were improved when the reaction was carried out in the presence of an additional electrophile that is able to trap the enamine intermediate generated after the conjugate addition process. As was mentioned previously, this drives all the equilibria participating in the catalytic cycle towards the formation of the final

[12] Jiang, H.; Nielsen, J. B.; Nielsen, M.; Jørgensen, K. A. *Chem. Eur. J.* **2007**, *13*, 9068.

product, avoiding the retro-processes and furnishing the α,β-diamination products in a single step (see Scheme 2.19).



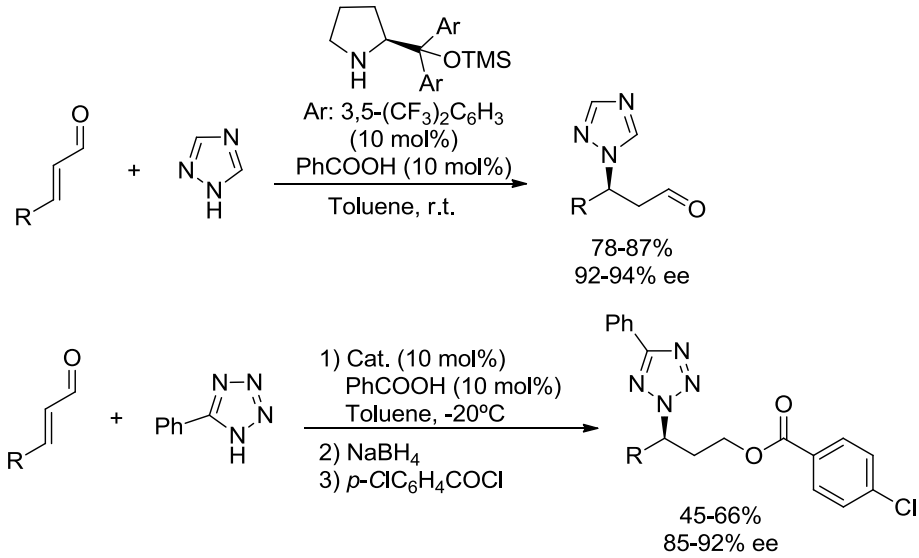
Scheme 2.7

Some aromatic nitrogen heterocycles have also been the subject for study as pro-nucleophiles in organocatalytic aza-Michael reactions, due to their prevalence in medicinal chemistry and material science applications.[13] In this sense, Jørgensen and co-workers presented a detailed study on the addition of some nitrogen heterocycles (*i.e.* 1*H*-1,2,4-triazole, 2*H*-1,2,3-triazole, 1*H*-benzo[*d*][1,2,3]triazole and 5-phenyl-1*H*-tetrazole) to α,β-unsaturated aldehydes, employing a *O*-trimethylsilyl diarylprolinol derivative as catalyst.[14] These heterocycles contain a highly acidic N-H group (pKa~5) and display an intrinsic tendency to perform 1,4-addition in preference to 1,2-addition. It was shown that utilizing 1*H*-1,2,4-triazole as the nucleophile provided the best results, generating configurationally stable compounds in very good yields and enantioselectivities when aliphatic α,β-unsaturated aldehydes were employed (Scheme 2.8). On the contrary, the use of aromatic enals once again resulted in low conversion. It should be highlighted that reactions with this nucleophile could be carried out at room temperature, without

[13] For some examples, see: a) Purwanto, M. G. M.; Weisz, K. *Curr. Org. Chem.* **2003**, *7*, 427; b) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379; c) Ghannoum, M. A.; Rice, L. B. *Clin. Microbiol. Rev.* **1999**, *12*, 50.

[14] Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983.

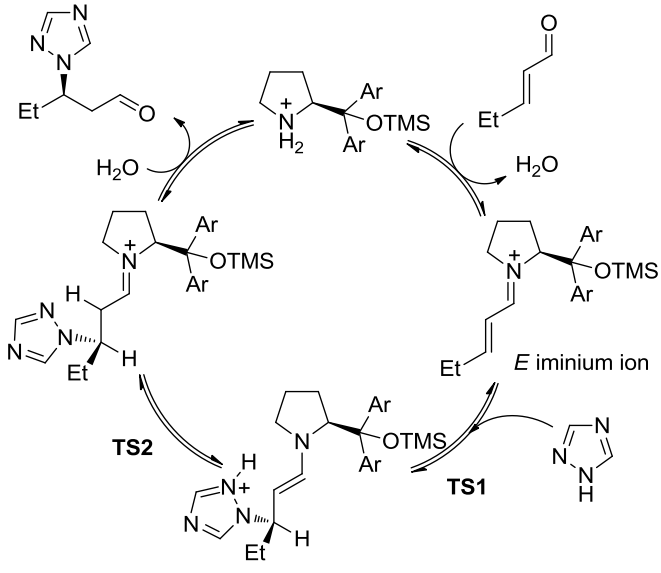
negatively influencing the enantioselectivity. Other heterocycles were employed to examine the scope of the reaction, obtaining excellent enantioselectivities and good yields when 5-phenyl-1*H*-tetrazole was used as the pro-nucleophile. However, in this case the reaction had to be carried out at lower temperatures, and also required *in situ* reduction and esterification of the adducts in order to make the isolation and purification feasible.



Scheme 2.8

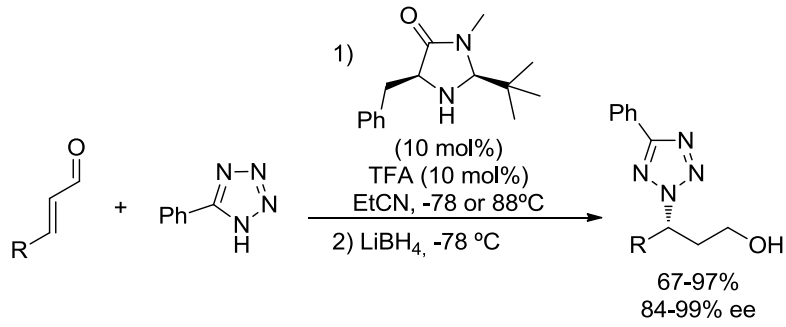
In an attempt to achieve an improved understanding of the reaction mechanism, a plausible catalytic cycle was proposed and the reaction intermediates and transition states involved were studied computationally using DFT calculations. According to their proposal (see the catalytic cycle in Scheme 2.9), the process starts with the condensation of the α,β-unsaturated aldehyde with the amine catalyst that renders the corresponding *E*-iminium ion, which then undergoes conjugate addition with the nitrogen heterocycle. An enamine intermediate is generated, where

one of the nitrogen atoms of the heterocyclic moiety is still protonated. Subsequently, an intramolecular proton transfer between the protonated heterocycle and the nucleophilic enamine moiety (*via* a water molecule) generates a second iminium ion intermediate. Final hydrolysis of this iminium ion releases the aza-Michael addition product and the catalyst, ready to re-enter the catalytic cycle. Analysis of the data obtained from the calculations indicated that there was a $\Delta\Delta G$ of 1.4 kcal/mol between the free energy of the transition state for the conjugate addition of the nucleophile to the initial iminium ion (TS1), and the free energy for the subsequent intramolecular protonation of the enamine (TS2), being lower for the second. This observation suggested that for this particular case the rate-limiting step of the reaction was the conjugate addition step. However, it should be pointed out that subtle changes in the structure of the catalyst, nucleophile or the reaction conditions (*i.e.* solvent, additives, etc.) might influence in this situation.



Scheme 2.9

Independently, and almost simultaneously, our research group developed an alternative protocol for carrying out the conjugate addition of 5-phenyl-1*H*-tetrazole to α,β-unsaturated aldehydes, employing a chiral imidazolidinone as the catalyst (Scheme 2.10).[15] Similarly to the previous example by Jørgensen, the obtained adducts were configurationally unstable at room temperature and racemized rapidly. This implied that the reaction had to be conducted at low temperatures and also that *in situ* reduction of the aza-Michael adduct was mandatory for the isolation of the final products as highly enantiopure material. The use of low temperatures (-78 or -88 ºC) was translated into the need for extended reaction times to achieve synthetically useful yields. In a similar way to the previous examples, aromatic enals either proved unreactive or provided racemic products.

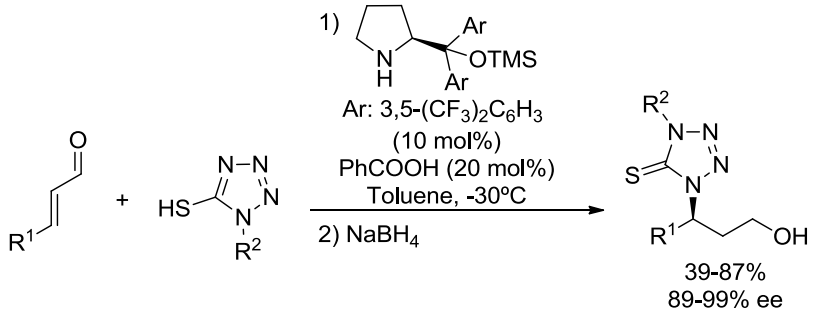


Scheme 2.10

Later on, and in an attempt to broaden the utility of this reaction, our group identified 1*H*-tetrazol-5-(4*H*)-thiones as alternative heterocyclic Michael donors.[16] Interestingly, despite the ambidentate nature of these compounds to act as either *N*- or *S*-nucleophiles, a fully chemoselective aza-Michael reaction was observed under the employed reaction conditions. The reaction was shown to be general and

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

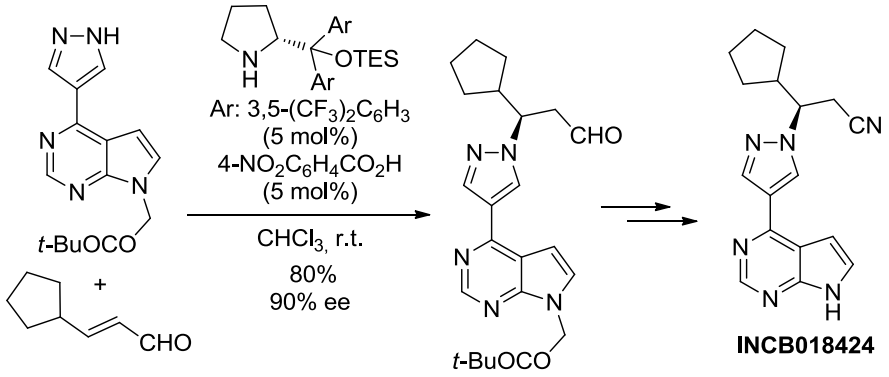
provided products in very high yields and excellent enantioselectivities for a variety of enals, using a diarylprolinol derivative as catalyst (Scheme 2.11). In contrast to the example presented before, this reaction provided the final aza-Michael adducts in excellent enantioselectivities also when β-aryl substituted enals were employed as substrates.



Scheme 2.11

Another example that utilizes heterocyclic compounds as Michael donors in the aminocatalytic aza-Michael reaction describes the addition of conveniently substituted pyrazoles to 3-cyclopentyl-2-propenal, employing an *O*-TES diarylprolinol derivative as catalyst (Scheme 2.12).[17] The methodology was directed to the synthesis of the Janus kinase inhibitor INCB018424. Aza-Michael adducts were obtained in high yields and enantioselectivities, which permitted the three-step synthesis of the target molecule in 60-70% overall yield.

[17] Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999.



Scheme 2.12

More recently, another example of an aminocatalytic aza-Michael reaction employing aromatic nitrogen heterocycles has been applied to the synthesis of optically active acyclonucleosides and acyclonucleotides.[18] A variety of purine bases were successfully added to differently substituted enals promoted by a *O*-trimethylsilyl diarylprolinol catalyst (see Scheme 2.13). Similarly to some of the previously described examples, low temperatures and *in situ* reduction of the conjugate addition products were required in order to avoid racemization. It is noteworthy that the major enantiomer of the product obtained in this reaction is opposite to that expected according to the mechanistic studies proposed by Jørgensen and co-workers,[14] suggesting that in this case the conjugate addition step might not be the rate limiting step of the process. Recent mechanistic and kinetic studies carried out for this type of reaction also defend this hypothesis.[19]

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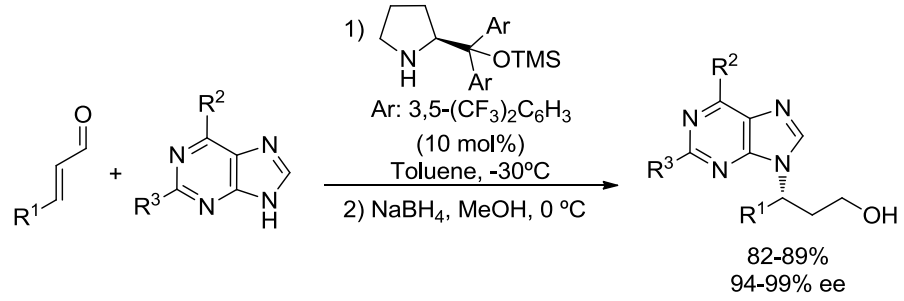
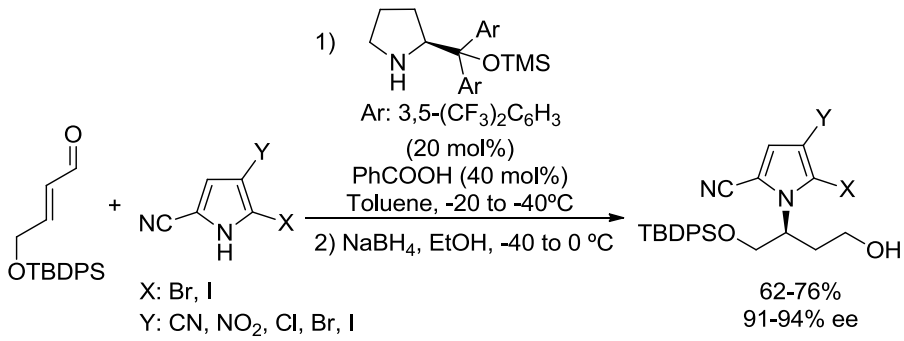
[18] Guo, H.-M.; Yuan, T.-F.; Niu, H.-Y.; Liu, J.-Y.; Mao, R.-Z.; Li, D.-Y.; Qu, G.-R. *Chem. Eur. J.* **2011**, *17*, 4095.

[19] a) Lakhdar, S.; Baidya, M.; Mayr, H. *Chem. Commun.* **2012**, *48*, 4508; b) Wong, C. T. *Tetrahedron* **2010**, *66*, 8267.



Scheme 2.13

There is also a report on the conjugate addition of heterocycles to enals that presents easy access to bromopyrrole alkaloids by means of an aza-Michael reaction of substituted pyrrolonitriles to protected (*E*)-4-hydroxybut-2-enals, catalyzed by an *O*-trimethylsilyl diarylprolinol catalyst.[20] The reaction proceeds smoothly, providing products in high yields and excellent enantioselectivities for a variety of pyrroles. Low temperatures, as well as *in situ* reduction of the conjugate addition products are required (see Scheme 2.14).

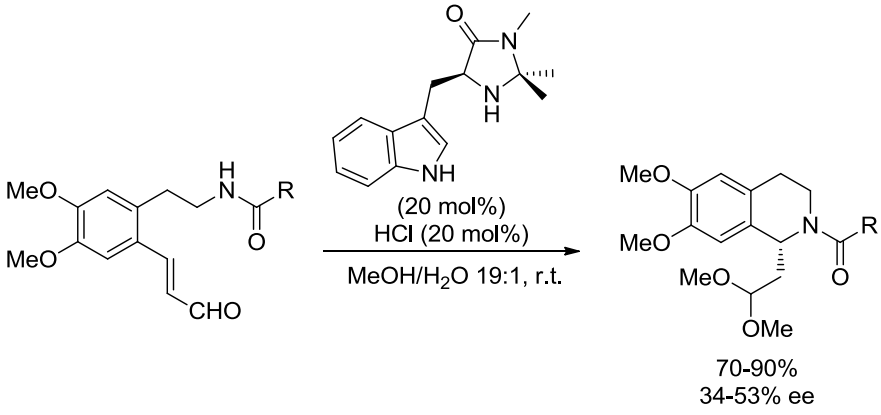


Scheme 2.14

[20] Lee, S.-J.; Youn, S.-H.; Cho, C.-W. *Org. Biomol. Chem.* **2011**, *9*, 7734.

1.1.2. Intramolecular reactions

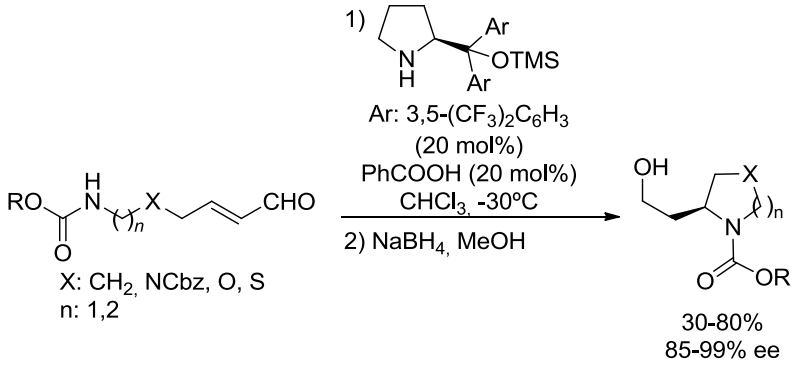
The intramolecular version of the aminocatalytic aza-Michael reaction is a very useful approach for the preparation of nitrogen heterocycles, especially when the products are obtained in a stereocontrolled manner. In this context, Ihara and co-workers described the first intramolecular aminocatalytic version of the aza-Michael addition in 2003,[21] which preceeded the first intermolecular aza-Michael reaction reported by MacMillan, shown in Scheme 2.2. In this case, a conveniently functionalized starting material containing a α,β-unsaturated aldehyde unit linked to a secondary amide moiety, located at the appropriate distance, enabled the formation of a six-membered ring product in the presence of an imidazolidinone-type catalyst (Scheme 2.15). The products were obtained in good yields, although only low to moderate enantioselectivities were reached.



Scheme 2.15

[21] Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51.

Following this initial disclosure, Fustero and co-workers reported the first highly enantioselective version of this transformation.[22] Similiarly to the previous example, functionalized α,β-unsaturated aldehydes were tethered, in this case, to a carbamate moiety, which played the role of the nitrogen nucleophile. The reaction took place smoothly and in an enantioselective manner in the presence of an *O*-TMS diarylprolinol catalyst (Scheme 2.16). The methodology presented a wide scope, providing the synthesis of a variety of five- and six-membered nitrogen heterocycles in yields ranging from 30-80%, and in excellent enantioselectivities. *In situ* reduction of the formyl moiety was required for the isolation of the final compounds, since the authors found that the obtained adducts were configurationally unstable due to reversibility issues. The applicability of the reaction was demonstrated by the synthesis of three piperidine alkaloids (*sedamine*, *allosedamine* and *coniine*) and, in a later publication, targeting the synthesis of three quinolizidine alkaloids (*myrtine*, *lupinine* and *epiequinamide*).[23]

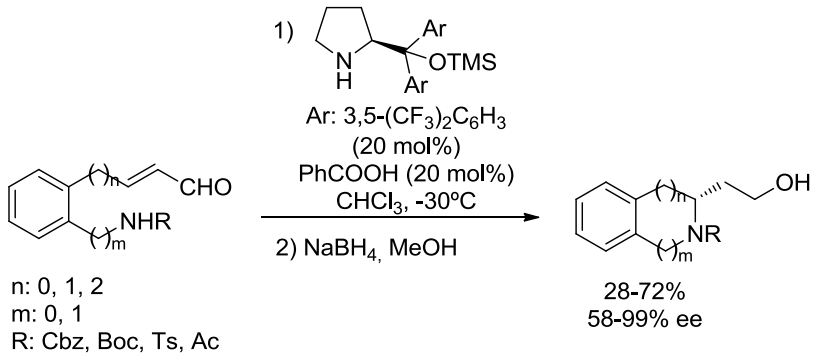


Scheme 2.16

[22] Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283.

[23] Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Flores, S.; Guerola, M.; del Pozo, C. *Tetrahedron* **2010**, *67*, 7412.

Later on, the same group studied a similar intramolecular reaction directed to the synthesis of benzo-fused nitrogen heterocycles, such as tetrahydroquinolines, tetrahydroisoquinolines or indoles (Scheme 2.17).[24] Thus, *ortho*-substituted anilines and benzylamines containing a lateral chain with an α,β-unsaturated aldehyde moiety were employed. These substrates performed equally well, providing a clean intramolecular reaction in the presence of the same chiral secondary amine catalyst. The target heterocycles were obtained in good yields and very good enantioselectivities in most cases, which were further highlighted in the three-step synthesis of alkaloid (*S*)-(+)-*angustureine*.



Scheme 2.17

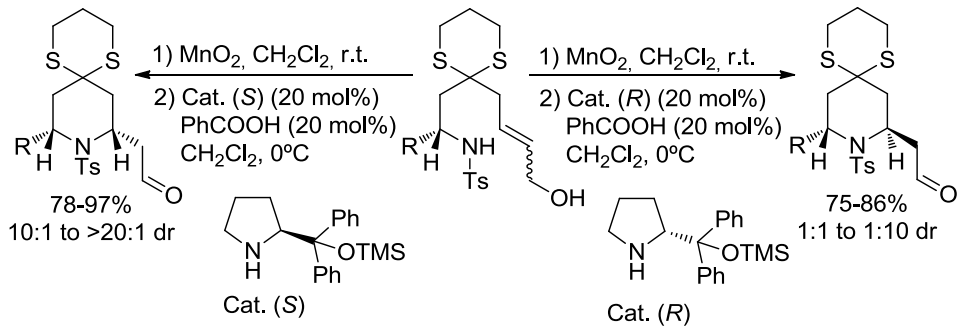
Carter *et al*. employed a very similar strategy for the synthesis of pyrrolidine, piperidine and indoline derivatives by introducing slight changes to the reaction conditions initially reported by Fustero.[25] In particular, a different solvent and the addition of a co-catalyst were required in order to obtain the target products in good

[24] Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868.

[25] Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem*. **2008**, *73*, 5155.

yields and good to excellent enantioselectivities. The utility of this reaction was illustrated with the straightforward total synthesis of the alkaloid *pelletierine*.

Finally, Hong *et al.* reported another example of the potential of the intramolecular aza-Michael reaction for the facile synthesis of heterocyclic compounds, which focused on the synthesis of (+)-*myrtine* and (-)-*epimyrtine*.[26] The authors introduced a 1,3-dithiane group to overcome the low reactivity of sulfonamides by promoting the ideal conformation for cyclization through the *geminal*-disubstituent effect. Additionally, the substrate for the reaction was an allylic alcohol instead of the typical α,β-unsaturated aldehyde. This was oxidized prior to subjection to the aza-Michael reaction in an efficient tandem process (see Scheme 2.18).[27] Using an enantiopure staring material, each enantiomer of an *O*-trimethylsilyl diphenylprolinol derivative provided a different diastereoisomer of the piperidine ring; 2-6-*trans*- and 2,6-*cis*-piperidines were obtained in high yields and moderate to good or good to excellent stereoselectivities respectively.



Scheme 2.18

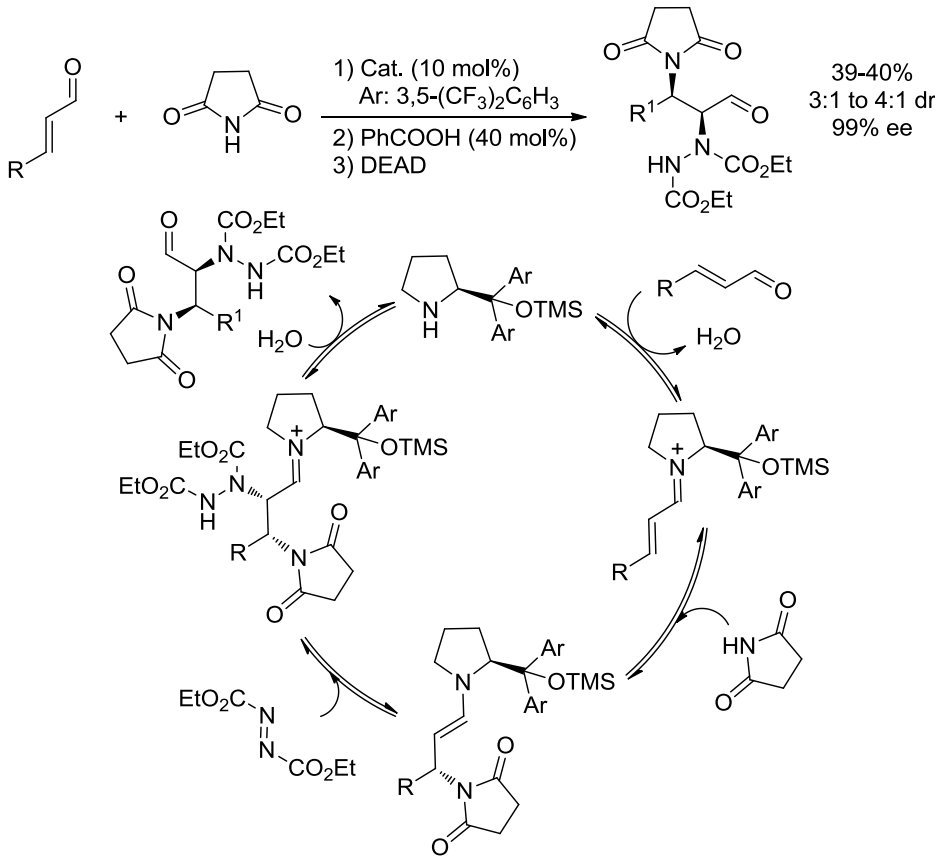
[26] Ying, Y.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 796.

[27] For analogous pioneering tandem allylic oxidation/oxa-Michael reaction, see: a) Kim, H.; Park, Y. Hong, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7577; b) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880.

1.1.3. Aza-Michael initiated domino reactions: iminium-enamine manifold

As mentioned before, and demonstrated by some of the previous examples, the aza-Michael reaction under iminium catalysis presents an important reversibility issue, which normally requires the process to be carried out with extreme care at low temperatures. Another commonly employed method to overcome this problem is the inclusion of an electrophilic reagent, able to react with the enamine intermediate generated after the conjugate addition step in a typical domino process. This electrophilic motif can be present as an external source or can be incorporated into the substrate.

In this sense, Jørgensen and co-workers employed this strategy in order to provide a solution to the reversibility issue found with the reaction presented in Scheme 2.7.[12] Therefore, after consumption of the initial starting materials (α,β-unsaturated aldehyde and succinimide), diethyl azodicarboxylate (DEAD) was incorporated to the reaction mixture resulting in the formation of the corresponding diaminated products from this aza-Michael/α-amination cascade process (Scheme 2.19). These highly enantioenriched compounds were obtained in moderate yields albeit as a mixture of diastereoisomers.

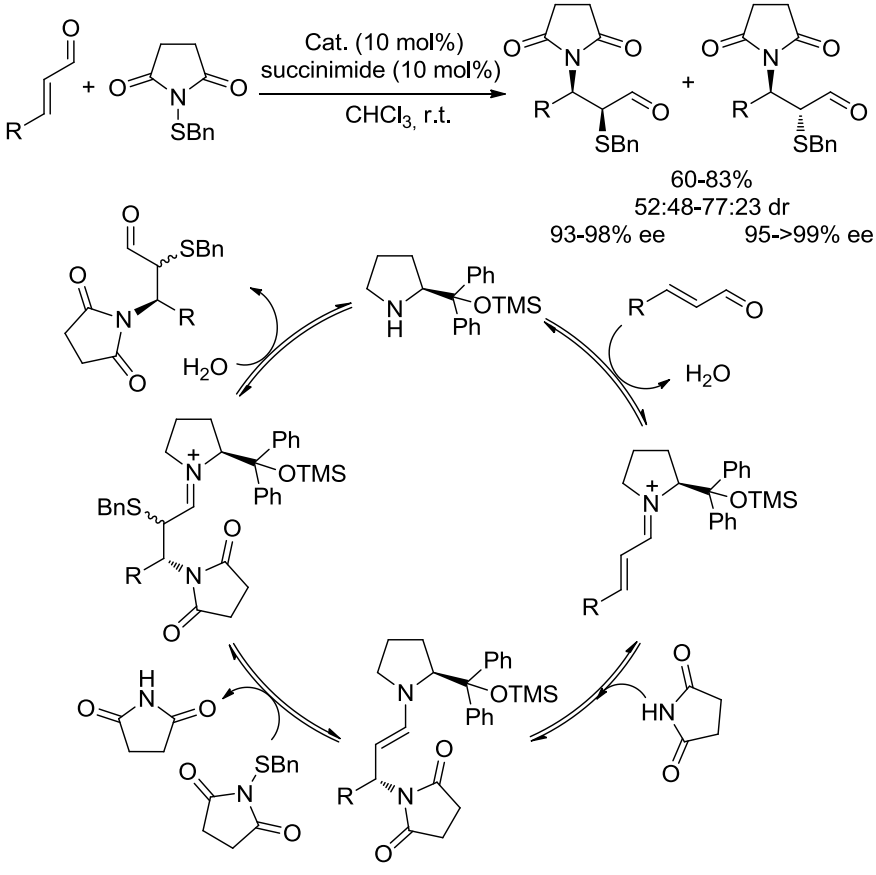


Scheme 2.19

In a similar approach, the group of Córdova introduced a different concept consisting of the use of a single reagent (*N*-benzylthiosuccinimide) as the source of both the nucleophilic and the electrophilic species, participating in an enantioselective intermolecular aza-Michael/α-aminosulfenylation cascade process, using an *O*-TMS diphenylprolinol derivative as catalyst (Scheme 2.20).[28] This

[28] Zhao, G. -L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468.

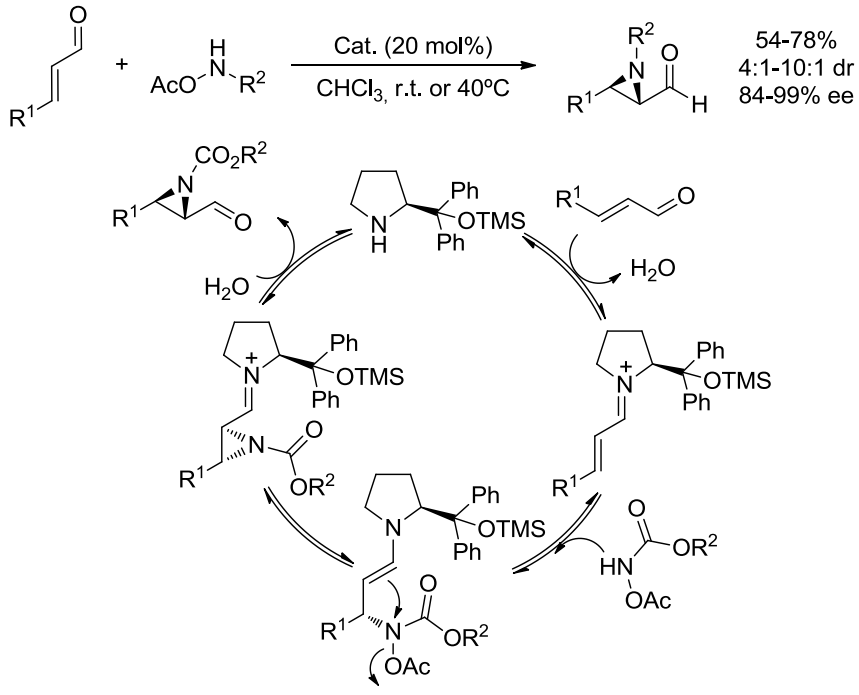
reagent participates as the initial external electrophile but also incorporates the nucleophilic motif in the form of a leaving group. Thus, a catalytic amount of free nucleophile is required to initiate the reaction, and then, after the electrophilic addition step, a new equivalent of the nucleophile is released into the reaction media. This approach also reduces the amount of chemical waste generated in the process. The final products were obtained in good yields and high enantioselectivities, although as a mixture of diastereoisomers.



Scheme 2.20

The second and most commonly found situation is the one in which the process involves an intramolecular cascade. For example, the aziridination of α,β-unsaturated aldehydes can be performed *via* a cascade process involving an aza-Michael reaction/intramolecular nucleophilic displacement, as decribed by Córdova and co-workers.[29] In particular, *N*-acyloxy carbamates, similar to those employed in related intermolecular versions, were used as functionalized nitrogen nucleophiles in conjugate addition reactions under iminium activation, provided that the alkoxy moiety was conveniently transformed into a good leaving group (Scheme 2.21). 2-Formylaziridines were obtained in high enantioselectivities and the reaction was shown to be more efficient when higher temperatures were employed, suggesting that the intramolecular nucleophilic displacement step was in fact the driving force of the reaction. A series of aziridines were synthesized in high yields and with good chemo-, diastereo- and enantioselectivities from a variety of aliphatic enals.

[29] Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 778.



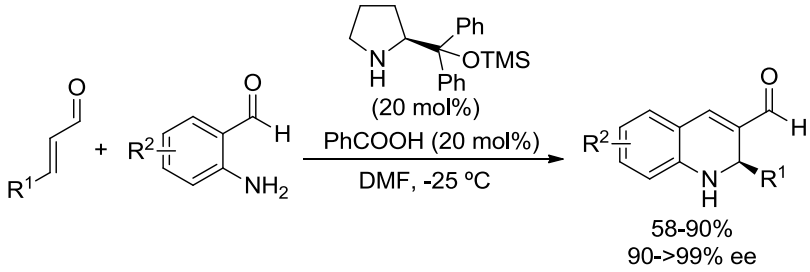
Scheme 2.21

Hamada and co-workers presented a variation of this aziridination reaction of enals by employing *N*-arenesulfonyloxycarbamates as nucleophiles.[30] Compared to the previous report by Córdova, this one enabled the use of aromatic enals as substrates, furnishing variable yields but rather high enantioselectivities. Also a base co-catalyst was required to increase the nucleophilicity of the nitrogen group.

Several examples of aza-Michael/aldol cascades have been developed, giving access to different families of heterocyclic systems. In this sense, Córdova and co-workers first developed this strategy for the asymmetric synthesis of 1,2-

[30] Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Letters* **2009**, *50*, 3329.

dihydroquinoline derivatives.[31] The aldol reaction offered the desired kinetic control, limiting the retro-conjugate addition and driving the reaction to completion. A final dehydration process provided the quinoline derivatives in high yields and enantioselectivities when using a protected diphenylprolinol-type catalyst at low temperatures (see Scheme 2.22). At the same time, Wang and co-workers reported a similar transformation, using *N*-protected 2-aminobenzaldehydes as the functionalized reagents that participate in an aza-Michael/intramolecular aldol/dehydration sequence.[32] Higher yields were reported presumably due to the introduction of a base as a co-catalyst to increase the nucleophility of the protected amine moiety by assisting its deprotonation.



Scheme 2.22

Hamada *et al*. reported an application of this strategy to access the chiral core of the *martinelline* natural product, which was constructed in a similar enantioselective aza-Michael/aldol cascade process where the reaction proceeded in a quantitative and enantioselective manner (see Scheme 2.23).[33]

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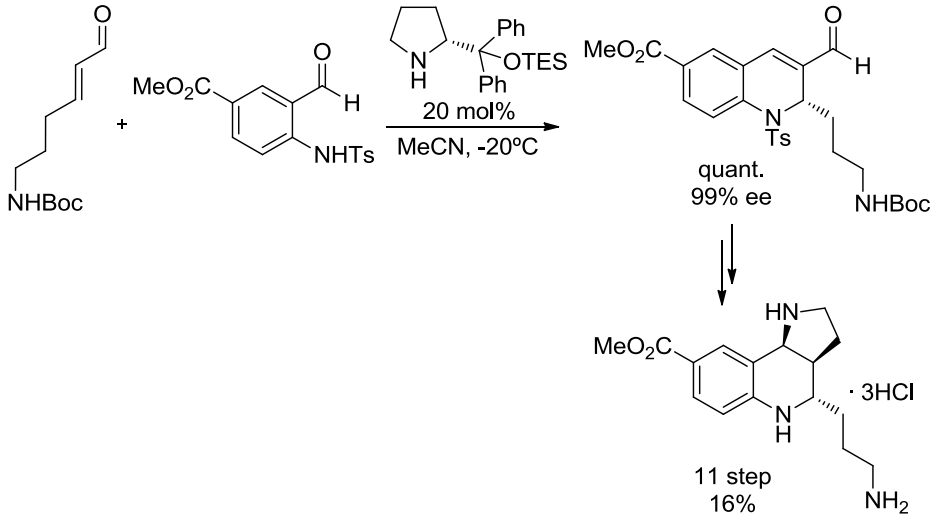
[31] Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827.
[32] Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, 9, 965.
[33] Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y. *Tetrahedron* **2008**, *64*, 11568.



Scheme 2.23

Based on the same reaction design (aza-Michael/aldol/dehydration sequence), independently and almost simultaneously, Enders and Wang developed a highly useful method for the construction of pyrrolo[1,2-*a*]indole-2-carbaldehydes.[34] In this approach, indole-2-carbaldehydes reacted with α,β-unsaturated aldehydes in the presence of a diphenylprolinol derivative, to yield a series of pyrroloindole adducts in good yields and enantioselectivities. In the same context, another example was reported in which pyrroles were chosen to react with enals under similar reaction conditions (Scheme 2.24).[35] Trichloroacetyl- or trifluoroacetyl- substitution was strategically introduced onto the pyrrole core in order to promote the intramolecular aldol reaction, but avoid the final dehydration step. The desired pyrrolizidines were synthesized as a single diastereoisomer, in moderate to good yields and excellent enantioselectivities.

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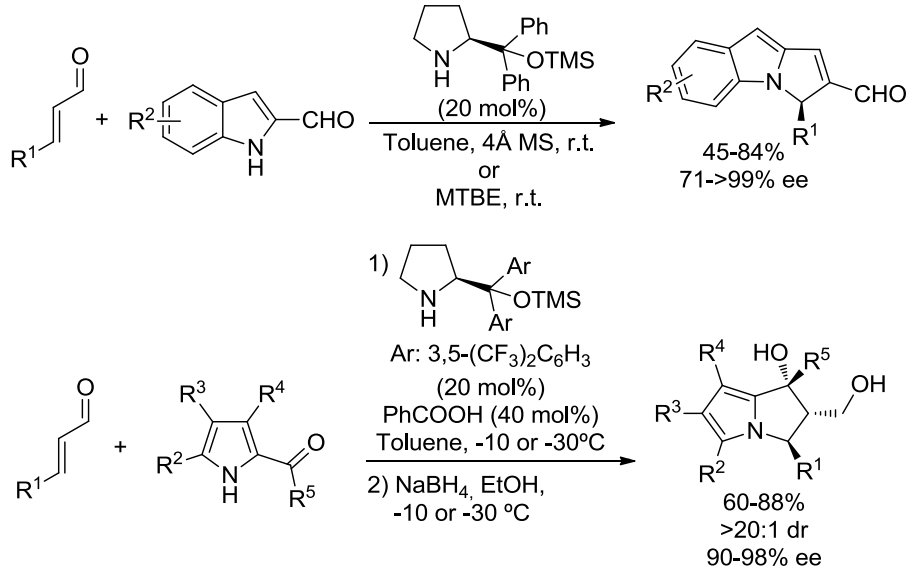
[34] a) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang R. *Chem. Eur. J.* **2010**, *16*, 440; b) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119.

[35] Bae, J.-Y.; Lee, H.-J.; Youn, S.-H.; Kwon, S.-H.; Cho, C.-W. *Org. Lett.* **2010**, *12*, 4352.



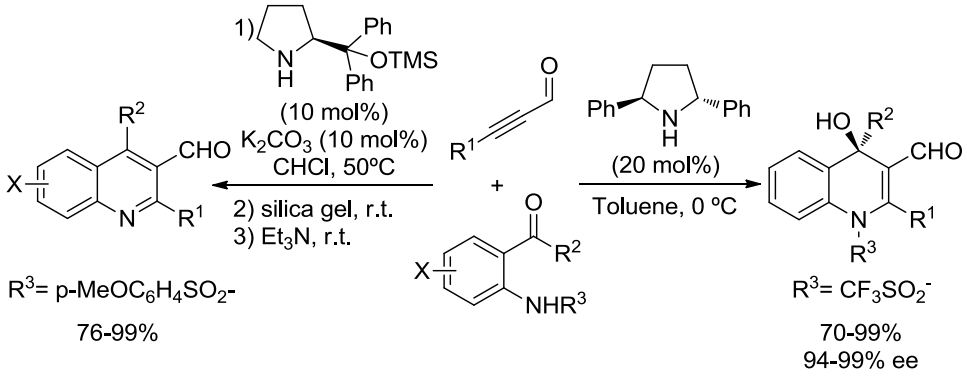
Scheme 2.24

In a very recent and interesting publication based on this aza-Michael/aldol domino process, Wang has presented a divergent cascade process that proceeds via a chiral allenamine intermediate.[36] The reaction of *N*-protected aminobenzaldehydes with ynals provided chiral quinolines and 1,4-dihydroquinolines from aza-Michael/aldol/aromatization and aza-Michael/aldol sequences respectively (Scheme 2.25).[37] Interestingly, the divergent nature of the reaction was dependant on the protecting group of the amino functionality. Aryl sulfonyl moieties with electron-donating groups favoured the final aromatization step to give polysubstituted

[36] For pioneering reports on cascade reactions *via* chiral allenamines, see: a) Michael/Michael: Zhang, X.-S.; Zhang, S.-L.; Wang W. *Angew. Chem. Int. Ed.* **2010**, *49*, 1481; b) Michael/aldol: Liu, C.-L.; Zhang, X.-S.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948; c) Michael/Mannich: Alemán, J.; Nuñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; García-Ruano, J. L. *Chem. Eur. J.* **2010**, *16*, 9453.

[37] Zhang, X.-S.; Song, X.-X.; Li, H.; Zhang, S-L. Chen, X.; Yu, X.-H.; Wang, W. *Angew. Chem. Int. Ed.* **2012**, *51*, 7282.

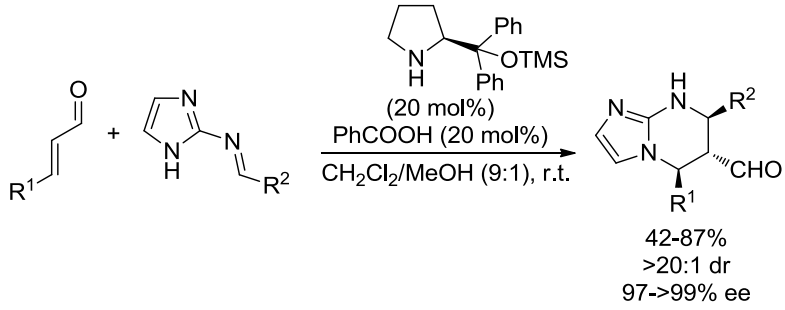
quinolines. However, when sulfonyl moieties with electron-withdrawing groups were employed, no dehydration/deprotection sequence was observed and chiral 1,4-dihydroquinolines were produced in excellent yields and enantioselectivities.



Scheme 2.25

Hu *et al.* have also reported a case of an aminocatalytic domino aza-Michael/Mannich reaction. On this occasion, an imino group was strategically introduced as a substituent on an aromatic nitrogen heterocycle.[38] This way, the enamine intermediate generated after the initial conjugate addition underwent intramolecular reaction with the azomethine moiety, leading to the formation of highly substituted tetrahydroimidazopyrimidines in good yields and excellent stereoselectivities (shown in Scheme 2.26); the substituents present on the α,β-unsaturated aldehydes and nucleophiles were always aromatic.

[38] Li, H.; Zhao, J.; Zeng, L.; Hu, W. *J. Org. Chem.* **2011**, *76*, 8064.

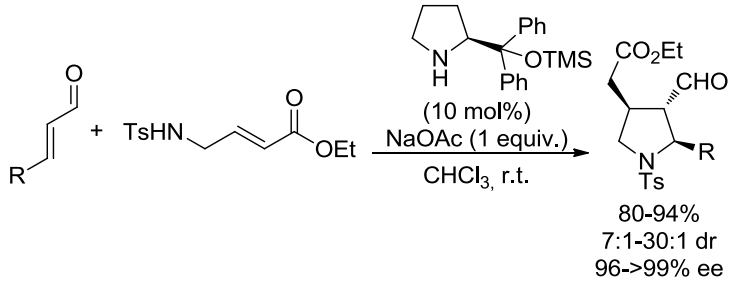


Scheme 2.26

Other combinations are also possible. For example, a work presented by Wang and co-workers described an enantio- and diastereoselective aza-Michael/Michael reaction sequence between α,β-unsaturated aldehydes and *trans*-γ-tosyl protected amino α,β-unsaturated esters (Scheme 2.27).[39] This powerful methodology presented a new strategy for the stereocontrolled synthesis of trisubstituted chiral pyrrolidines. Similar to what was observed for the previous domino processes, the enamine intermediate created after the initial aza-Michael reaction step reacts in an intramolecular manner with an α,β-unsaturated ester incorporated into the substrate. The nucleophile was meticulously designed, taking into consideration the reactivity and selectivity issues required for the reaction. On the one hand, a *para*-toluenesulfonyl group was chosen as the most appropriate *N*-protecting group for the success of the transformation, based on the ability of this group to increase the acidity of the NH group. This then favours *in situ* deprotonation and generates a more reactive nucleophilic species for the conjugate addition step that initiates the cascade process. On the other hand, the enoate system required *trans* geometry in order to reduce the possibility of intramolecular

[39] a) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636; b) A very similar approach has recently been described: Yokosaka, T.; Hamajima, A.; Nemoto, T.; Hamada, Y. *Tetrahedron Lett.* **2012**, *53*, 1245.

lactamization of the starting material. The reaction performed well for a wide range of aromatic enals, providing the final pyrrolidines with three contiguous stereocenters in good yields, excellent enantioselectivities and high diastereoselectivities. However, no examples were presented that showed the viability of the reaction with β-alkyl substituted enals.



Scheme 2.27

1.2. Chiral primary amines as catalysts: aza-Michael reaction with α,β-unsaturated ketones

Using enones as Michael acceptors under iminium activation presents a challenging situation, since the control of the geometry of the iminium ion is more complicated than in the case of enals. This is principally due to the similar size of both of the substituents attached to the azomethine carbon of the iminium ion intermediate, which may lead to the formation of a mixture of diastereoisomers and thus low reaction stereocontrontrol. Moreover, the catalytic activity of secondary amines in reactions where the activation of enones is required is generally lower than that of aldehydes, mainly due to two reasons: the lower electrophilicity of the carbonyl moiety and the higher steric congestion to overcome during the formation of the corresponding iminium ion. This situation justifies the fact that the number of publications on aza-Michael reactions with enones under iminium activation is

significantly lower to those utilizing α,β-unsaturated aldehydes. In this sense, the tendency has been to use chiral primary amines as a solution to this problem,[40] since they will undergo iminium ion formation more readily than the corresponding secondary amine counterparts and, in theory, would allow improved geometry control (Figure 2.2).

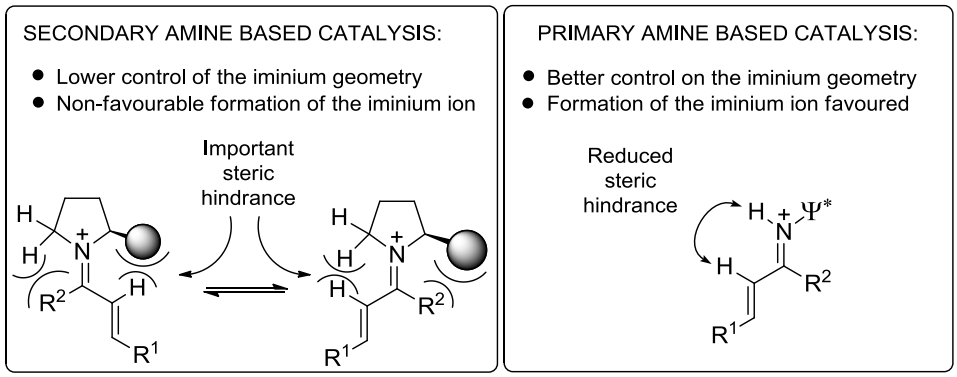


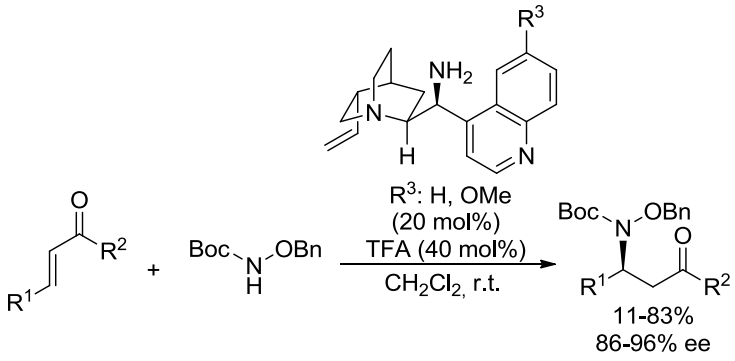
Figure 2.2

In this context, Deng and co-workers presented the first example of a chiral primary amine catalyzed aza-Michael reaction with enones.[41] In this example, based on MacMillan's pioneering report for the intermolecular version of the aminocatalytic aza-Michael reaction (shown in Scheme 2.28),[6] *N*-benzyloxycarbamates were chosen as appropriate nucleophiles to be reacted with enones in the presence of catalytic amounts of a primary amine derived from a *cinchona* alkaloid. Conjugate addition products were obtained in high levels of enantioselectivity for a wide range of β-alkyl and β-aryl substituted α,β-unsaturated ketones. This bifunctional catalyst was strategically selected since it contained both

[40] For a specific account on iminium activation using primary amines, see: Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759.

[41] Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 7710.

the primary amine, which is able to form the iminium ion, and a tertiary amine moiety (*i.e.* a Brønsted basic site) that can activate the Michael donor.

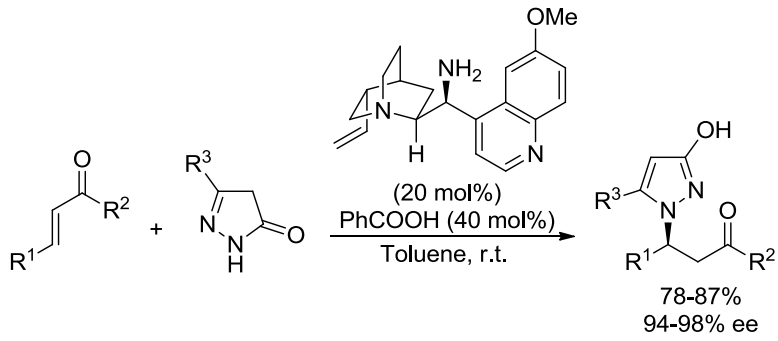


Scheme 2.28

Another approach to the conjugate addition of nitrogen-centered nucleophiles to enones describes the addition of aromatic nitrogen heterocycles. A few examples have been described in this context reporting the addition of various types of heterocycles (*e.g.* 1*H*-benzotriazole, 5-phenyltetrazole and 1,2,3-triazole) to cyclic or acyclic enones.[42] Zhao and colleagues described the most enantioselective method to date.[43] In this particular example, 2-pyrazolin-5-ones reacted efficiently with acyclic aliphatic enones, in the presence of the same primary amine catalyst used by Deng in the example shown in Scheme 2.28, to obtain the conjugate addition product in high yields and excellent enantioselectivities (Scheme 2.29).

[42] a) Lv, J.; Wu, H.; Wang, Y. *Eur. J. Org. Chem.* **2010**, 2073; b) Zhou, Y.; Li, X.; Li, W.; Wu, C.; Liang, X.; Ye, J. *Synlett* **2010**, 2357.c) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Synthesis* **2009**, 1564.

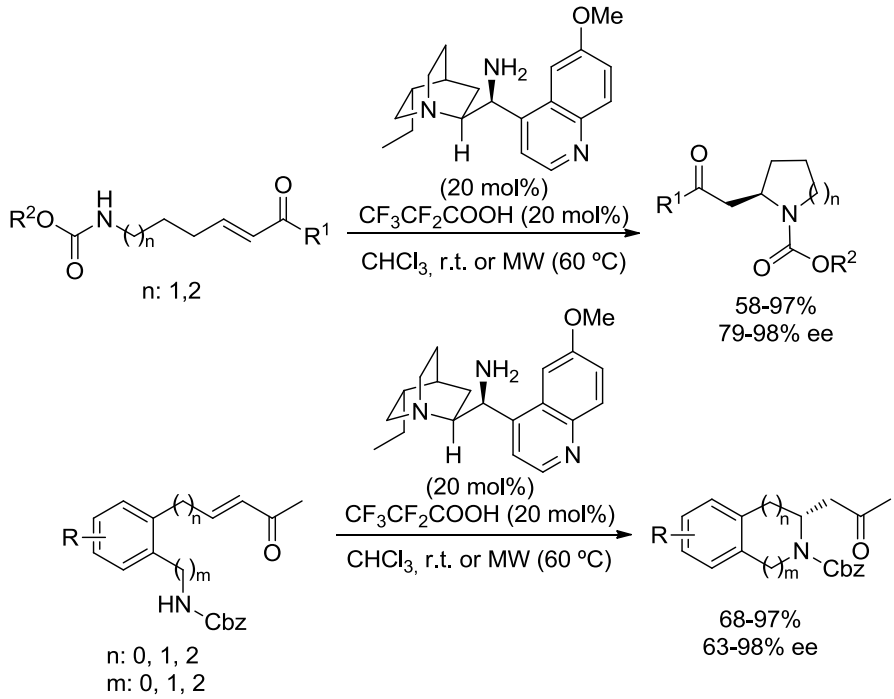
[43] Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249.



Scheme 2.29

An intramolecular version of this reaction has also recently been described. Based on a modification of their own previous investigations,[22a,24] the group of Fustero presented an elegant approach to the synthesis of a series of piperidines, pyrrolidines and the corresponding benzofused derivatives; using enones containing a strategically introduced nitrogen nucleophile within the structure, at the appropriate distance for cyclization.[44] Again, a bifunctional primary amine catalyst derived from *cinchona* alkaloids was used to activate the α,β-unsaturated carbonyl compound and the Michael acceptor (Scheme 2.30). Interestingly, the viability of the reaction was tested at both room temperature and under microwave irradiation, leading to comparable results in terms of yield and enantioselectivities. It should be noted that the microwave irradiation accelerated the process lowering the reaction time from 20 h to 1 h.

[44] Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sanchez-Roselló, M. *Chem. Eur. J.* **2011**, *17*, 14267.

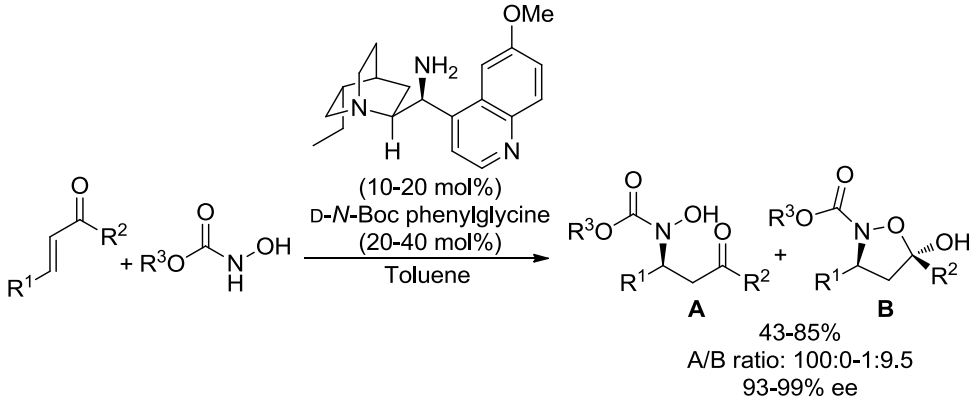


Scheme 2.30

Finally, and in line with the progresses made in the field, some domino processes have also been described for the aza-Michael reaction with α,β-unsaturated ketones. The first example was reported by the group of Melchiorre, describing the use of a chiral primary amine salt in the enantioselective conjugate addition of protected *N*-hydroxycarbamates to enones.[45] As shown in Scheme 2.31, this led to either β-hydroxylamino ketone adducts or 5-hydroxyisoxazolidines depending on the R^2 substituent attached to the carbonyl group of the enone system; the latter being the result of a second nucleophilic attack of the hydroxy group to the

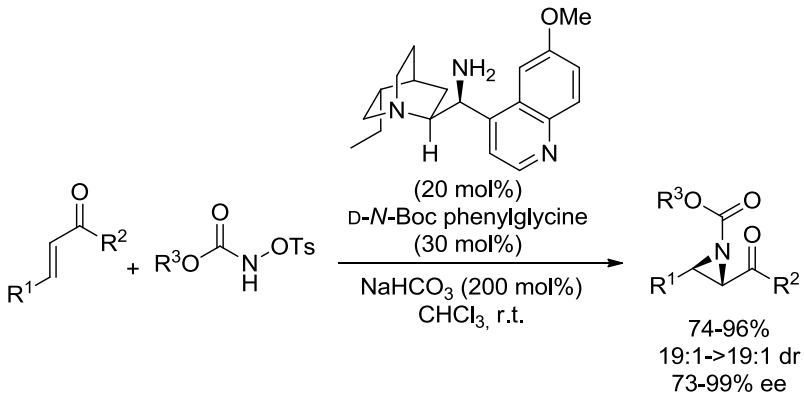
[45] a) Pesciaioli, F.; De Vicentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703; For a similar approach, see: b) Cruz-Cruz, D.; Sánchez-Murcia, A.; Jørgensen, K. A. *Chem. Commun.* **2012**, *48*, 6112.

pendant ketone moiety. In these studies it was suggested that the incorporation of chiral information in both the primary amine and Brønsted acid counterion was highly beneficial for good stereocontrol; therefore, the highest enantioselectivities were achieved when the correct *matched pair* was employed.



Scheme 2.31

Alternatively, modification of the Michael donor into a form that contains a better leaving group (*i.e.* tosylate *vs.* hydroxy) has been employed to promote an aza-Michael/intramolecular nucleophilic displacement cascade process leading to the formation of a variety of 2-acylaziridines in excellent yields and stereoselectivities (see Scheme 2.32).



Scheme 2.32

In summary, we could highlight the exponential advance that aminocatalytic aza-Michael reaction has undergone during these last years, specially considering that the first example in the field was a recent publication. Iminium catalysis has been shown to be a very interesting approach for enantioselective conjugate addition reactions using a variety of nitrogen-based nucleophiles and α,β-unsaturated carbonyl compounds, which enabled direct synthesis of a wide range of nitrogen-containing chiral compounds. In addition, it has also been demonstrated that the iminium/enamine manifold is applicable to this scenario, allowing a series of domino processes that generate high levels of molecular complexity in a single reaction. Moreover, publications with examples directed towards the synthesis of biologically active compounds or natural products have exemplified the applicability of the aminocatalyzed aza-Michael reaction. Nevertheless, we could conclude in saying that the area is still open to new discoveries, presumably focused on the use of lower catalyst loadings and/or reaction times and a wider scope of nitrogen pro-

nucleophiles. Also, contributions reporting novel applications of the developed methodologies in total synthesis could be expected.

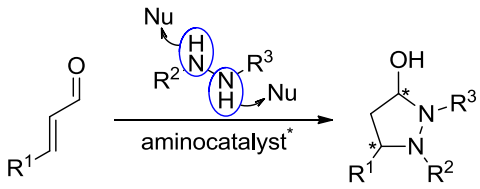
2. SPECIFIC OBJECTIVES AND WORK PLAN

We have already commented in Chapter 1 that the general objective for the present work is the development of new aminocatalytic methodologies involving conjugate addition reactions in which hydrazides and hydrazones are used as *N*- or *C*-nucleophiles. In this sense, the aim of this first section of work consists of the **development of new methodologies to carry out aza-Michael reactions, using hydrazides or hydrazones as the nitrogen donors and the iminium activation concept to activate the Michael acceptor and as a tool to achieve stereocontrol**.

We can appreciate from the literature summary presented in this chapter that the aminocatalyzed aza-Michael reaction has been thoroughly studied since its discovery in 2007. However, we should note that only a few families of nitrogen nucleophiles have been applied to the enantioselective aza-Michael reaction under iminium activation. In fact, at the beginning of this research work in 2008, most of the examples reported were based on the use of a narrow and structurally similar class of nitrogen nucleophiles, with carbamates and nitrogen containing heterocycles being the most common. On the other hand, literature precedents also highlight that aza-Michael initiated domino processes have been employed as excellent synthetic tools for the expediant access to nitrogen heterocycles.

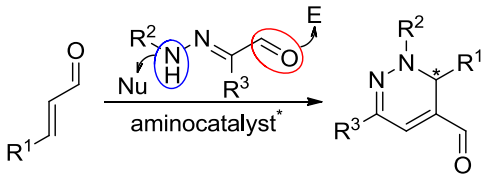
In this context, we considered that hydrazides and hydrazones could be useful nitrogen nucleophiles to be explored in aza-Michael reactions under iminium catalysis. Moreover, their multifunctional structure containing two reactive points could present an excellent platform to investigate domino processes. In this sense, we established the following objectives for this section of the work:

1. The use of hydrazides as double nitrogen nucleophiles able to perform an initial aza-Michael reaction followed by an intramolecular 1,2-addition step that avoids the reversibility issues of the process and would lead to the formation of a variety of pyrazolidine derivatives.



Scheme 2.33

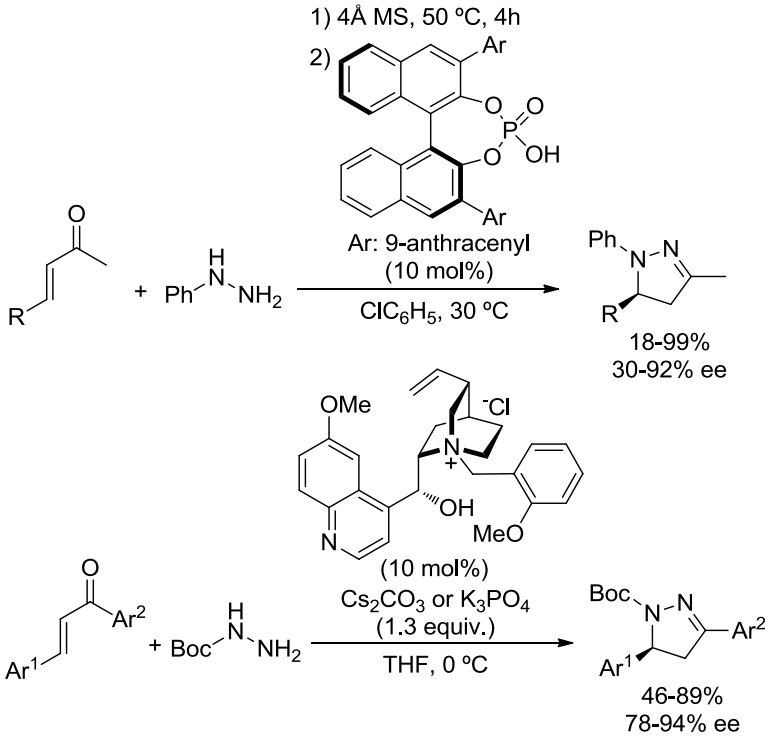
2. The use of hydrazones derived from pyruvaldehyde for the aza-Michael/aldol reaction cascade, leading to the synthesis of dihydropyridazines. In this context, we thought that a hydrazone substrate containing both a nucleophilic nitrogen, able to inititiate the conjugate addition, and an electrophilic site that would participate in a subsequent cascade process, might result in a powerful method for the preparation of dihydropyridazine derivatives.



Scheme 2.34

In the first objective, only a couple of examples have been reported since we began our investigations, describing the use of monosubstituted hydrazines to access related pyrazoline heterocycles under metal-free conditions (see Scheme 2.35). List and co-workers described a chiral Brønsted acid catalyzed version of the Fischer

reaction, in which methylalkenyl ketones reacted with primary hydrazines through a 6π-electrocyclization mechanism.[46] Also, Brière *et al.* have reported cyclocondensation of enones with primary monosubstituted hydrazides under chiral phase-transfer catalysis.[47]

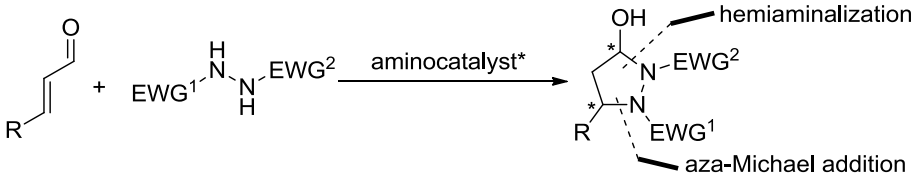


Scheme 2.35

In this sense, we envisioned that a comprehensively designed hydrazide reagent would be able to undergo successful aza-Michael addition to a variety of enals. Subsequently, the second nitrogen containing group would be able to react

[46] Müller, S.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9975.
[47] Mahé, O.; Dez, I.; Levacher, V.; Brière, J.-F. *Angew. Chem. Int. Ed.* **2010**, *49*, 7072.

with the formyl moiety in an intramolecular 1,2-addition process to deliver the corresponding pyrazolidines. Assuming that monosubstituted hydrazides would probably undergo undesired reactions (*i.e.* condensation with the enal to furnish stable hydrazone side products or, uncatalyzed cyclocondensation reactions) these were disregarded from the beginning and *N,N'*-disubstituted hydrazides were selected for further investigations. Also, considering that previous works on aza-Michael reactions showed that the enhanced acidity of N-H bonds grant increased reactivity of the nitrogen atom, we proposed the use of electron-withdrawing protecting groups. Moreover, it should be pointed out that for the cases in which the two substituents of the hydrazide are different, we would have to deal with an additional regioselectivity issue.

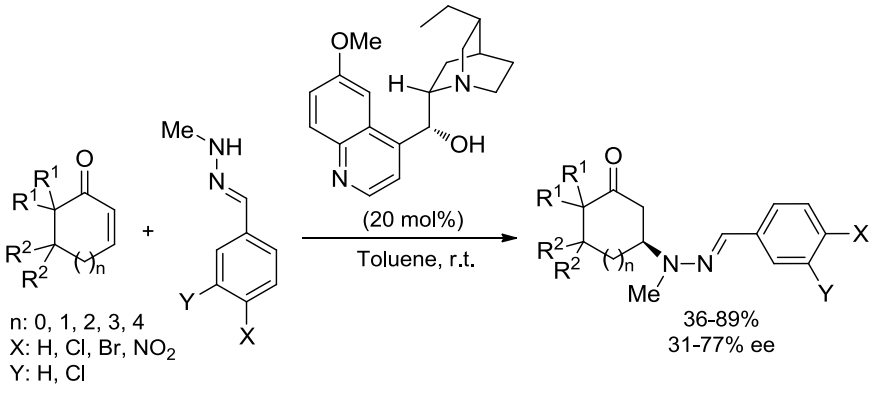


Scheme 2.36

In our second objective, we considered the use of functionalized hydrazones as bifunctional reagents, able to undergo aza-Michael initiated cascade processes under the iminium/enamine manifold. Only one literature example was found involving hydrazones as nitrogen pro-nucleophiles for the organocatalytic aza-Michael reaction, which presented the addition of *N*-methylhydrazones derived from benzaldehydes to enones, using a chiral Brønsted base catalyst.[48] This example demonstrated the potential utility of this type of functionality as a nitrogen donor for the aza-Michael reaction, despite the achievement of only moderate

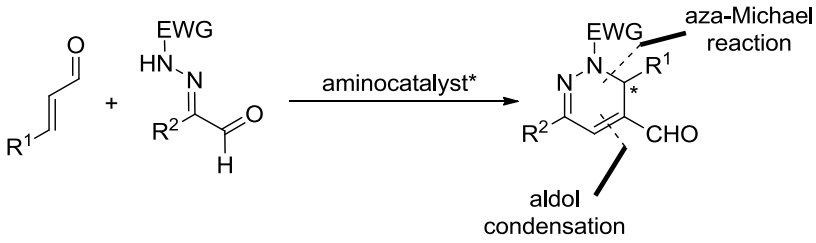
[48] Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem*. **2007**, *72*, 3565.

enantioselectivities (see Scheme 2.37). However, there were no examples exploring the use of functionalized hydrazones in cascade reactions.



Scheme 2.37

Based on the effectivness of the aza-Michael reaction/aldol condensation sequences described earlier, we postulated incorporating a formyl moiety adjacent to the azomethine carbon of the hydrazone. This way, there would be a four atom distance between the nucleophilic and electrophilic points, which would lead to the formation of a highly favoured six-membered ring after intramolecular aldol condensation. Also, as with the hydrazide objective, we proposed the incorporation of an electron-withdrawing group as a protective group for the nitrogen to increase the reactivity of the hydrazone towards the initial aza-Michael reaction.

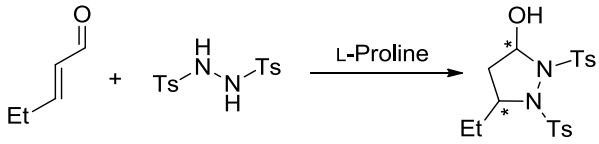


Scheme 2.38

Taking these considerations into account, the following work plan was designed:

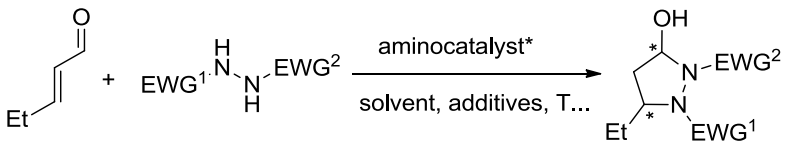
1. Reaction with hydrazides: aza-Michael reaction/hemiaminalization

- *Viability of the reaction*. *N,N'-Bis*-(*p*-toluenesulfonyl)hydrazide will be chosen as the model nucleophile. This commercially available hydrazide contains two highly acidic N-H groups that will presumably assist with both nucleophilic addition steps. Thus, proline-catalyzed addition of this hydrazide to 2-pentenal will be used as a model reaction to investigate the viability of the process.



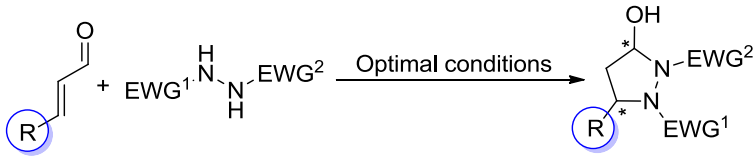
Scheme 2.39

- *Optimization of the reaction conditions*. The same reaction model will be employed for testing several chiral secondary amines in order to obtain the optimal stereoselectivity. Once the ideal catalyst has been chosen, other experimental variables such as solvent, temperature and the effect of the additives will be evaluated in an attempt to obtain the optimal chemical yield and stereocontrol. In addition, the requirements of the hydrazide reagent will be studied, by altering the substituents present on the nitrogen atoms and evaluating the influence of these changes on the reaction performance.



Scheme 2.40

- *Scope of the reaction*. Once the optimal conditions for the reaction are established, we will evaluate the application of the reaction to the use of different Michael acceptors, with the intention of evaluating the influence that the β-substituent of the enal has on the reactivity and stereoselectivity of the process.

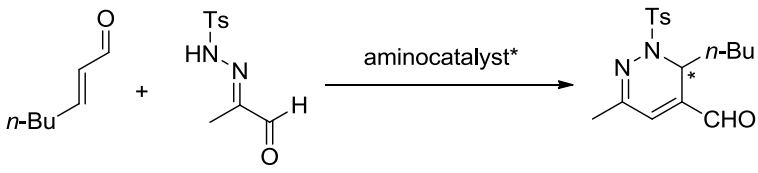


Scheme 2.41

- *Transformation of the products*. Finally, once a robust synthetic methodology has been designed, we will evaluate the reactivity of the hemiaminal moiety present in the obtained adducts in order to access to other related structures of interest, by using simple and high yielding transformations.

2. Hydrazones as bifunctional reagents: aza-Michael addition/aldol sequence

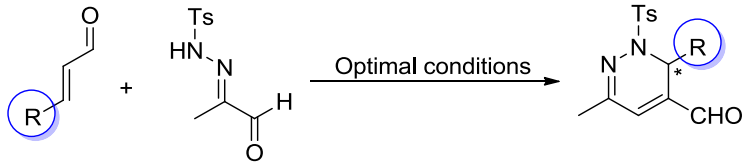
- *Viability of the reaction*. Considering all the points mentioned above, a tosylhydrazone derived from pyruvaldehyde will be selected as a Michael donor for the reaction. In a similar way as for the previous reaction, a model reaction between 2-heptenal and the tosylhydrazone will be selected to evaluate the viability of the transformation.



Scheme 2.42

- *Optimization of the reaction conditions*. Using the same reaction model, we will evaluate a series of reaction conditions, in an attempt to achieve optimal yields and enantioselectivities. Thus, different catalysts, solvents, temperatures or additives will be tested.

- *Scope of the reaction*. We will evaluate the application of the methodology to the use of a series of α,β-unsaturated aldehydes, with different substituents at the β-position to study their influence on the reaction performance.



Scheme 2.43

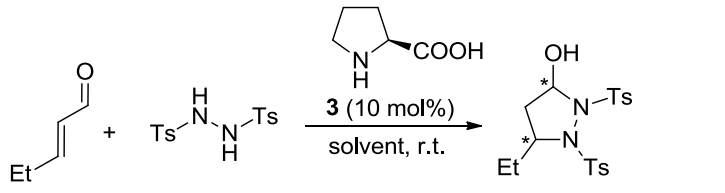
3. RESULTS AND DISCUSSION

Having reviewed and commented on the main literature methodologies relating to the topic, and stipulated our specific objectives and work plan, we will proceed with the presentation and subsequent discussion of the most relevant results achieved in our research; dealing with the use of hydrazides and hydrazones as functionalized *N*-donors in aza-Michael reaction with α,β-unsaturated aldehydes under iminium activation.

3.1. Reaction with hydrazides: aza-Michael/hemiaminalization

3.1.1. Viability of the reaction

We began the design of a new enantioselective organocatalytic method to carry out an aza-Michael/intramolecular nucleophilic 1,2-addition by evaluating the viability of the reaction. For this purpose, we took the reaction between 2-pentenal and *N,N'-bis*-(*p*-toluenesulfonyl)hydrazide as a model, using L-proline as the catalyst, according to the general reaction shown in the Scheme 2.44, and simultaneously evaluating the effect of two different solvents.



1a **2a** **4a**

88%, >90:10 dr (in CH_2Cl_2)
62%, >90:10 dr (in Toluene)

Scheme 2.44

These preliminary results showed that the proposed reaction proceeded in an efficient manner, providing the pyrazolidin-3-ol in high yields and as a single diastereoisomer. Pleasingly, the postulated hypothesis was verified; *N,N'-bis*-(*p*-toluenesulfonyl)hydrazide does act as a highly acidic nucleophile for a cascade process initiated by conjugate addition to the enal and followed by an intramolecular nucleophilic addition that renders the final pyrazolidin-3-ol product.

At this point, the relative configuration of the stereogenic centers formed during the process was determined, utilizing a selective n.O.e. NMR experiment conducted on pyrazolidin-3-ol derivative **4a** (see Figure 2.3). No n.O.e. was observed between the H^3 and H^5 protons, indicating a *trans* relative configuration of OH and ethyl substituents. This assumption was reinforced by the observation of n.O.e. effects between the methynic H^3 or H^5 protons and one of the two diastereotopic H^{4a} and H^{4b} protons exclusively. Also, the protons on the aromatic rings of each tosyl group showed interactions only with the neighbouring H^3 and H^5 protons.

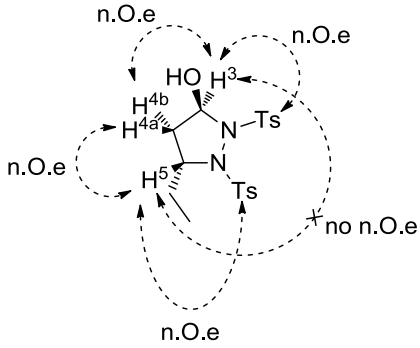
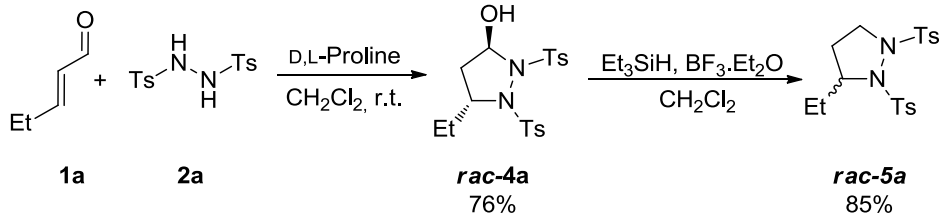


Figure 2.3

Prior to screening for the optimal catalyst to carry out the reaction in a stereoselective manner, first we needed to establish a method to determine the

enantiomeric excess of the obtained product by HPLC analysis on chiral stationary phase. Thus, we proceeded to prepare the corresponding racemic standard using D,L-proline as catalyst. The pyrazolidin-3-ol ***rac*-4a** was isolated and HPLC separation conditions of the enantiomers were attempted. However, we were unable to obtain adequate separation conditions with the chiral columns available at that point, so we decided to carry out a derivatization of the product. As shown in the Scheme 2.45, we carried out the reduction of the hemiaminal moiety by treatment of ***rac*-4a** with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid,[49] which provided pyrazolidine ***rac*-5a** in high yield.



Scheme 2.45

The separation of the enantiomers of the pyrazolidine ***rac*-5a** was achieved using a chromatographic Chiralpak IA column, in a 1.0 mL/min flow and a *n*-hexane/*i*-PrOH (90:10) solvent system (see Figure 2.4). We next applied these conditions to the adducts **4a** obtained in the L-proline-catalyzed model reaction shown in Scheme 2.44, observing that a 37% ee was achieved for the reaction performed in toluene, whereas only 7% ee was attained when dichloromethane was used.

[49] Previously reported in: Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2008**, *47*, 9971.

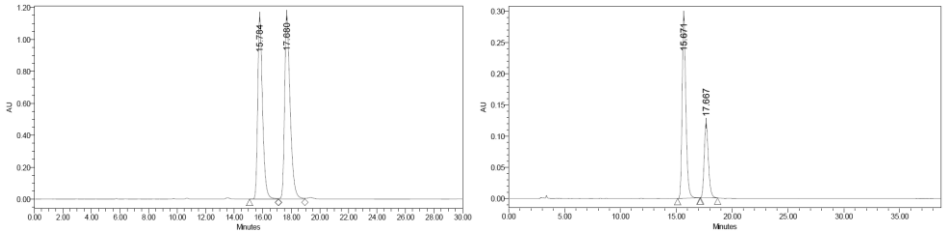


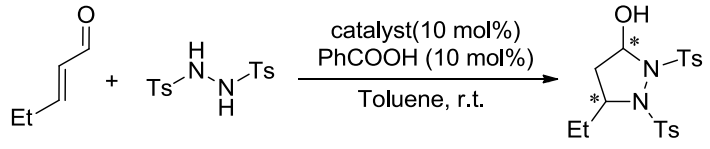
Figure 2.4

3.1.2. Optimization of the reaction conditions

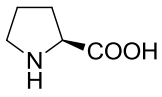
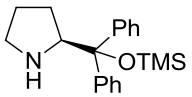
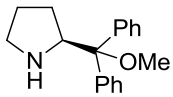
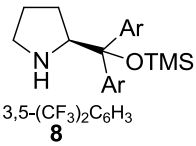
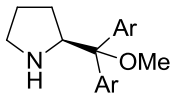
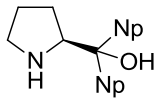
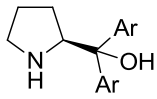
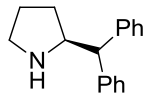
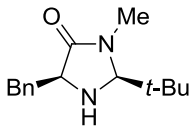
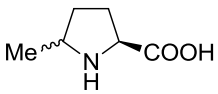
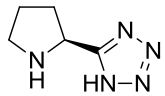
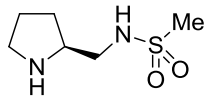
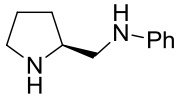
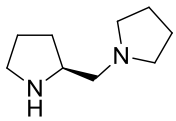
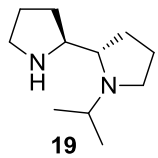
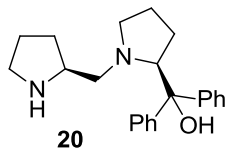
Next, and according to the established work plan, we proceeded with the evaluation of a series of potential catalysts for the reaction, aiming to obtain the highest stereoselectivity possible. The solvent chosen for these initial experiments was toluene, based on the better enantioselectivity obtained in our preliminary experiments. The reactions were carried out at room temperature, with a 10 mol% catalyst loading and benzoic acid as co-catalyst, which is often employed in aminocatalysis to facilitate the initial iminium formation.

As mentioned previously, the stereoselectivity of the reaction depends on the ability of the catalyst to form an iminium intermediate with a defined configuration, and also on its ability to exert an efficient stereochemical control on the reaction; typically by preventing the attack of the nucleophile from one of the two diastereotopic faces of the iminium ion. In this sense, we investigated the use of catalysts containing groups of enhanced steric presence at the 2-position of the pyrrolidine ring (catalysts **6-12** in Table 2.1), which provided the pyrazolidin-3-ol **4a** again as a single diastereoisomer. *O*-Protected diphenylprolinol derivatives (catalysts **6-7**) performed well in terms of chemical yield, but did not present suitable steric hindrance to provide acceptable enantioselectivities.

Table 2.1. Evaluation of a series of secondary amine catalysts.



1a **2a** **4a**

			
3[a]	**6**	**7**	**8**
62%[b]	83%	80%	54%
-37% ee[c]	20% ee	11% ee	97% ee
			
9	**10**	**11**	**12**
30%	76%	34%	80%
92% ee	8% ee	48% ee	7% ee
			
13[d]	**14**	**15**	**16**
67%	>99%	62%	45%
45% ee	0% ee	-10% ee	-10% ee
			
17	**18**	**19**	**20**
85%	80%	87%	79%
-50% ee	-40% ee	-15% ee	-6% ee

[a] Reaction performed in absence of benzoic acid. [b] Yield of the pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the reduced adduct **5a**. [d] Reaction performed using TFA as co-catalyst instead of PhCOOH.

However, catalysts possessing large groups at the 2-position (catalysts **8-9** in Table 2.1) were able to furnish the product in excellent stereoselectivity, although with a slight decrease in the isolated yield. Similar behaviour was observed for diarylprolinol derivatives **10-12**, noticing a significant decrease in the enantiocontrol when the size of aryl groups was reduced. Next, imidazolidinone **13** was investigated in the reaction. Our group had previously used this catalyst with excellent results for conjugate addition reactions of nitrogen nucleophiles,[15] but in this case, a moderate yield, poor enantiomeric excess and complete loss of diastereoselectivity was afforded. As a second approach, we considered the evaluation of a series of catalyst presenting different functional groups able to interact with the nucleophile, thus potentially directing its approach from one of the stereotopic faces of the acceptor (bifunctional catalysts). A series of bifunctional catalysts related to proline were tested (catalysts **14-20** in Table 2.1), containing functional groups able to promote hydrogen bonding, or containing acidic or basic points on their structures. These catalysts seemed to be effective in terms of reactivity and diastereoselectivity, offering the pyrazolidin-3-ol **4a** as a single diastereoisomer, although the desired product was isolated as a racemate or in poor enantioselectivities.

Based on the data obtained during this catalyst study, the *O*-trimethylsilyl diarylprolinol derivative **8** was selected for further optimization experiments, since it provided the most promising stereoselectivities. It has to be remembered that the enantiomeric excess for pyrazolidine **4a** was measured after reduction to pyrazolidine **5a**. Figure 2.5 shows the HPLC chromatogram corresponding to the enantiomerically enriched pyrazolidine **5a** when catalyst **8** was used.

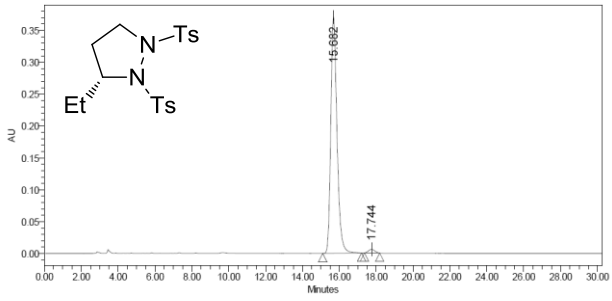


Figure 2.5

At this stage we were also able to determine the absolute configuration of the product obtained in this aza-Michael/hemiaminalization sequence. Single crystal X-ray analysis of the pyrazolidine adduct **5a,** obtained from the reaction in which catalyst **8** was used (97% ee), provided monocrystal structures showing a 5*R* absolute configuration (shown in Figure 2.6). With this information, together with the results obtained from the previous n.O.e. NMR experiments, we could conclude that the absolute configuration for the pyrazolidin-3-ol **4a** was 3*R*,5*R*.

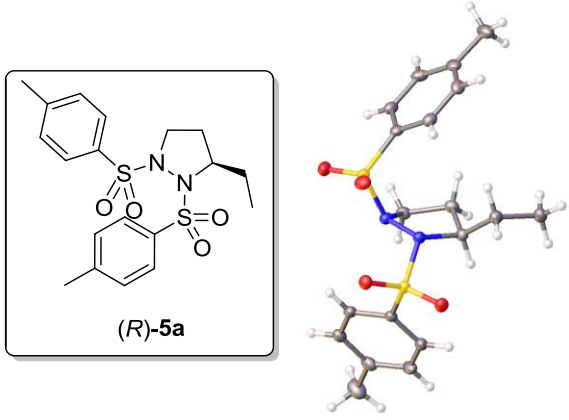
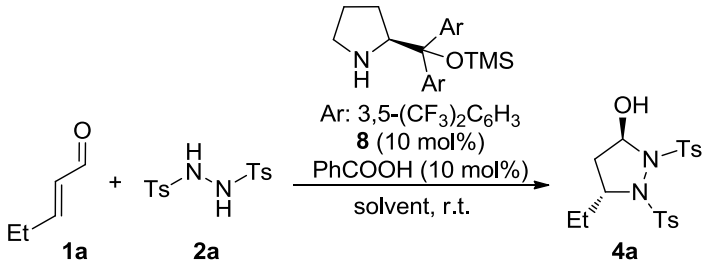


Figure 2.6

Once the optimal catalyst had been identified, our next experiments were directed towards the improvement of the yield of the reaction. Thus, we started investigating the influence that the solvent has on the reaction.

As we can appreciate in Table 2.2, the reaction was shown to be extremely sensitive to the solvent used; where the change to more polar solvents not only showed a significant drop in the yield but was also translated into reduced enantiomeric excesses. Thus, it was considered that the use of toluene as the solvent for the reaction was necessary in order to obtain the desired products in high levels of enantioselectivity.

Table 2.2. Study of the effect of the solvent on the reaction.



Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Toluene	54	97
2	CH_2Cl_2	24	38
3	$CHCl_3$	<10	n.d.[c]
4	CH_3CN	38	36
5	EtOH	32	39

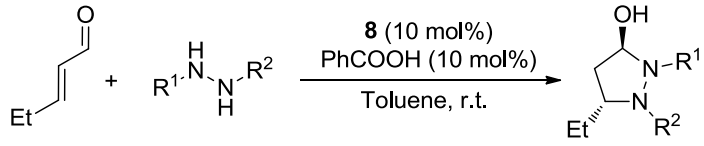
[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding reduced pyrazolidine **5a**. [c] n.d.: not determined.

The use of a series of co-catalysts was also studied to further promote the reaction. However, the inclusion of a variety of Brønsted acids or bases[50] did not display a positive effect on the reaction outcome and neither did increasing the additive stoichiometry.

For this reason we decided to focus on the evaluation of the effect that different substitution patterns on the hydrazides would have on the reaction, giving special attention to the variation in the acidity of the N-H groups (Table 2.3). Initially, no reaction was observed when the less acidic hydrazide **2b** was used, suggesting that a hydrazide with at least one acidic N-H group was required for the reaction to occur. In contrast, the reaction between the enal **1a** and the unsymmetrically substituted *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide **2c**, which presents enhanced acidity in one of the N-H groups, proceeded smoothly, providing the desired pyrazolidin-3-ol **4b** in excellent yield, enantioselectivity and as a single regioisomer. On the other hand, the need for a second acidic substituent, able to carry out the hemiacetal formation, was confirmed when hydrazides **2d**, **2e** and **2f** were unsuccessfully tested. Finally, when phthalhydrazide **2h** was employed as the Micheal donor a low yield of the corresponding pyrazolidin-3-ol adduct was obtained.

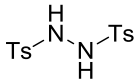
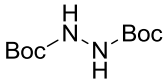
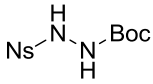
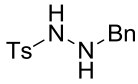
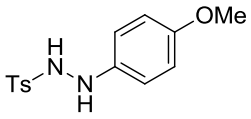
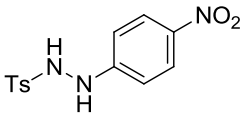
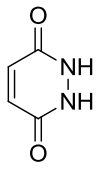
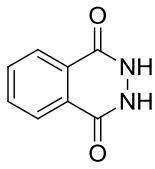
[50] PhCOOH, *p*-$NO_2C_6H_4COOH$, AcOH, Ph_3CCOOH, DABCO, DBU, 1,1,3,3-tetramethylguanidine and NaOAc were tested as co-catalysts (10 mol%).

Table 2.3. Evaluation of the performance of a series of hydrazides.



1a **2**

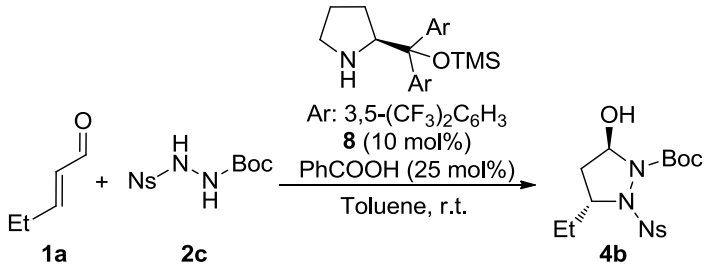
4a: R^1=Ts, R^2=Ts
4b: R^1=Ns, R^2=Boc

			
2a 54%[a] >90:10 dr[b] 97% ee[c]	**2b** <5% -	**2c**[d] 87% >90:10 dr 93% ee	**2d** <5% -
			
2e <5% -	**2f** <5% -	**2g** <5% -	**2h** 23% 67:33 dr n.d.[e]

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 25% benzoic acid was added. [e] n.d.: not determined.

The excellent results obtained for the *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide **2c** were understood in terms of the higher acidity of the N-H group attached to the nosyl substituent, which would presumably render this nitrogen more nucleophilic for the initial aza-Michael addition step, not only improving the reactivity but also enhancing the regioselectivity of the reaction. This would also explain the higher reactivity of hydrazide **2c** in this process compared to that observed with *N*,*N*'-*bis*-(*p*-toluenesulfonyl)hydrazide **2a**.

In conclusion, after a wide range of experimental variables had been explored, we selected *O*-trimethylsilyl diarylprolinol catalyst **8** and co-catalytic benzoic acid, with toluene as the solvent at room temperature as the optimal conditions to carry out the aza-Michael/intramolecular 1,2-addition reaction of α,β-unsaturated aldehydes and hydrazides. In addition, *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide **2c** was chosen as the most appropriate hydrazide for the reaction, presenting two acidic N-H groups that favoured both steps of the process (Scheme 2.46).

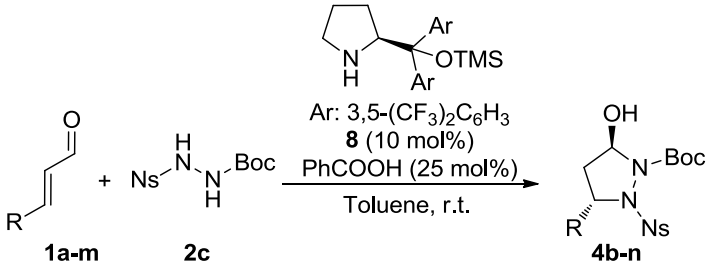


Scheme 2.46

3.1.3. Scope of the reaction

After initial optimization of the reaction conditions and subsequent idenfitication of the most effective hydrazide, we next proceeded to investigate the use of other α,β-unsaturated aldehydes with different substitution patterns, in order to survey the scope of the reaction and its performance in the preparation of a variety of substituted pyrazolidin-3-ols. In this sense, we studied the addition of *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide **2c** to a series of commercially available α,β-unsaturated aldehydes under the optimized conditions.

Table 2.4. Scope of the reaction using a series of differently substituted α,β-unsaturated aldehydes.



Entry	R (1)	Prod.	Yield (%)[a]	dr[b]	ee (%)[c]
1	Et (**1a**)	**4b**	87	91:9	93
2[d]	Me (**1b**)	**4c**	93	91:9	85
3	*n*-Pr (**1c**)	**4d**	99	>95:5	92
4	*n*-Bu (**1d**)	**4e**	91	>95:5	94
5	*n*-C_5H_{11} (**1e**)	**4f**	95	>95:5	93
6	*n*-C_6H_{13} (**1f**)	**4g**	78	>95:5	93
7	*n*-C_7H_{15} (**1g**)	**4h**	78	>95:5	92
8	*n*-C_8H_{17} (**1h**)	**4i**	99	>95:5	94
9	*Z*-EtCH=CH$(CH_2)_2$ (**1i**)	**4j**	68	>95:5	90
10	*i*-Pr (**1j**)	**4k**	50	>95:5	97
11	CO_2Et (**1k**)	**4l**	65	95:5	89
12	$(MeO)_2$CH (**1l**)	**4m**	95	>95:5	>99
13	Ph (**1m**)	**4n**	<10	n.d.[e]	n.d.[e]

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction performed at 0 ºC. [e] n.d.: not determined.

From the results summarized in the Table 2.4 we observed that the reaction proceeded efficiently with most of the α,β-unsaturated aldehydes examined. Substrates containing linear alkyl chains of different length and size at the β-

position (entries 1-8) provided the desired pyrazolidin-3-ols in high yields and high levels of stereoselectivity. We could mention that the reaction had to be conducted at 0 ºC in order to achieve a high enantiomeric excess when crotonaldehyde **1b** was employed (entry 2). Furthermore, branched and unsaturated β-alkyl substituents were tested within the reaction (entries 9 and 10). These performed well providing excellent enantioselectivities and slighly decreased yield. Additionally, functionalized α,β-unsaturated aldehydes such as **1k** or **1l** were also applied to the reaction, furnishing the final adducts in high yield and stereocontrol (entries 11 and 12). We should highlight that all these examples presented the formation of a single regioisomer, regardless of the substitution pattern present on the enal reagent.

However, when cinnamaldehyde was examined as the Michael acceptor, poor conversion was observed even after longer reaction times (entry 13). Similarly, other β-aryl substituted enals were tested (*i.e.* 4-methoxycinnamaldehyde and 4-nitrocinnamaldeyde), which also provided products in very low conversions. The low reactivity of these species was attributed to the lower electrophilicity that these compounds present, due to the extended conjugation of the α,β-unsaturated system with the aromatic ring.

We should mention that as part of the Lilly *Open Innovation Drug Discovery* program, pyrazolidinol **4b** was submitted for appraisal in a variety of primary biological assays. The proteins selected in this screening were specially targeted since they are known to be interesting targets in cancer, diabetes, Alzheimer and bone formation pathways. The data collected from these studies presented three potentially interesting results. First of all, pyrazolidinol **4b** showed 34% inhibition (at a concentration of 0.2 μM) of GSK3β inh pretreated K-*ras* Wnt (HCT116 KrasSL). In addition, for the mGlu2R antagonist assay, pyrazolidin-3-ol **4b** appeared to have an adverse effect, since negative values of -55% and -40%

inhibition were observed at 10 and 100 μM concentration respectively. Finally, this molecule showed 46% inhibition (at a concentration of 20 μM) of hexokinase 2 (hHK2 ADP-FP) that has a function within cancer glycolysis.

3.1.4. Transformation of the adducts

At this point, having established a robust methodology for the aza-Michael/hemiaminalization reaction sequence that enabled the synthesis of an array of interesting pyrazolidin-3-ol structures,[51,52] we proceeded to run a series of simple transformations in order to access other related structures of interest, by exploiting the intrinsic reactivity of the hemiaminal functionality present in the obtained adducts.

In this sense, the treatment of compounds **4b-i** with TFA led to a deprotection/dehydration sequence, providing access to a series of interesting pyrazoline derivatives (**21b-i**).[53] These compounds were cleanly isolated after short reaction times, providing the pyrazolines in excellent yields and with retention of the enantioselectivity (see Table 2.5).

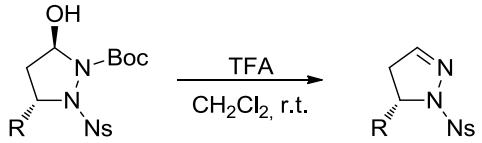
---

[51] For pyrazolidines in natural products and synthetic bioactive compounds, see: a) Rahman, M. T.; Nishino, H.; Qian, C.-Y. *Tetrahedron Lett.* **2003**, *44*, 5225; b) Chauveau, A.; Martens, T.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2002**, 1885; c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G. *Tetrahedron* **1997**, *53*, 12798; d) Kim, H.-O.; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935.

[52] For some examples of biologically active pyrazolidines, see: a) Witherington, J.; Bordas, V.; Gaiba, A.; Green, P. M.; Naylor, A.; Parr, N.; Smith, D. G.; Takle, A. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2256; b) Kutterer, K. M. K.; Davis, J. M.; Singh, G.; Yang, Y.; Hu, W.; Severin, A.; Rasmussen, B. A.; Krishnamurthy, G.; Faillic, A.; Katzc, A. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2527; c) Ahn, J. H.; Kim, J. A.; Kim, H.-M.; Kwon, H.-M.; Huh, S.-C.; Rhee, S. D.; Kim, K. R.; Yang, S.-D.; Park, S.-D.; Lee, J. M.; Kim, S. S.; Cheon, H. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1337.

[53] For a review on biological activity of pyrazolines, see: a) Kumar, S.; Bawa, S.; Drabu, S.; Kumar, R.; Gupta, H. *Recent Pat. Anti-infective Drug Discov.* **2009**, *4*, 154; For recent examples of biologically active pyrazolines, see: b) El-Sayed, M. A.-A.; Abdel-Aziz, N. I.; Abdel-Aziz, A. A.-M.; El-Azab, A. S.; El-Tahir, K. E. H. *Bioorg. Med. Chem.* **2012**, *20*, 3306; c) Hassan, S. Y. *J. Braz. Chem. Soc.* **2011**, *22*, 1286.

Table 2.5. Access to pyrazolines **21** from deprotection/dehydration of pyrazolidin-3-ols **4**.



4b-i **21b-i**

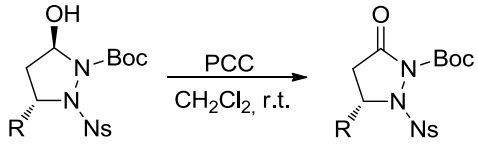
Entry	R (4)	Prod.	Yield (%)[a]	ee (%)[b]
1	Et (**4b**)	**21b**	97	92
2[c]	Me (**4c**)	**21c**	85	85
3	*n*-Pr (**4d**)	**21d**	99	92
4	*n*-Bu (**4e**)	**21e**	99	91
5	*n*-C_5H_{11} (**4f**)	**21f**	87	91
6	*n*-C_6H_{13} (**4g**)	**21g**	86	90
7	*n*-C_7H_{15} (**4h**)	**21h**	99	92
8	*n*-C_8H_{17} (**4i**)	**21i**	99	90

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction performed at 0 ºC.

On the other hand, we considered oxidation of the hemiaminal functionality, which would lead to the synthesis of the corresponding pyrazolidin-3-ones (**22b-i**). In a similar manner as with the pyrazolines synthesized previously, these heterocycles also present high synthetic interest due to their bioactivity.[54] In this sense, direct treatment of the pyrazolidines with PCC provided a series of oxidized adducts in excellent yields and enantioselectivities. The results obtained are summarized in Table 2.6.

[54] For some examples of bioactivity of pyrazolidinones, see: a) Vora, J. J.; Patel, A. R.; Patel, D. R.; Dholakia, S. *Int. J. Pharm. Sci. Res.* **2012**, *3*, 162; b) Bhosale, S. K.; Bhosale, N. S. *Int. J. Chem. Sci.* **2008**, *6*, 2256; c) Panfil, I.; Urbanczyk-Lipkowska, Z.; Suwinska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199.

Table 2.6. Access to pyrazolidinones **22** from oxidation of pyrazolidin-3-ols **4**.

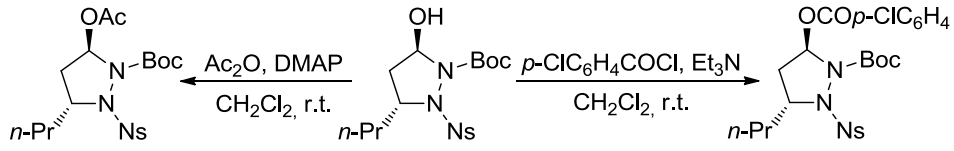


4b-i **22b-i**

Entry	R (4)	Prod	Yield (%)[a]	ee (%)[b]
1	Et (**4b**)	**22b**	95	93
2[c]	Me (**4c**)	**22c**	94	84
3	*n*-Pr (**4d**)	**22d**	97	92
4	*n*-Bu (**4e**)	**22e**	90	90
5	*n*-C_5H_{11} (**4f**)	**22f**	97	91
6	*n*-C_6H_{13} (**4g**)	**22g**	93	91
7	*n*-C_7H_{15} (**4h**)	**22h**	96	91
8	*n*-C_8H_{17} (**4i**)	**22i**	94	90

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction performed at 0 ºC.

Continuing with the examination of the transformations based on the hemiaminal functionality, we successfully esterified the secondary alcohol *via* acetylation or *p*-chlorobenzoylation conditions, yielding esters **23d** and **24d** respectively in high yields and without erosion of enantiopurity (see Scheme 2.47).



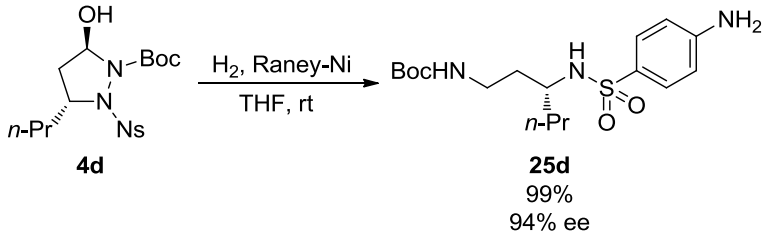
23d
99%
>95:5 dr
95% ee

4d

24d
89%
90:10 dr
91% ee

Scheme 2.47

Finally, it was envisaged that another potential transformation was the possible cleavage of the N-N bond, to access enantioenriched 1,3-diamines that are synthetically useful chiral building blocks.[55] With this intention, exposure of pyrazolidin-3-ol **4d** to H_2, in the presence of Raney-Ni, resulted in the hydrogenolysis of the N-N bond to afford enantioenriched 1,3-diamine **25d**, in which simultaneous reduction of the nitro group present on the nosyl substituent had also occurred (Scheme 2.48). Alternative attempts to cleave this N-N bond without the concomitant reduction of the nitro group were unsuccessful.



4d **25d** 99% 94% ee

Scheme 2.48

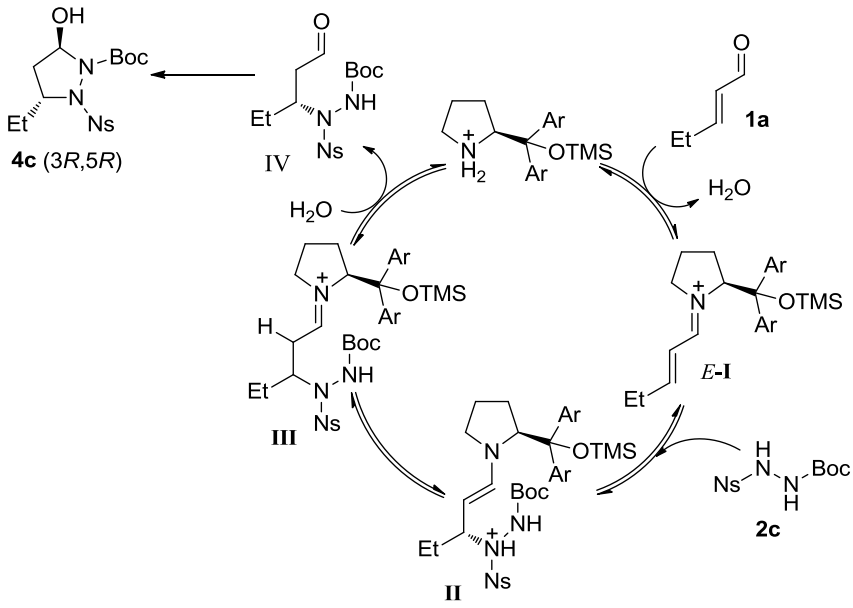
Once again, diamine **25d** was submitted to Lilly *Open Innovation Drug Discovery* program, for evaluation with the same set of proteins as pyrazolidinol **4b**. In this case, two potentially interesting results were achieved. On the one hand, diamine **25d** showed 43% inhibition (at a concentration of 20 μM) of hexokinase 2 (hHK2 ADP-FP), similar to the case of the pyrazolidinol **4b**. On the other hand, the diamine appeared to have a stimulating effect rather than an inhibiting effect in the case of the DLD-1 KrasSL assay, since a negative value of inhibition (-74%) was observed at 0.2 μM concentration. For the remaining enzyme assays studied, low activity was displayed.

---

[55] For some examples of the synthesis of 1,3-diamines, see: a) Sibi, M. P.; Standley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, *348*, 2371; b) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276; c) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502.

3.1.5. Mechanistic insights

Based on the results obtained throughout this section, and considering that the stereochemical outcome of the pyrazolidin-3-ol adducts **4** (*i.e* 3*R*,5*R*) was in good agreement with published examples of conjugate addition using nitrogen nucleophiles catalyzed by diarylprolinol ethers,[9,14] we propose the mechanism shown in Scheme 2.49 for the developed aza-Michael/hemiaminalization reaction.



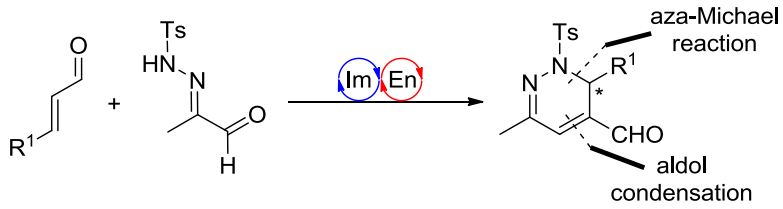
Scheme 2.49

The catalytic cycle starts with the initial reversible condensation of the α,β-unsaturated aldehyde with the aminocatalyst, to access the iminium ion. According to the previously mentioned studies, the nature of the catalyst promotes the formation of the more stable *E* iminium ion (***E*-I**) preferentially, in which the *Si* face is hindered by the large substituent on the catalyst. Therefore, the *Re* face will be more accesible for the addition of *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide **2c**.

Following the aza-Michael reaction, the resulting enamine intermediate (**II**) undergoes an intramolecular proton transfer (most likely *via* a water molecule), which provides a second iminium intermediate (**III**). Hydrolysis of this intermediate, releases the catalyst and the corresponding conjugate addition product (**IV**), in which the second nucleophilic N-H adds in an intramolecular manner to the formyl group to generate the observed hemiaminal product **4c**. The origin of the high *trans* diastereoselectivity achieved from this step can be explained in terms of a presumable anomeric effect between the hydroxy group and the non-bonding electrons on the adjacent nitrogen atom.

3.2. Pyruvaldehyde derived hydrazones as bifunctional reagents: aza-Michael/aldol cascade

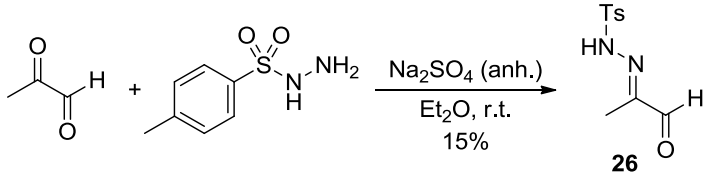
As stipulated in the specific objectives, the second section of this chapter is based on the use of hydrazones derived from pyruvaldehyde for the aza-Michael reaction/aldol condensation sequence, exploiting the iminium/enamine manifold and leading to the synthesis of dihydropyridazines.



Scheme 2.50

3.2.1. Viability of the reaction

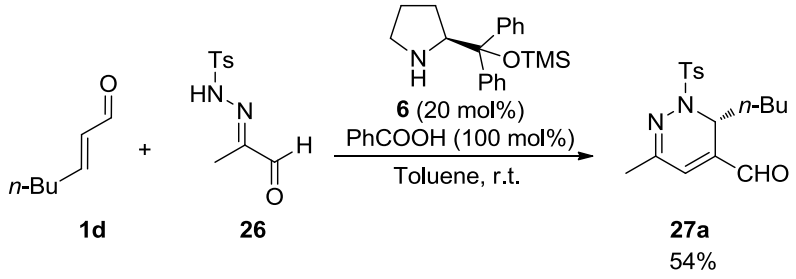
The investigations began with the synthesis of hydrazone nucleophile **26** by condensation of *p*-toluenesulfonylhydrazide and methylglyoxal (Scheme 2.51).



Scheme 2.51

With the nucleophile at hand, we evaluated the viability of the reaction with the *O*-trimethylsilyl-protected diphenylprolinol derivative **6** as a potential catalyst. For this purpose, we selected *trans*-2-heptenal as the model acceptor, using toluene

as solvent and with benzoic acid as an additive at room temperature (Scheme 2.52).[56]



1d **26** **27a**
54%

Scheme 2.52

The desired 2,3-dihydropyridazine product **27a** was delivered in moderate isolated yield, demonstrating that this functionalized hydrazone derived from the pyruvaldehyde was indeed a suitable reagent to perform an aza-Michael reaction/aldol condensation process under iminium/enamine activation.

Next, in order to determine the enantiomeric excess of the obtained product we needed to establish a method for HPLC analysis of these compounds on a chiral stationary phase. In this context, we proceeded to prepare the corresponding racemic standard using a 1:1 ratio of (*R*)- and (*S*)-catalyst **6**.[57] The separation of the enantiomers was successful when using a chromatographic Chiralpak AD-H column, with a 1.0 mL/min flow rate and eluting with *n*-hexane/*i*-PrOH (90:10). Applying these conditions it was shown that pyridazine **27a**, obtained from the reaction catalyzed by the chiral secondary amine **6**, was obtained in a promising level of enantiocontrol (82% ee).

---

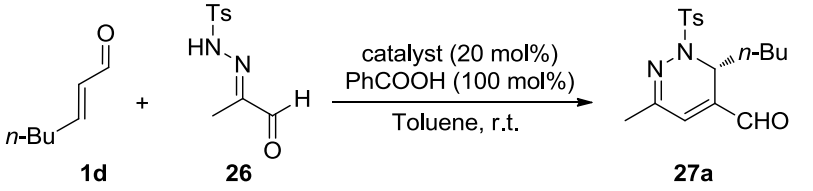
[56] Note: 100 mol% co-catalyst was added since a previous trial with 10 mol% benzoic acid provided poor conversion.

[57] Note: D,L-Proline was inactive in this reaction.

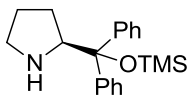
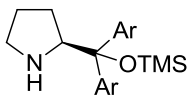
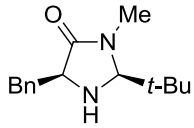
3.2.2. Optimization of the reaction conditions

In an attempt to increase the enantioselectivity, we decided to evaluate the performance of different chiral secondary amines. Specifically, the most commonly employed catalysts for the aza-Michael reaction were selected. In this sense, the use of the bulkier *O*-TMS diarylprolinol derivative **8** further improved the stereocontrol, in conjunction with a moderate increase in the conversion of the reaction. On the contrary, when imidazolidinone **13** was tested, only traces of the desired product were observed. Thus, as in the addition of hydrazides, the *O*-trimethylsilyl diarylprolinol aminocatalyst **8** was selected for further reaction optimization.

Table 2.7. Evaluation of chiral secondary amines as catalysts of the reaction.



1d **26** **27a**

		
6	**8**	**13**[c]
54%[a]	60%	<5%
82% ee[b]	98% ee	n.d.[d]

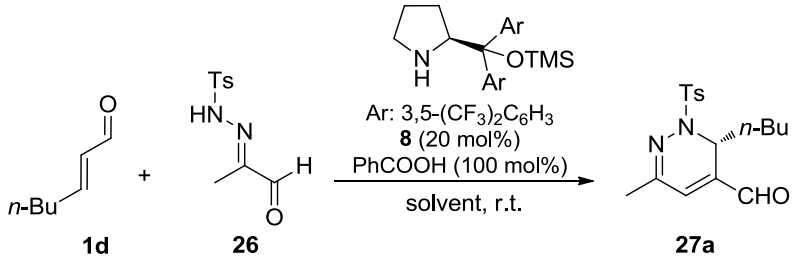
Ar: 3,5-$(CF_3)_2$-C_6H_3

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction carried out using TFA as co-catalyst. [d] n.d.: not determined.

We continued our investigations with the evaluation of the best experimental conditions in an attempt to improve the yield of the reaction. In this sense, we started by examinating the effect of the solvent on the course of the reaction, under otherwise identical experimental conditions. From the results summarized in the

Table 2.8, we concluded that toluene was the most efficient solvent in terms of both conversion and enantioselectivity. Mildly polar solvents yielded the desired adduct with high stereocontrol but together with a noticable drop in isolated yield (entries 2-4). Surprisingly enough, this tendency was even more acute when strongly polar solvents were used; despite these solvents finding success in the other reported examples of aza-Michael/aldol sequences (entries 5-8).[31-33]

Table 2.8. Study of the influence of the solvent on the reaction.



1d **26** **27a**

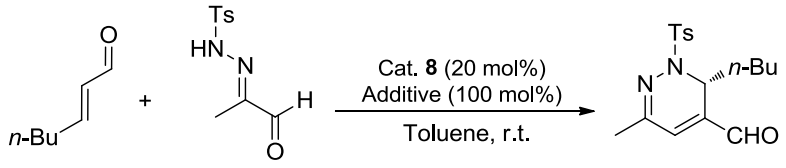
Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Toluene	60	98
2	$CF_3C_6H_5$	52	96
3	CH_2Cl_2	30	94
4	$CHCl_3$	24	94
5	THF	13	n.d.[c]
6	EtOH	18	n.d.[c]
7	CH_3CN	<5	n.d.[c]
8	DMF	<5	n.d.[c]

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] n.d.: not determined.

We next proceeded to evaluate the effect of using different co-catalysts. The results obtained are summarized in the Table 2.9. First of all, other benzoic acids, with substituted aromatic rings, were tested; although this resulted in reduced yields

regardless of the substitution pattern employed (entries 2-4). Acetic acid and the more acidic diphenylacetic acid presented a slightly improved conversion with respect to the substituted benzoic acids examined. However, the isolated yields were lower than that obtained using benzoic acid as the co-catalyst (entries 5-6 *cf.* entry 1). We also evaluated the use of a reduced stoichiometry of co-catalyst, but this resulted into a significant drop in the isolated yield again (entry 7).

Table 2.9. Effect of the different co-catalysts.

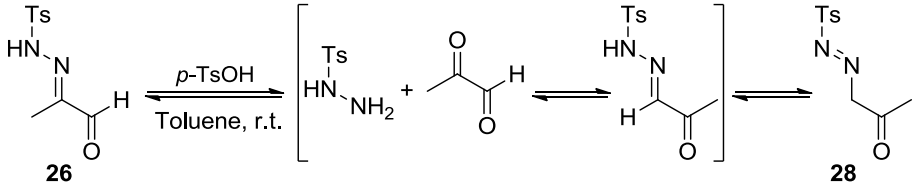


1d **26** **27a**

Entry	Additive	pKa[a]	Yield (%)[b]	ee (%)[c]
1	PhCOOH	4.20	60	98
2	*p*-$NO_2C_6H_4COOH$	3.44	31	98
3	*p*-$MeOC_6H_4COOH$	4.47	36	98
4	*p*-FC_6H_4COOH	4.14	33	98
5	AcOH	4.76	42	98
6	$Ph_2CHCOOH$	3.94	48	98
7[d]	PhCOOH	4.20	36	98
8	*p*-TsOH	-2.80	<5	n.d.[e]
9	DABCO	-	<5	n.d.[e]

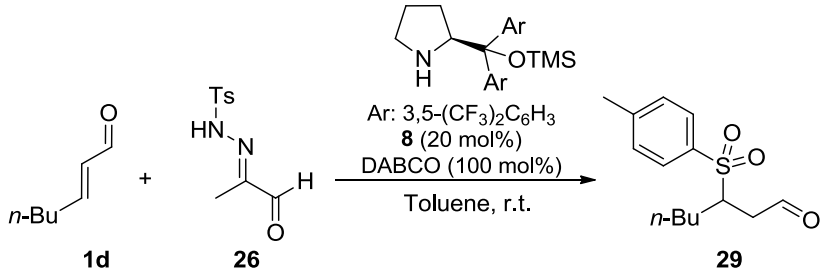
[a] pKa in water: a) *pKa Predictions for Organic Acids and Bases* (Eds.: Perrin, D. D.; Serjeant, E. P.; Dempsey, B.), Chapman and Hall, London, **1981**; b) Guthrie, P. P. *Can. J. Chem.* **1978**, *56*, 2342; c) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492; d) *Determination of Organic Structures by Physical Methods* (Ed.: Brown, H.C.), Academic Press, New York, **1955**. [b] Yield of the pure product isolated after flash chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction performed using 20 mol% of additive. [e] n.d.: not determined.

On the other hand, when using the highly acidic *p*-toluensulfonic acid we observed the formation of an unreactive by-product **28**, which arose from the hydrolysis/condensation/isomerization process of the hydrazone (shown in Scheme 2.53).



Scheme 2.53

Moreover, when a base co-catalyst was incorporated to the reaction media an unexpected product **29** was also produced. We found that the base was able to deprotonate the hydrazone, promoting the release of a nucleophilic sulfonate species that was able to add to the β-position of the unsaturated aldehyde, yielding sulfone **29** as a racemate (shown in Scheme 2.54). We discovered that even trace amounts of base were able to promote this side-reaction.

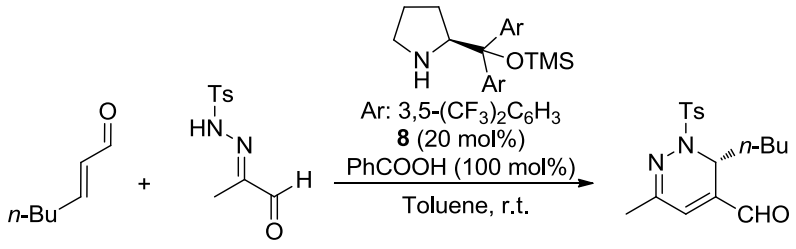


Scheme 2.54

In a final set of experiments designed to improve the yield of the reaction, we investigated varying the concentration of the reaction, as well as varying the

proportions of the reagents (results shown in the Table 2.10). In this sense, we found that diluting the reaction provided improved conversion (*i.e.* entry 3 *vs.* entries 1-2) although the effect was not very significant. However, variation of the proportion of the nucleophile with respect to the Michael acceptor provided a much more notable improvement in yield (entries 4-6). Increasing the amount of the hydrazone reagent with respect to the enal to a ratio of 2:1 translated into a concomitant increase in the formation of the desired product, which afforded the product in an improved 84% yield.

Table 2.10. Effect of concentration and the proportion of the reagents.



1d **26** **27a**

Entry	Conc. (M)	Equiv. 1d	Equiv. 26	Yield (%)[a]	ee (%)[b]
1	0.1	1	1	60	98
2	0.3	1	1	33	96
3	0.05	1	1	65	98
4	0.05	1.5	1	65	98
5	0.05	1	1.5	69	98
6	0.05	1	2	84	96

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

Therefore, it was concluded that conditions shown in the entry 6 of the Table 2.10 were optimal to carry out the projected aza-Michael/aldol reaction/dehydration

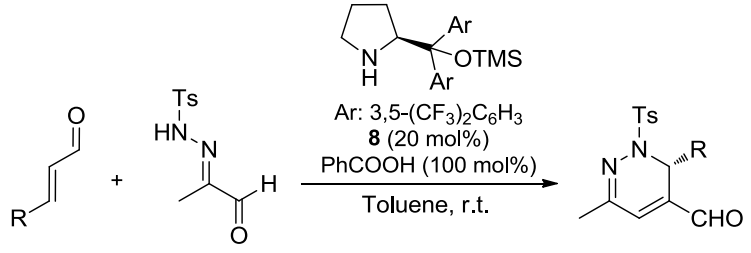
sequence with hydrazones; *i.e.* 20 mol% catalyst **8** and benzoic acid in toluene (0.05M) at room temperature, using a hydrazone/enal stoichiometry of 2:1.

3.2.3. Scope of the reaction

Once these optimal conditions for the aza-Michael/aldol reaction/dehydration sequence with hydrazone **26** had been established, we next proceeded to extend the reaction scope to the use of a variety of α,β-unsaturated aldehydes possessing different substitutions at the β-position.

From these results summarized in Table 2.11, it can be seen that the reaction tolerates well the use of α,β-unsaturated aldehydes containing linear alkyl chains of different length and size (entries 1-5). Dihydropyridazine products **27a-e** were obtained in high yields and excellent enantioselectivities in all cases, only noticing a slight decrease in the yield as the size of the chain increased. Furthermore, an alkene-containing β-alkyl substituent was also tested, which provided the desired adduct in good yield and high stereocontrol (entry 6). Additionally, the use of other functionalized α,β-unsaturated aldehydes such as **1l** or **1n** was also investigated, furnishing the final adducts in high yield and enantioselectivities (entries 7 and 8).

Table 2.11. Scope of the reaction using a series of differently substituted α,β-unsaturated aldehydes.



1a-r **26** **27a-m**

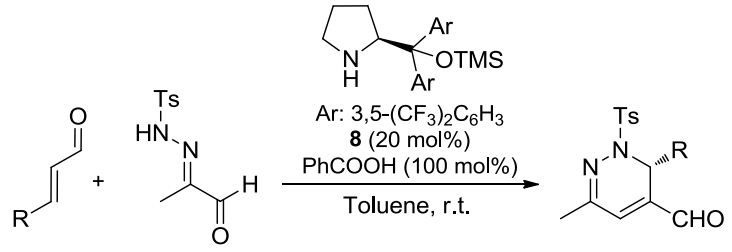
Entry	R (1)	Prod.	Yield (%)[a]	ee (%)[b]
1	*n*-Bu (**1d**)	**27a**	84	96
2	Me (**1b**)	**27b**	91	89
3	Et (**1a**)	**27c**	74	96
4	*n*-Pr (**1c**)	**27d**	72	96
5	*n*-C_8H_{17} (**1h**)	**27e**	63	97
6	*Z*-EtCH=CH$(CH_2)_2$ (**1i**)	**27f**	68	97
7	$(MeO)_2CH$ (**1l**)	**27g**	61	97
8	$BnOCH_2$ (**1n**)	**27h**	69	96
9	Ph (**1m**)	**27i**	19	86

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

In addition, and contrary to what had been observed previously for the reaction with hydrazides, aromatic enals were shown to be reactive towards this aza-Michael/aldol reaction cascade, although the products were isolated in lower yields (*e.g.* using cinnamaldehyde in entry 9). However, the exceptional enantioselectivity encouraged us to try to find improved conditions to perform the reaction more efficiently with aromatic α,β-unsaturated aldehydes. This was successfully accomplished by a simple change in the proportion of reagents; from

using excess of hydrazone in the optimized conditions for aliphatic or functionalized enals to employing an excess of Michael acceptor, which provided a significant increase in the isolated yield with cinnamaldehyde (see entry 1 on Table 2.12). This modification was successfully extended to other aromatic enals (entries 2-5).

Table 2.12. Scope of the reaction using aromatic α,β-unsaturated aldehydes.[a]



1m-r **26** **27i-m**

Entry	R (1)	Prod.	Yield (%)[b]	ee (%)[c]
1	Ph (**1m**)	**27i**	49	89
2	*p*-$NO_2C_6H_4$ (**1o**)	**27j**	52	95
3	*p*-$MeOC_6H_4$ (**1p**)	**27k**	60	85
4	*p*-CNC_6H_4 (**1q**)	**27l**	72	94
5	5-NO_2Furyl (**1r**)	**27m**	55	90

[a] Reactions performed using a 2:1 acceptor/donor proportion. [b] Yield of the pure product isolated after flash chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

Products were obtained in moderate to good yields and high enantioselectivities (see Table 2.12). The electronic nature of the aromatic ring did not display an acute effect on the reactivity of the reaction. However, we could point out that it seemed that the incorporation of electron-withdrawing groups on the ring resulted in a slight increase in stereocontrol for the process, whereas electron-

donating substituents gave slightly lower enantioselectivities (*i.e.* entries 2, 4-5 *vs.* entry 3).

At this point, the absolute configuration of the products furnished by the aza-Michael reaction/aldol condensation domino process still had to be determined. For this purpose, we performed the reduction of the formyl group on dihydropyridazine derivative **27j**. The obtained secondary alcohol product **30j** provided monocrystal structures suitable for single crystal X-ray analysis (shown in Figure 2.7). The absolute stereochemical outcome showed a *3R* absolute configuration, which was extended by analogy to the remaining synthesized adducts **27a-m**, assuming an identical configuration based on the mechanistic understanding of the process.

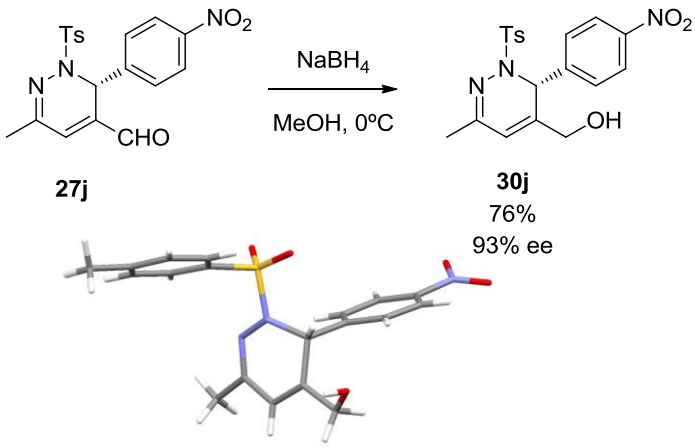
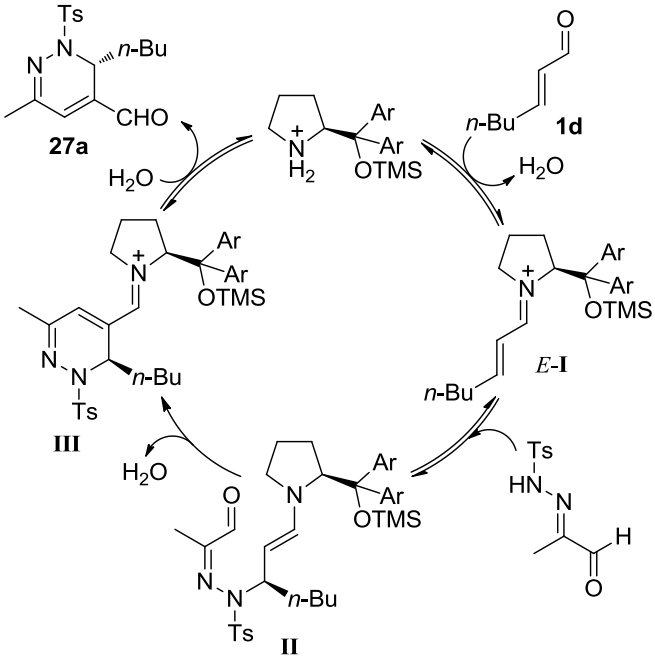


Figure 2.7

The stereochemical outcome obtained for the reaction suggested that the initial conjugate addition of the nucleophile proceeded according to the expected catalytic cycle for this type of reaction, in a similar manner as for the previous example using hydrazides. In this sense, the catalyst initially reacts with the α,β-unsaturated aldehyde, forming the most stable iminium ion (*E*-**I**). Next, the

conjugate addition of the nitrogen nucleophile takes place from the less hindered face of the iminium ion, leading to the formation of an enamine intermediate (**II**). Given the nucleophilic nature of this intermediate, it is able to engage in a domino process, carrying out an aldol condensation with the formyl group provided by the hydrazone and forming the second iminium intermediate (**III**). A final hydrolysis step releases the enantioenriched tetrahydropyridazine **27a** and the catalyst, which can re-enter the catalytic cycle (see Scheme 2.55).



Scheme 2.55

4. CONCLUSIONS

Considering the results presented throughout this chapter, a series of conclusions can be drawn:

- Hydrazides and hydrazones are adequate bifunctional reagents to carry out aza-Michael initiated cascade processes with α,β-unsaturated aldehydes under iminium activation.

- The conjugate addition/intramolecular nucleophilic 1,2-addition reaction sequence of *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide with enals takes place efficiently in the presence of the *O*-TMS diarylprolinol catalyst **8**, leading to the synthesis of pyrazolidines in complete regioselectivity, high yields and excellent stereocontrol. The reaction presents a wide scope for a variety of enals with different substitution at the β-position; however, aromatic enals could not be employed. The acidity of the N-H groups has proven to be a determining factor for the high performance of the reaction. Two highly acidic N-H groups are required in order to favour both the initial addition step and the subsequent formation of the hemiaminal.

- The resulting pyrazolidine adducts are interesting building blocks for synthesis. Simple and efficient modifications of these heterocycles give access to a series of important products, such as pyrazolines, pyrazolidinones and 1,3-diamines.

- We have also developed an efficient methodology to perform an aza-Michael/aldol reaction/dehydration sequence between hydrazones and α,β-unsaturated aldehydes using the same diarylprolinol derivative **8** as catalyst, which provides a series of 2,3-dihydropyridazines in high yields and excellent enantioselectivities. It is noteworthy that this reaction allows the use of enals with

aromatic substituents at the β-position, thus overcoming the limitations that these reagents present in the asymmetric aminocatalytic aza-Michael reaction.

3

3

Hydrazones as *C*-nucleophiles for aminocatalytic conjugate addition of acyl anion equivalents

1. INTRODUCTION: ORGANOCATALYTIC CONJUGATE ADDITION OF ACYL ANION EQUIVALENTS

Even though the *umpolung* concept had been previously mentioned,[1] it was in 1979 that Seebach reintroduced the term in the way we know it today,[2] as "any process by which donor or acceptor reactivity of an atom is interchanged".[3] In this work, Seebach proposed a systematic nomenclature for the synthons created from bond disconnections, based on the consideration that reactions most frequently used in organic synthesis are *polar* in nature. Therefore, bond formation and cleavage should occur between a nucleophile (or donor – d) and an electrophile (or acceptor – a). Also, he noted that most target molecules in a synthesis have functional groups containing heteroatoms, which impose an alternating acceptor/donor reactivity pattern to the carbon skeleton. In this sense, it is considered that a reagent has a *normal* reactivity pattern (type I) when the molecule possesses acceptor properties at carbons C-1, C-3, C-5, etc., and donor properties at the carbons C-2, C-4, C-6, etc. (with the heteroatom being a donor center). The combination of components with type I reactivity provides 1,(2n+1)-disubstituted products ($n \geq 1$; *i.e.* 1,3-, 1,5-, 1,7-, etc.) exclusively, with an odd number of carbon atoms between the functional groups. On the contrary, an even number of carbon atoms between the functional groups of a molecule lead to anomalous disconnections. Therefore, from a retrosynthetic perspective, we need to interchange the polarity/normal reactivity of a

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[1] a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231; b) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075; c) Wittig, G.; Davis, P; Koenig, G. *Chem. Ber*. **1951**, *84*, 627.

[2] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

[3] a) *Umpoled Synthons. A Survey of Sources and Uses in Synthesis* (Ed.: Hase, T. A.), Wiley-Interscience, **1987**; b) Lever Jr., O. W. *Tetrahedron* **1976**, *32*, 1943; c) Seebach, D.; Kolb, M. *Chem. Ind.* **1974**, 687; d) Callear, A. B.; Fleming, I.; Ottewill, R. H.; Waiwright, K.; Warren, S. G.; Prince, R. H. *Chem. Ind.* **1974**, 910.

synthon to access an *umpolung* process in order to make these disconnections feasible (Figure 3.1).

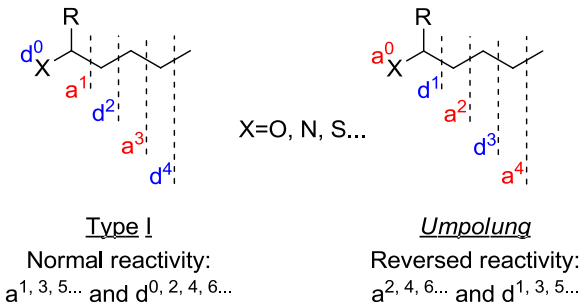

Figure 3.1

The archetypal example of umpolung reactivity is the inversion of polarity of the carbonyl group; a widely employed tool in organic synthesis, especially for the construction of C-C bonds.[4] This reactivity is usually achieved by using synthetic equivalents (*e.g. acyl anion equivalents*) that are able to temporarily reverse the normal type I acceptor (a^1) reactivity of the carbonyl group into a donor (d^1) synthon. Once the new C-C bond has been formed, the carbonyl group can be regenerated from these acyl anion equivalents by simple transformations.

In particular, conjugate addition of acyl anion equivalents to electron deficient olefins shows as a very interesting application of umpolung reactivity, enabling the preparation of 1,4-dicarbonyl compounds that are difficult to access by conventional methods.[5] Enantioselective catalytic variants of the reaction that use either transition

[4] Johnson, J. S. *Curr. Opin. Drug Discov. Devel*. **2007**, *10*, 691; b) Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326.

[5] For some reviews on conjugate additions of acyl anion equivalents, see: a) *Handbook of Reagents for Organic Synthesis: Reagents for Silicon-Mediated Organic Synthesis* (Ed.: Fuchs, P. L.), **2011**; b) Vora, H. U.; Rovis, T. *Aldrichim. Acta* **2011**, *44*, 3; c) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629; d) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.

metal catalysis[6] or organocatalysis[7] to access these compounds in an enantiomerically enriched fashion have been reported over the last few years.

As shown in Chapter 2, the field of organocatalysis presents a very interesting alternative method to promote conjugate additions. Both acceptor and donor substrates can be activated using organocatalysts, by selecting the most appropriate methodology in each case. In this sense, and referring to the organocatalytic *umpolung* conjugate addition of acyl anion equivalents, direct β-acylations of α,β-unsaturated carbonyl compounds have been fundamentally approached using the Stetter reaction under chiral *N*-heterocyclic carbene (NHC) catalysis.[8] These catalysts are able to temporarily reverse the reactivity pattern of an aldehyde (*i.e.* now behaving as a nucleophile) and at the same time introduce the necessary chiral information for the stereocontrol of the reaction. In this sense, after Enders introduced the first asymmetric intramolecular Stetter reaction in 1996,[9] a wide variety of catalysts have been used for the development of highly enantioselective versions of this reaction. Particularly, Rovis and co-workers have developed a series of very efficient triazolium catalysts, applicable to both the intramolecular and the intermolecular versions (some representative examples are shown in the Scheme 3.1).[10]

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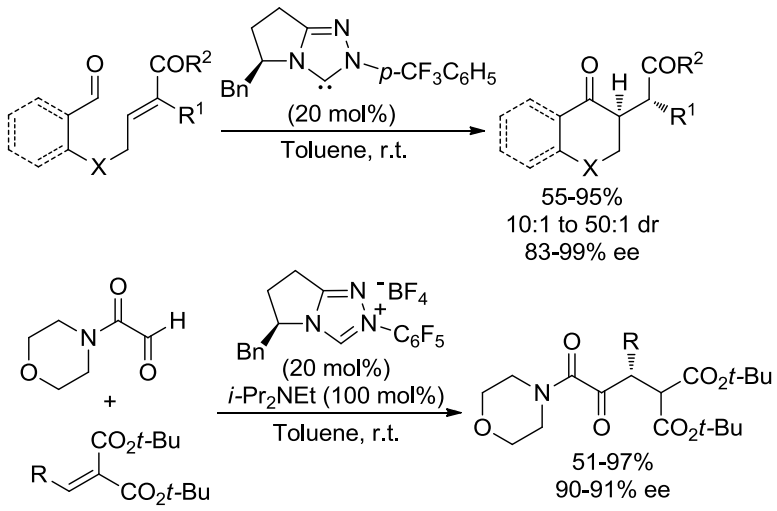
6 Linghu, X.; Potnik, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070.

7 Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.

8 For specific reviews on Stetter reaction, see: a) DiRocco, D. A.; Rovis, T. *Science of Synthesis, Stereoselective Synthesis* Vol. 2, p. 835-862 (Ed.: De Vries, J. G.; Molander, G. A.; Evans, P. A.), **2011**; b) Cee, V. J. *Name Reactions for Homologations* Pt. 1, p. 576-587 (Ed.: Li, J. J.), **2009**; c) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189.

9 Enders, D.; Breuer, K.; Runsink, J. H. *Helv. Chim. Acta* **1996**, 1891.

10 For the example of the intramolecular version, see: a) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284; For the intermolecular reaction, see: b) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066.



Scheme 3.1

This approach proved to be very efficient for a large number of direct asymmetric acylation reactions.[11] However, its development also made the limitations apparent. The main problem associated with this approach is the presence of the competitive benzoin condensation (*i.e.* self-condensation of the aldehyde by 1,2-addition), which in many cases is the dominant process, leading to the 1,2-addition product instead of the desired 1,4-addition adduct. Thus, highly electrophilic Michael acceptors are ususally required in order to overcome this chemoselectivity issue and direct the addition to the β-position. This meant that the intermolecular version of the reaction remained barely investigated until the end of the last decade.[12] Even now, most of the examples reported show the use of highly electrophilic species such as nitroalkenes or alkylidenemalonates.

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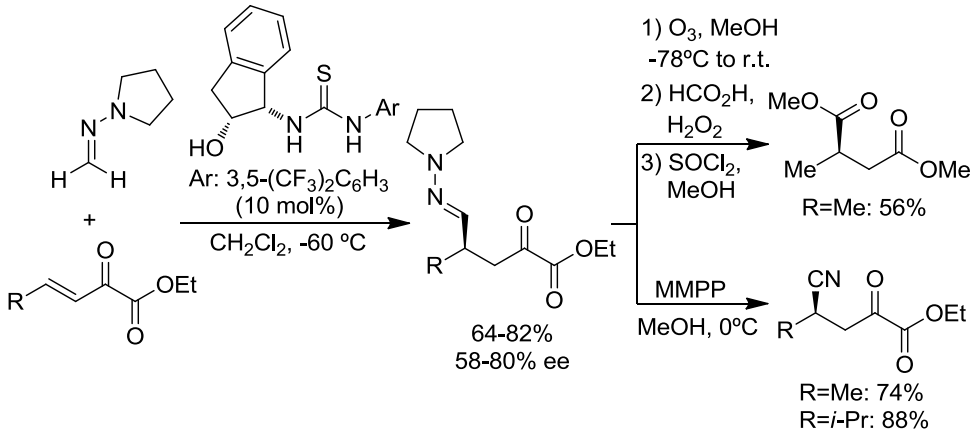
[11] For a review, see: Enders, D.; Niemeyer, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

[12] For some representative examples, see: a) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 239; b) Jousseaume, T.; Wurz, N. E; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1410; c) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872; d) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, *34*, 3989.

In this sense, the indirect conjugate addition of acyl anion equivalents using different organocatalytic activation methods presents a significant advance, enabling the use of other types of electrophiles for the intermolecular variant of this reaction. An early attempt was reported by Lassaletta and co-workers in 2007. The work described the formal enantioselective conjugate addition of *N*,*N*'-dialkylhydrazones, as synthetic equivalents of the formyl group, to β,γ-unsaturated α-ketoesters (Scheme 3.2).[13] Thiourea catalysts were chosen to activate the Michael acceptors based on the hydrogen bonding activation approach. In this sense, the 1,2-dicarbonyl group present on the electrophile was proven essential for efficient activation. Both oxygen atoms are proposed to hydrogen-bond to the thiourea, thus facilitating the activation of the acceptor and arranging the stereocontrol of the process. The latter was also assisted by the presence of a hydroxy group at the C-1 position of the catalyst, which is able to enagage in an additional hydrogen bond with the nucleophile, activating it and also directing its approach to the acceptor. Despite this, the reaction still presented some stereocontrol issues, rendering the desired γ-hydrazono compounds in high yields but moderate levels of enantioselectivity. The methodology was directed towards overcoming another issue associated with the Stetter reaction – *i.e.* the lack of applicability to the formylation reaction. In this sense, the potential of the reaction was exemplified by two simple transformations of the final adducts: oxidative cleavage of the hydrazone moiety to render β-nitrile carbonyl functionality and ozonolytic cleavage, followed by oxidation and esterification, which gave access to a succinate derivative.

[13] Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett*. **2007**, *9*, 3303.

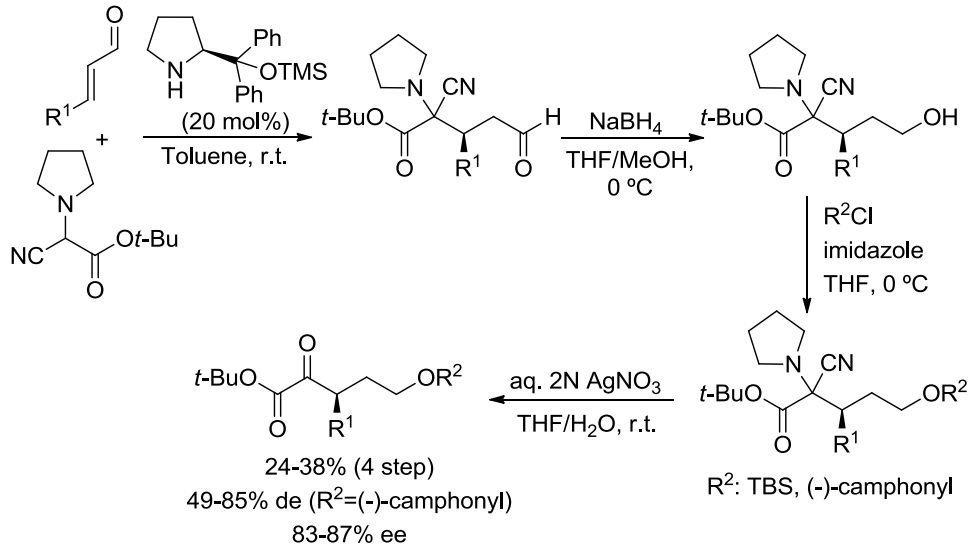


Scheme 3.2

In a different approach, and in the line with his previous studies on the use of α-aminonitriles as acyl anion equivalents,[14] Enders described the aminocatalytic conjugate addition of this type of nucleophiles to α,β-unsaturated aldehydes in a formal β-glyoxylation process.[15] The presented sequence consisted of four steps as shown in Scheme 3.3; following the initial secondary amine-catalyzed conjugate addition to the enals, the aldehyde was reduced to the corresponding alcohol, protected, and finally the masked carbonyl group (*i.e.* the α-aminonitrile moiety) was released, affording the desired α-ketoesters in moderate yield and enantioselectivities between 83-87% ee.

[14] For some examples, see: a) Enders, D.; Bonten, M. H.; Raabe, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2314; b) Pierre, F.; Enders, D. *Tetrahedron Lett.* **1999**, *40*, 5301; c) Enders, D.; Lotter, H.; Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *Nouv. J. Chim.* **1984**, *8*, 747.

[15] Enders, D.; Bonten, M. H.; Raabe, G. *Synlett* **2007**, 885.

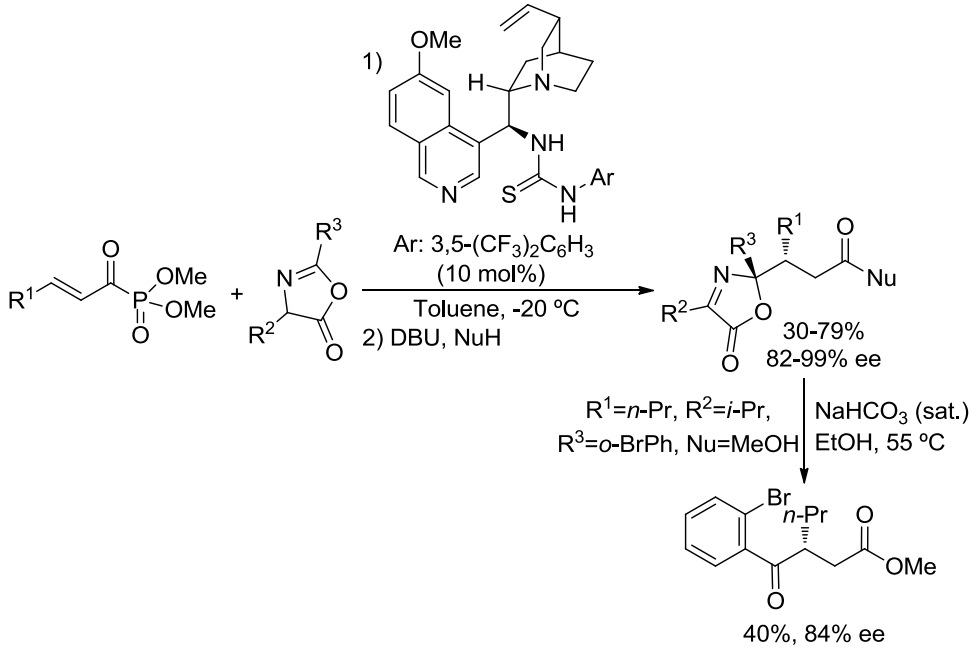


Scheme 3.3

The use of oxazolones as acyl anion equivalents has been the most studied approach in this field. In this sense, Jørgensen and co-workers studied the possibility of carrying out the conjugate addition reaction of this type of pro-nucleophile to acyl phosphonates, using a chiral thiourea as the catalyst.[16] In a similar manner as that described by Lassaletta,[13] the catalyst allows the double activation of both the donor and the acceptor. The thiourea catalyst applied to this situation is able to activate the acyl phosphonate by hydrogen bonding, and also contains a *cinchona* subunit with a tertiary amine able to deprotonate the nucleophile. The oxazolone unit contained two reactive points at C-2 and C-4, which could be modulated based on the substituents introduced at each position. Oxazolones with aryl substituents at C-2 position and bulky alkyl substituents at C-4 favoured the attack *via* C-2 (*i.e.* the position acting as an acyl anion equivalent of ketones). This methodology was

[16] Jiang, H.; Paixao, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2010**, *132*, 2775.

extended to the use of a series of phosphonates and oxazolones with different substituents, obtaining the conjugate addition products in good yields and excellent enantioselectivities (see Scheme 3.4). The base hydrolysis of one of these compounds released the corresponding masked 1,4-dicarbonyl product, demostrating the utility of the oxazolone ring as an umpolung equivalent of the carbonyl unit.

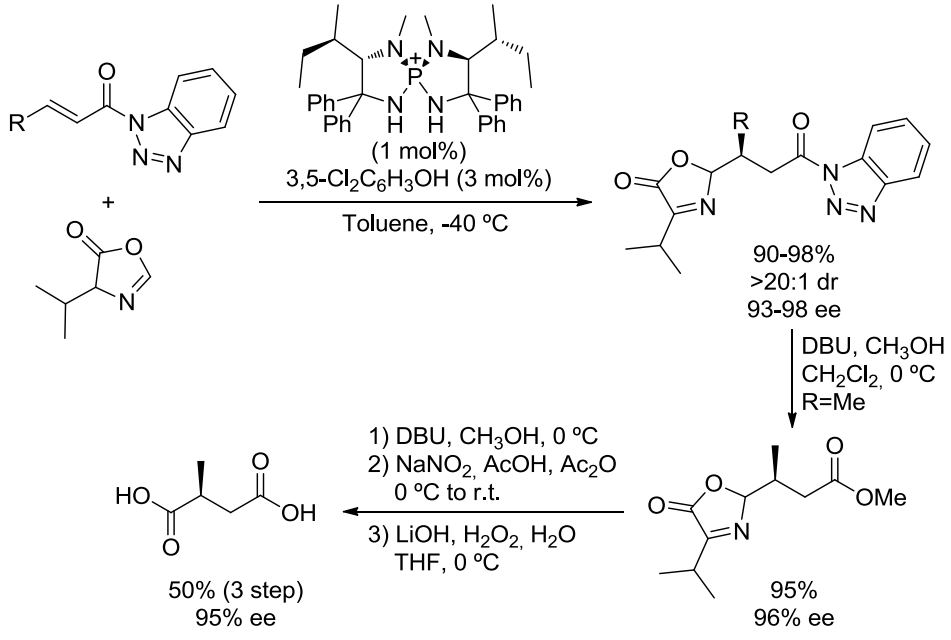


Scheme 3.4

A highly interesting contribution to the field was reported by Ooi and co-workers, proving that structurally discrete chiral supramolecular catalysts are able to promote a highly stereoselective conjugate addition of oxazolones to α,β-unsaturated ester surrogates with a broad substrate scope (shown in Scheme 3.5).[17]

[17] Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120.

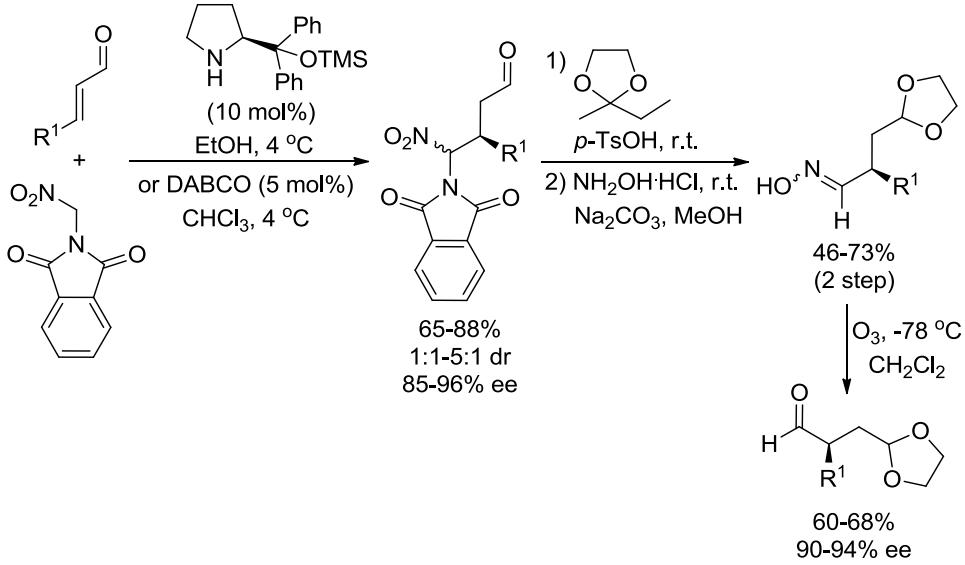
In particular, the treatment of a chiral tetraaminophosphonium cation with phenol resulted in the molecular assembly of a catalytically active supramolecular architecture through intermolecular hydrogen bonding. In solution, all these structural components in the assembly cooperatively participated in the activation of the Michael donor and also played an important role in the stereocontrol of the reaction. The synthetic potential of the reaction was also highlighted by the successful derivatization of one of the obtained compounds into methylsuccinic acid in four steps, showing the ability of the oxazolones to behave as hydroxycarbonyl equivalents. This methodology has recently been extended to the use of nitroolefins as Michael acceptors, obtaining the Michael adducts again in excellent yields and stereoselectivities.[18]



Scheme 3.5

[18] Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842.

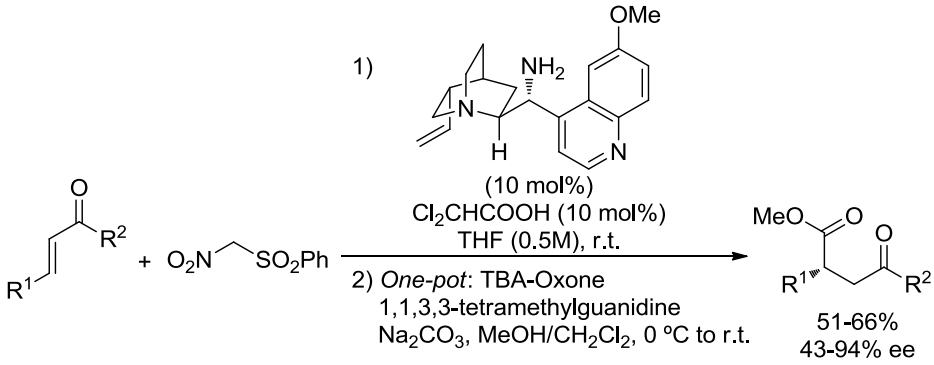
Our research group investigated the use of *N*-nitromethylphthalimide as acyl anion equivalent in the organocatalytic conjugate addition. In particular, this compound is able to operate as a synthetic equivalent of a formyl moiety, which is added to α,β-unsaturated aldehydes using secondary amine catalysis.[19] The initial conjugate addition reaction performed well for a wide range of aldehydes, allowing both aromatic and aliphatic substitutions at the β-position, and yielding the products in high yields and excellent enantioselectivities. A simple modification on these products allowed the synthesis of a series of β-hydroxymoyl substituted aldehydes. This disclosure was the first example describing the use of a hydroxymoyl anion equivalent as a Michael donor. Furthermore, treatment of the derived oximes with ozone released the formyl functionality, confirming that the initially used functionalized nitroalkane nucleophile is a synthetic equivalent of this carbonyl group (Scheme 3.6).



Scheme 3.6

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

Finally, a very recent example in the literature describes the use of nitro(phenylsulfonyl)methane as a different type of acyl anion equivalent that can be used in organocatalysis. Particularly, the synthesis of α-stereogenic γ-ketoesters by conjugate addition of this reagent to α,β-unsaturated ketones has been reported, using a *cinchona* alkaloid based primary amine as catalyst.[20] The reaction performed well for a series of chalcones, giving the final products in moderate yields but generally high enantioselectivities. The interesting feature of this work relies on the fact that the oxidative cleavage of the Michael adducts can be performed in a *one-pot* fashion, obtaining the corresponding γ-ketoester compounds in a single step (Scheme 3.7).



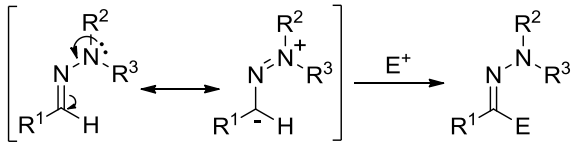
Scheme 3.7

[20] Surya-Prakash, G. K.; Wang, F.; Zhang, Z.; Ni, C.; Haiges, R.; Olah, G. A. *Org. Lett.* **2012**, *14*, 3260.

2. SPECIFIC OBJECTIVES AND WORK PLAN

From the presented literature review, we can appreciate that the organocatalytic conjugate addition reaction of acyl anion equivalents is an area in which a lot of research has yet to be done. Specifically, only three examples of the aminocatalytic version of this reaction can be found, and even more, only one of these were previous to the beginning of this work in 2008.

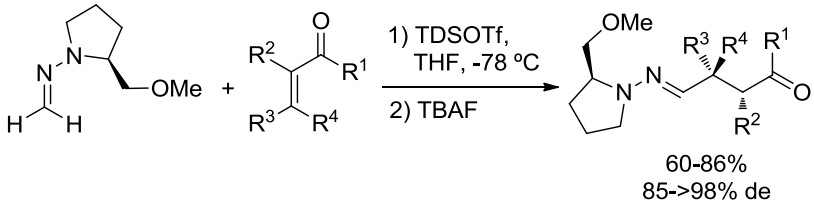
In this sense, and considering that the general objective of the present research studies was focussed on the development of new aminocatalytic conjugate addition reactions using hydrazides and hydrazones as Michael donors, we established as our **specific objective** for the second part of this work to study the possibility of **applying the iminium concept concurrently with the use of hydrazones as masked acyl anion equivalents**. In Chapter 2 we employed the hydrazone functional group as an efficient nitrogen donor for aza-Michael reactions. On the contrary, in this proposal we became interested in exploiting a completely different reactivity profile of hydrazones; with the azomethine carbon, instead of the nitrogen, now being the nucleophilic point.



Scheme 3.8

This reactivity of hydrazones as *C*-based Michael-donors for conjugate addition reactions has been widely studied.[5c] Lassaletta described in 1996 the

enantioselective conjugate addition of formaldehyde SAMP-hydrazone to enones,[21] demonstating that tertiary electron-donating amino groups favoured the formation of the mesomeric aza-enamine structure, increasing the nucleophilicity of the azomethine carbon (see Scheme 3.9). Several organocatalytic transformations employing *N*,*N*'-dialkylhydrazones and pyrrolidinyl hydrazones derived from formaldehyde as nucleophiles have been subsequently reported afterwards.[22]



Scheme 3.9

Aiming to add further novelty to the field, we envisioned the use of *N*-monosubstituted hydrazones for carrying out this reaction. Baldwin and co-workers had already described that metalated aldehyde *tert*-butylhydrazones were able to react with different electrophiles, including crotonates (see Scheme 3.10).[23] However, the enantioselective variant of this reaction remains elusive.

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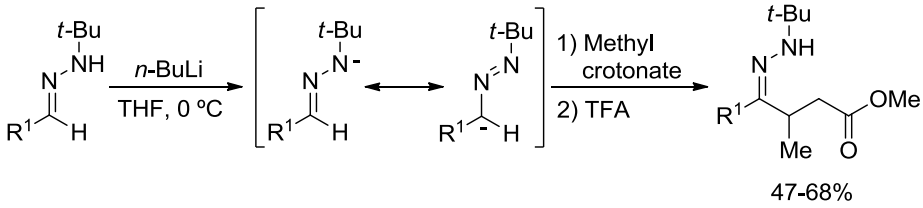
[21] For pioneering reports, see: a) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Díez, E. *J. Am. Chem. Soc.* **1996**, *118*, 7002; b) Fernández, R.; Gascha, C.; Lassaletta, J. M.; Llera, J. M. *Tetrahedron Lett.* **1994**, *35*, 471.

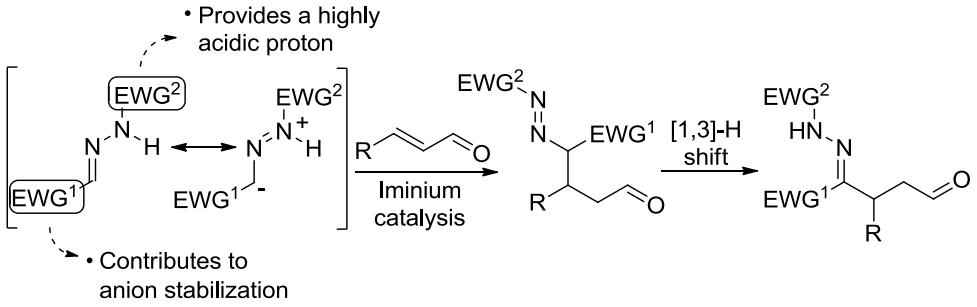
[22] For some examples, see: a) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556; b) Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *15*, 2867; c) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Kockritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065; d) Dixon, D. J.; Tillman, A. L. *Synlett* **2005**, 2635.

[23] For a pioneering work on the *umpolung* reactivity of *N*-monosubstituted hydrazones in conjugate additions, see: Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Kolhe, J. N.; Perry, M. W. D.; Jain, A. U. *Tetrahedron* **1986**, *42*, 4223.



Scheme 3.10

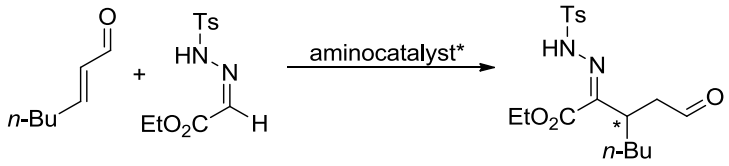
With these precedents in mind, and in a similar fashion as in Chapter 2, we decided to carry out a rational design of the hydrazone moiety in order to instill the appropriate properties to promote the proposed reaction. First of all, we thought that a highly acidic N-H group would enable the formation of a species of similar properties to the azo anion intermediate proposed by Baldwin (shown in the Scheme 3.10). Thus, we considered the introduction of a protecting group that would increase the acidity at that point. In addition, we thought that an electron-withdrawing substituent at the azomethine carbon would enhance the reactivity towards the conjugate addition to the iminium ion intermediate, by stabilization of the partial negative charge generated in the azo intermediate. Presumably, the combination of these factors would result in a highly productive situation.



Scheme 3.11

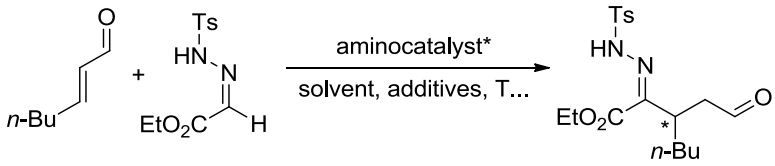
Considering all the aspects mentioned, the following work plan was designed:

- *Viability of the reaction*. Bearing in mind the good results obtained for tosylhydrazones previously, we will investigate their performance in this reaction. Thus, a tosylhydrazone derived from ethyl glyoxylate will be selected as the initial Michael donor. The reaction between this hydrazone and 2-heptenal will be used as a model reaction to test the viability.



Scheme 3.12

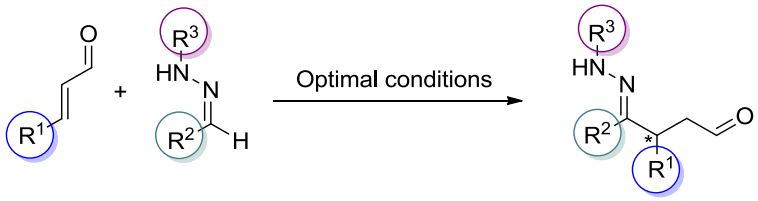
- *Optimization of the reaction conditions*. Using the same model reaction, several chiral secondary amine catalysts will be screened, in an attempt to achieve optimal stereocontrol. With the best catalyst at hand, other experimental variables will be evaluated in a search for the most efficient reaction.



Scheme 3.13

- *Scope of the reaction*. Once the viability of the reaction has been proved, and the best reaction conditions have been established, we will evaluate the application of the methodology with different substrates. First, we will examine a series of α,β-unsaturated aldehydes containing different substitution patterns at the β-position.

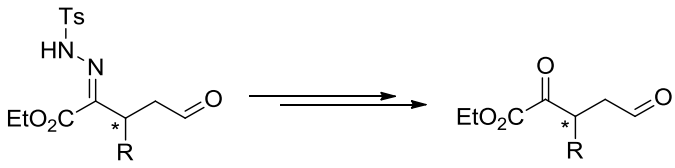
Then we will proceed to evaluate the influence of the various substituents on the hydrazone, aiming to achieve a greater understanding of the complex reactivity that they possess.



Scheme 3.14

- *Transformation of the products. Synthesis of 1,4-dicarbonyl compounds*.

Finally, we will attempt the cleavage of the synthesized β-hydrazono substituted compounds. This will release the masked carbonyl functionality confirming that *N*-monosubstituted hydrazones can actually behave as acyl anion equivalents in the reaction.



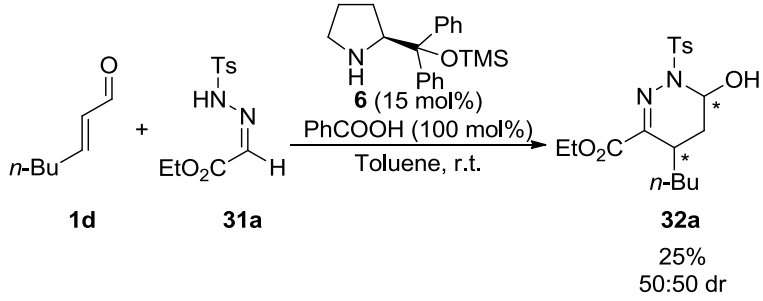
Scheme 3.15

3. RESULTS AND DISCUSSION

Once our hypothesis and objectives for this part of the research work had been defined, we will proceed with the description and discussion of the most relevant results achieved when using hydrazones as potential *C*-donors for the conjugate addition reaction to α,β-unsaturated aldehydes under iminium activation. According to the work plan presented above, the research will begin by testing the viability of the reaction.

3.1. Viability of the reaction: tosylhydrazone as the nucleophile

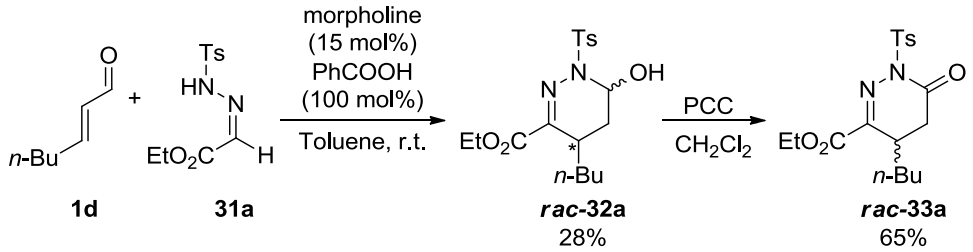
We decided to evaluate the viability of our proposal for the conjugate addition of *N*-monosubstituted hydrazones to enals, taking the reaction between 2-heptenal **1d** and tosylhydrazone **31a** as a model system, postulating that the high acidity of the N-H group would favour the nucleophilicity at the azomethine carbon. We started with *O*-trimethylsilyl α,α-diphenylprolinol catalyst **6**, using toluene as solvent and in the presence of benzoic acid co-catalyst, according to the general reaction shown in the Scheme 3.16.



Scheme 3.16

This initial trial showed that the hydrazone reacted in the expected fashion, adding to the β-carbon of the α,β-unsaturated aldehyde from the azomethine carbon. The conjugate addition occurred together with a subsequent intramolecular 1,2-addition to the formyl group, presumably due to the high nucleophility of the nitrogen atom enhanced by the *N*-tosyl group present. Thus, the reaction rendered the 1,4,5,6-tetrahydropyridazine motif **32a** shown in Scheme 3.16, as a mixture of α- and β-anomers.

In order to determine the enantiomeric excess of the product obtained from the reaction, first we needed to prepare the corresponding racemic standard for chiral stationary phase HPLC analysis. Using morpholine as a catalyst for the transformation,[24] racemic tetrahydropyridazine ***rac*-32a** was isolated and HPLC separation conditions of the enantiomers were attempted. However, we were unable to obtain conditions that provided adequate separation of the four stereoisomers formed in the reaction. Thus, we decided to carry out a derivatization of the product that would simplify the chromatographic separation. As shown in the Scheme 3.17, we decided to oxidize the compound using PCC,[25] which provided the product ***rac*-33a** in moderate yield.



Scheme 3.17

[24] Note: D,L-Proline was proved inactive in this trasformation.

[25] For previous reports in hemiaminal oxidation mediated by PCC, see: Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2008**, *47*, 9971.

The separation of the enantiomers of ***rac*-33a**, shown in the Figure 3.2, was achieved using a chromatographic Chiralpak AD-H column, employing a 1.0 mL/min flow rate and an *n*-hexane/*i*-PrOH (90:10) solvent system. Now, we were able to measure the enantiomeric excess obtained using catalyst **6**, which disappointingly, showed that tetrahydropyridazine **32a** had been obtained as a racemic mixture.

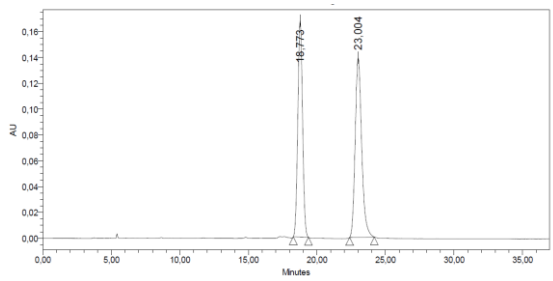


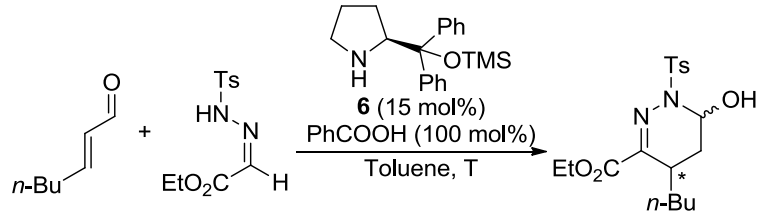
Figure 3.2

3.2. Optimization of the reaction conditions

Based on these results, and prior to evaluating a series of catalysts, we decided to try the reaction at lower temperatures to examine how this variable affected the stereocontrol of the process. With this purpose, four different temperatures were tested.

As shown in the Table 3.1, the reaction temperature did play a crucial role in the transfer of chirality. In fact, whereas when the temperature was lowered to 4 ºC the product was still obtained in low enantiopurity, a further decrease to -30 ºC resulted in the isolation of the product as a single enantiomer (entry 2 *vs.* entry 3). However, there was no sign of reactivity when the reaction was carried out at -78 ºC (entry 4).

Table 3.1. Study of the effect of the temperature in the stereocontrol of the reaction.



1d **31a** **32a**

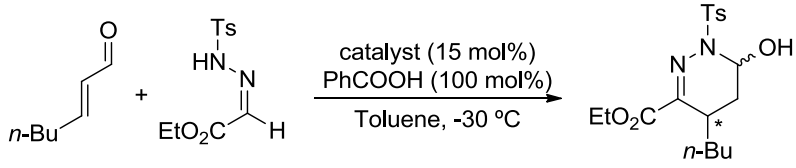
Entry	T (ºC)	Yield (%)[a]	ee (%)[b]
1	r.t.	25	0
2	4	43	6
3	-30	39	99
4	-78	<5	n.d.[c]

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding oxidized adduct **33a**. [c] n.d.: not determined.

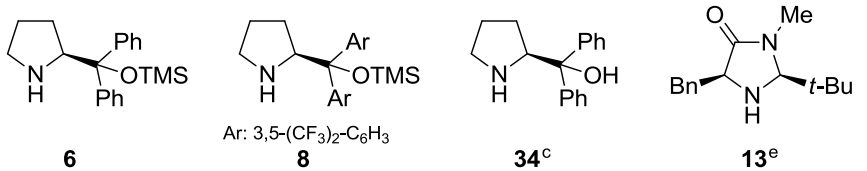
Assuming that the reaction had to be performed at low temperatures in order to achieve stereocontrol, we next proceeded with the evaluation of a series of potential catalysts that could provide the desired products not only in high enantioselectivity, but also with improved yield at -30 ºC. As in the previous examples described, a series of catalysts able to activate the enal were chosen, which presented different functional groups on their structures. In this sense, protected diaryl prolinol derivative **8**, provided tetrahydropyridazine **32a** in lower yields as well as diminished enantioselectivity comparing to the results offered by catalyst **6**. Moreover, when unprotected diphenyl prolinol **34** was utilized, only trace amounts of product were observed. Next, imidazolidinone **13** was investigated in the reaction and resulted in only trace quantities of desired product. Considering the poor reactivity achieved up to this moment, we investigated the use of bifunctional catalysts that could provide an ancillary role in the reaction *via* activation of the nucleophile. Nevertheless, these trials proved unsatisfactory, and resulted in either

no reactivity (catalysts **3** and **14**) or provided the desired adduct in poor yields and enantioselectivities (catalysts **18** and **16**). These results are summarized in Table 3.2.

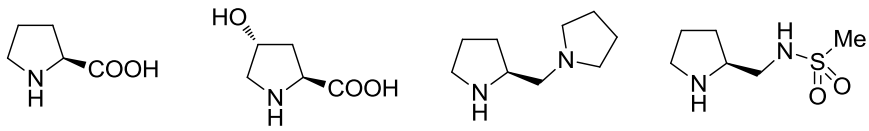
Table 3.2. Secondary amine catalyst screening.



1d **31a** **32a**



6	**8**	**34**[c]	**13**[e]
39%[a]	31%	<5%	<5%
99% ee[b]	30% ee	n.d.[d]	n.d.[d]



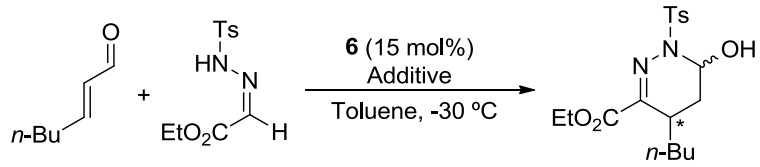
3	**14**	**18**	**16**
<5%	<5%	36%	11%
n.d.[d]	n.d.[d]	4% ee	24% ee

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding oxidized adduct **33a**. [c] In absence of benzoic acid. [d] n.d.: not determided. [e] Using TFA as co-catalyst intead of PhCOOH.

Based on the data obtained during this catalyst study, the *O*-trimethylsilyl diphenylprolinol derivative **6** was selected for further optimization experiments, since it provided the most promising results. Our next experiments were directed towards the improvement of the yield. We started investigating the influence that the

solvent has on the reaction, but we observed that other solvents (*e.g.* THF, CH_2Cl_2 or $CHCl_3$) did not provide the desired reactivity. Consequently, we focussed on examining a variety of co-catalysts. The results compiled in this series of experiments are summarized in Table 3.3.

Table 3.3. Study of the addition of different co-catalysts.



1d **31a** **32a**

Entry	Additive	Amount (%)	Yield (%)[a]	ee (%)[b]
1	*p*-$NO_2C_6H_4COOH$	15	29	24
2	TsOH	15	<5	n.d.[c]
3	Ph_3CCOOH	15	36	10
4	DABCO	15	<5	n.d.[c]
5	PhCOOH	15	30	20
6	PhCOOH	-	11	14
7	$PhCOOH/H_2O$	100/100	37	86
8	PhCOOH	100	38	36

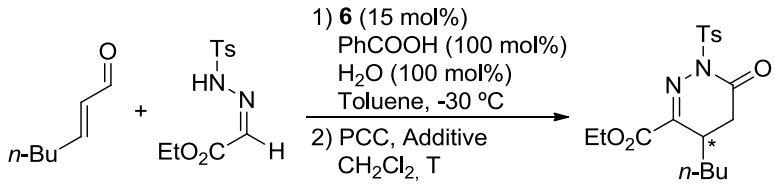
[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding oxidized adduct **33a**. [c] n.d.: not determined.

The use of Brønsted acid additives did not exhibit a positive effect on the reaction (entries 1-3); the reaction yields were not improved and in all cases a decrease in the enantiomeric excess was observed. We also explored the use of a base as co-catalyst; however, this showed the same reactivity profile observed in our previous work with tosylhydrazones (Chapter 2, Scheme 2.54), which consisted of the ability of a base to promote the release of the sulfonate protecting group, which

subsequently undergoes nucleophilic addition to the β-position of the α,β-unsaturated aldehyde. Thus, we moved to explore the effects of the use of different amounts of benzoic acid. To our surprise, lower amounts of benzoic acid (entries 5 and 6) also resulted into poor enantioselectivities and an attempt using both a stoichiometric quantity of acid co-catalyst and the inculsion of water seemed to regain the stereoselectivity of the process to a certain extent, although it was lower than the expected (entry 7). This led us to repeat our experiment that provided excellent results previously, to realize that the enantioselectivity obtained was not reproducible (entry 8).

Considering that identical conditions had been used for all experiments, we thought that the origin of this irreproducibility issue had arisen from the oxidation step, since it was the only point of the sequence where the conditions were not rigourously controlled. In this sense, we decided to carry out a series of experiments in order to obtain the optimal oxidation protocol that would provide us with high enantioselectivities.

Table 3.4. Experiments performed in the search for the optimal oxidation conditions.



1d **31a** **33a**

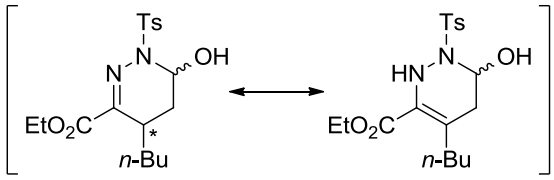
Entry	PCC (equiv.)	Addition T (º C)	Additives	t (h) oxidation	ee (%)[a]
1	1	r.t.	-	18	32
2	3	r.t.	-	18	60
3	5	r.t.	-	18	88
4	5	4	-	18	92
5	5	4	MS (4Å)	4	94
6	5	4	Silica gel	18	74
7	5	4	Celite	18	82

[a] Determined by HPLC analysis on a chiral stationary phase.

From the results shown in Table 3.4 we observed that indeed the oxidation process had a strong influence on the enantioselectivity. Higher proportions of the oxidant provided better results (entries 1-3), which could be further improved by lowering the reaction temperature prior to the addition of PCC (entry 4). Furthermore, additives able to accelerate the PCC mediated oxidation process were tested.[26] We observed that only the addition of molecular sieves gave the expected rate acceleration of the reaction (entries 5-7), which also resulted in a further increase of the enantiopurity of the final product. We attributed these partial racemization events to the high acidity of this oxidant. From our point of view, the

[26] *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice* (Eds.: Tojo, G.; Fernández, M.), Springer, **2006**.

acidic environment of the oxidation step is able to promote a tautomerization between the hydrazone and an enamine-type intermediate, which would result in the racemization of the enantio-enriched hydrazones (Scheme 3.18). In this sense, we postulated that the acceleration of the oxidation process, as well as the lower temperatures, limited the extent of the tautomerization of the products.



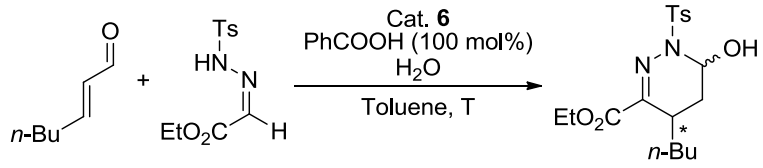
32a

Scheme 3.18

Once we addressed the issues of reproducibility, we returned to the optimization of the reaction. In this sense, we decided to investigate the use of different proportions of Michael donor and acceptor, as well as different catalyst loadings, and wether the addition of an equivalent of water was essential.

The results summarized in the Table 3.5 showed that a higher catalyst loading only gave a slight improvement in the isolated yield (entry 1 *vs.* entry 2). Increasing the proportion of the hydrazone with respect to the enal resulted in an additional improvement in conversion (entry 3), whereas having an excess of the enal led to diminished conversion and an acute drop in the enantioselectivity (entry 4). The most significant effect on the yield was observed when carrying the reaction out at slightly elevated temperatures (*i.e.* -20 ºC; entry 5), providing the desired compound in high yield and excellent enantioselectivity. Moreover, the necessity of the addition of water was shown when comparing to the results where water was absent (entry 3 *vs.* entry 6 and entry 5 *vs.* entry 7).

Table 3.5. Study of the effect of the proportion of the substrates.



1d **31a** **32a**

Entry	31a:1d (equiv.)	Cat. (mol%)	H_2O (equiv.)	T (º C)	Yield (%)[a]	ee (%)[b]
1	1:1	15	1	-30	38	94
2	1:1	20	1	-30	42	94
3	2:1	20	1	-30	54	96
4	1:2	20	1	-30	40	60
5	2:1	20	1	-20	71	92
6	2:1	20	0	-30	42	86
7	2:1	20	0	-20	69	84

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding oxidized adduct **33a**.

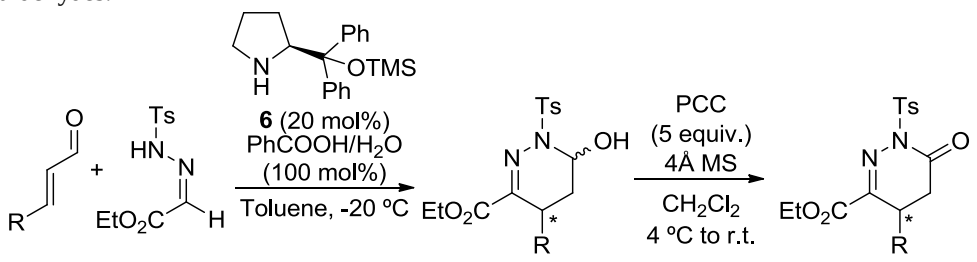
Thus, after carrying out a wide variety of optimization experiments, the conditions shown in the entry 5 of the Table 3.5 were selected as the optimal conditions to carry out the conjugate addition/hemiaminalization sequence with hydrazones; *i.e.* catalyst **6**, benzoic acid and water in toluene at -20 ºC, using a 2:1 donor/acceptor proportion.

3.3. Scope and limitations: use of other α,β-unsaturated aldehydes and hydrazones

After the exhaustive optimization process and with the optimal conditions in hand, we proceeded to investigate the use of other α,β-unsaturated aldehydes with different substitution patterns and how these variations influenced the reaction. In this sense, we studied the addition of the tosylhydrazone **31a** to a series of α,β-unsaturated aldehydes containing different functionality at the β-position.

The results summarized in the Table 3.1 showed that the reaction was highly dependant on the size and nature of the β-substituted α,β-unsaturated aldehyde employed in each case. More specifically, the length of the aliphatic side chain at the β-position had a drastic influence on the enantioselectivity of the reaction. Substrates containing alkyl chains like butyl or longer performed well in the reaction, yielding the product in high yields and excellent enantioselectivities (entries 1 and 5-8), but decreasing the length of the side chain coincided with an acute drop in the enantiomeric excesses of the products (entries 2-4). Entry 9 seemed to be an exception to this hypothesis, with the introduction of an unsaturation in the aliphatic side chain also providing the corresponding adduct in poor enantioselectivity. On the other hand, a functionalized α,β-unsaturated aldehyde such as **1l** was also applied to the reaction, furnishing the final adduct in high yield and stereocontrol (entry 10). In the same way, enals containing aryl substituents were tested; noticing that the presence of aromatic rings possessing electron-withdrawing groups favoured the reaction and provided the desired compounds with excellent enantiocontrol (entries 11-12), whereas other aromatic substituents, such as unsubstituted phenyl or those containing electron-donating groups, led to a very slow reaction and with significant decrease in the enantioselectivities.

Table 3.6. Scope of the reaction using a series of differently substituted α,β-unsaturated aldehydes.



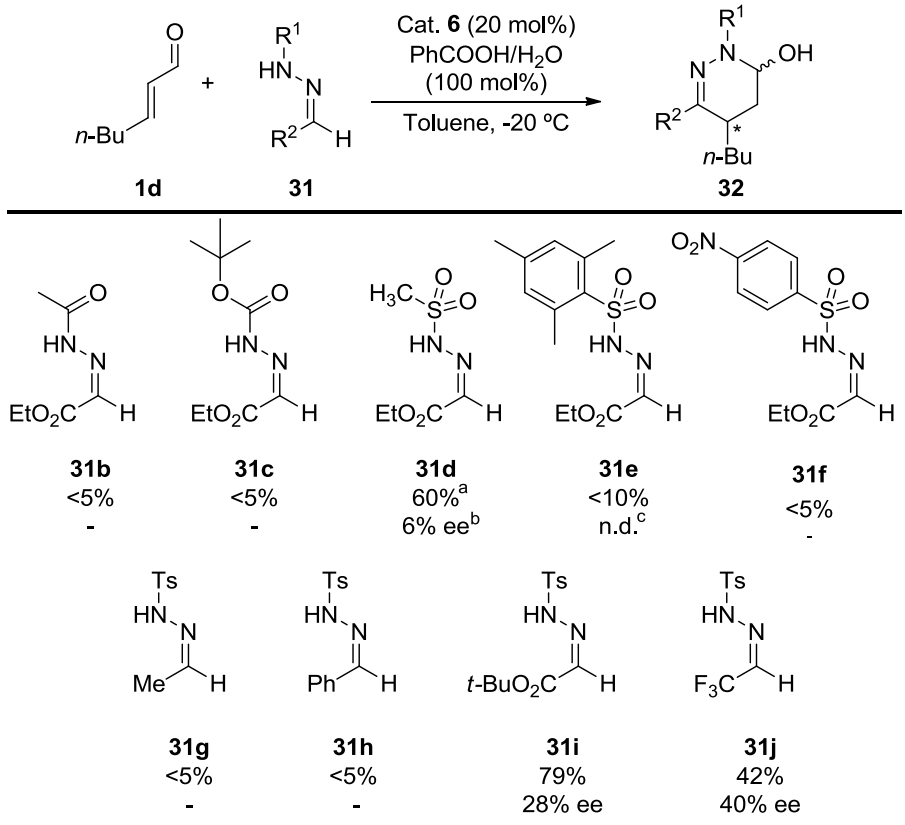
1a-s **31a** **32a-l** **33a-l**

Entry	R (1)	Prod.	Yield (%)[a]	Prod.	Yield (%)[b]	ee (%)[c]
1	*n*-Bu (**1d**)	**32a**	71	**33a**	81	92
2[d]	Me (**1b**)	**32b**	94	**33b**	72	26
3	Et (**1a**)	**32c**	68	**33c**	71	20
4	*n*-Pr (**1c**)	**32d**	76	**33d**	74	76
5	*n*-C_5H_{11} (**1e**)	**32e**	85	**33e**	62	99
6	*n*-C_6H_{13} (**1f**)	**32f**	66	**33f**	58	93
7	*n*-C_7H_{15} (**1g**)	**32g**	63	**33g**	62	99
8	*n*-C_8H_{17} (**1h**)	**32h**	94	**33h**	77	95
9	*Z*-EtCH=CH$(CH_2)_2$ (**1i**)	**32i**	54	**33i**	71	30
10	$(MeO)_2CH$ (**1l**)	**32j**	99	**33j**	60	92
11	*p*-$NO_2C_6H_4$ (**1o**)	**32k**	72	**33k**	45	90
12	*o*-$NO_2C_6H_4$ (**1s**)	**32l**	29	**33l**	52	96

[a] Yield of the pure isolated product **32** as a mixture of anomers (see experimental section). [b] Yield of the isolated pure product **33**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction performed using catalyst **8**.

Having studied a series of Michael acceptors in the reaction, we decided to investigate the use of other hydrazones as nucleophiles, using 2-heptenal and the optimal conditions developed. In particular, we wanted to study the effect that different substitution patterns would have on the reaction (Table 3.7).

Table 3.7. Study of the use of different hydrazones.

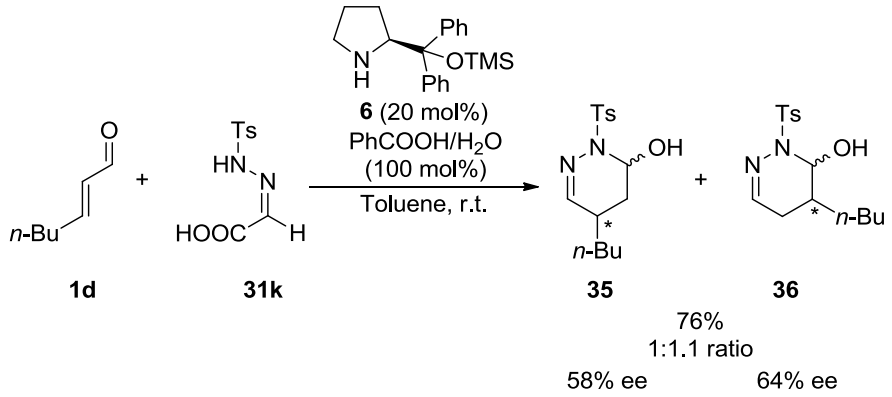


[a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the corresponding oxidized compound. [c] n.d.: not determined.

Initially, the effect of the group placed at the nitrogen was studied, keeping the carboxylate group untouched (hydrazones **31b-f**). The need for a strongly electron-withdrawing substituent was confirmed when no reaction was observed when less electron-withdrawing groups were present (**31b-c**). The influence of the steric presence of the sulfonyl group also became evident. A hydrazone containing a methyl sulfonyl group (**31d**) was compatible with the reaction conditions, although the enantioselectivity of the product was strongly diminished. On the contrary, when a hydrazone containing a larger mesityl sulfonyl group (**31e**) was applied, the reaction rate was severly affected, providing the desired compound in only 10% yield. Also, the performance of the nosyl group was examined (**31f**), which had previously provided excellent results in other investigations described in this work due to the enhanced acidity that it provides to the adjacent N-H group. However, no reactivity was observed in this case. On the other hand, the importance of the substituent at the azomethine carbon was also studied, to determine that an electron-withdrawing group was also required at this position. In fact, hydrazones containing methyl or phenyl groups at the azomethine carbon did not react (**31g-h**), while the presence of electron-withdrawing groups like *tert*-butoxycarbonyl (**31i**) or trifluoromethyl (**31j**) led to the formation of the corresponding tetrahydropyridazines in moderate to high yields but with poor enantioselectivities.

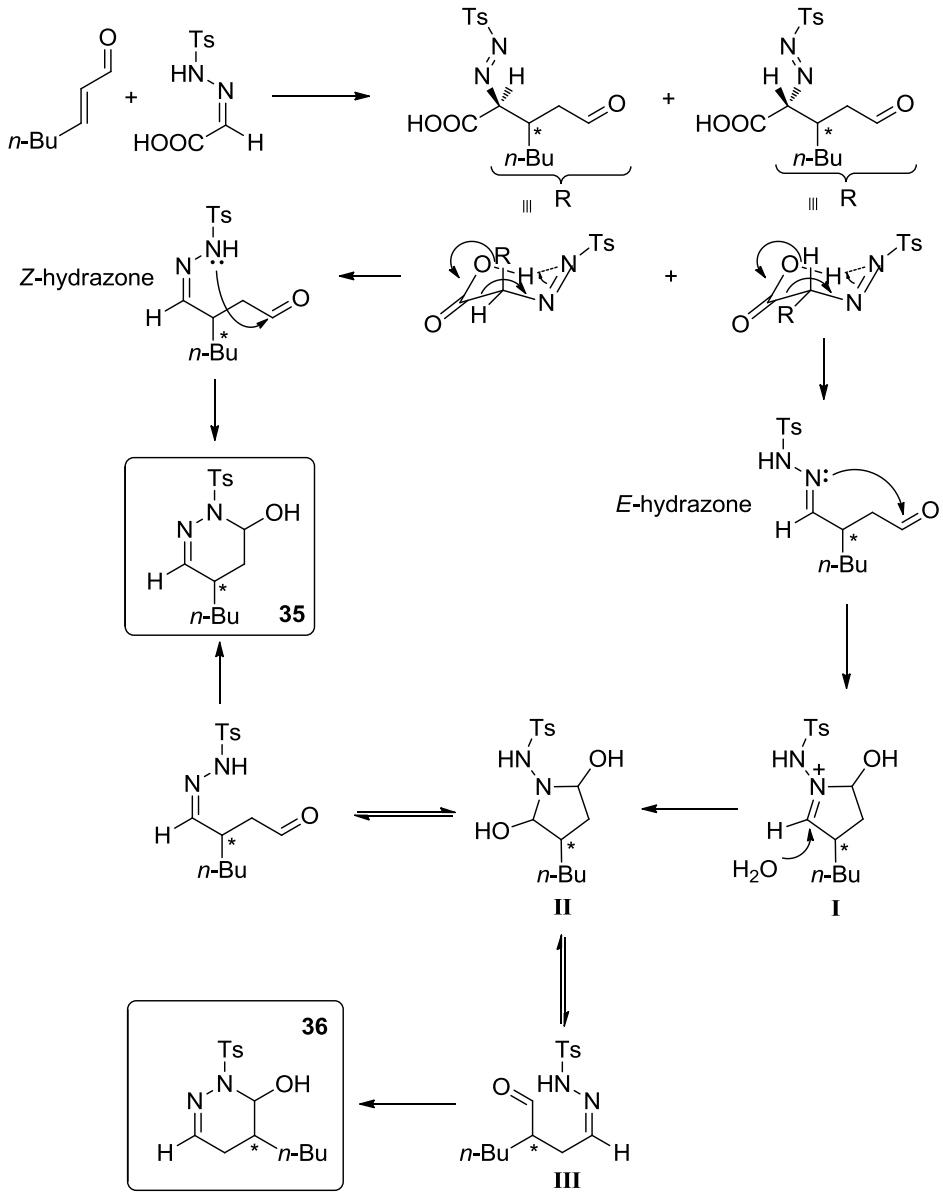
Finally, when a carboxylic acid substituent was examined a slight deviation in the reaction pathway was observed (**31k**, see Scheme 3.19). This hydrazone showed a pronounced tendency to decarboxylate throughout the process, accelerating the reaction rate considerably and yielding the product in high yield. However, the compound was obtained as a ~1:1 mixture of regioisomers. Furthermore, enantioselectivities of both isomers were around 60% ee. A series of experiments varying the reaction conditions (*i.e.* catalyst, co-catalyst, solvent, temperature, proportions, etc.) were attempted in order to try to obtain a single isomer and

improve the enantioselectivity of the process. However, none of the introduced variables produced significant changes in the results, and products **35** and **36** were always recovered in similar proportions and with enantiomeric ratios not greatly exceeding 80:20.



Scheme 3.19

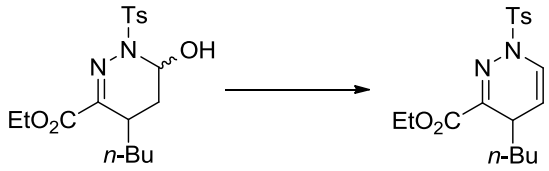
The formation of this second isomer can be tentatively explained from the fact that the hydrazone intermediate, after the conjugate addition/decarboxylation process, might be formed as two different isomers. Assuming that the initial step can provide a mixture of diastereoisomers, each of them would render a different *Z* or *E* diastereoisomer after the decarboxylation. Now, while the *Z* hydrazone has the appropriate arrangement for the subsequent hemiaminalization step, the *E* isomer can react intramolecularly with the formyl group through the azomethine nitrogen atom. This would lead to the formation of a 5-membered ring hemiaminal intermediate (**I**), which after addition of water may form a double hemiaminal (**II**) that is in equilibrium with two acyclic structures (*i.e.* **III** and *Z*-hydrazone). Each of these intermediates will render the corresponding 6-membered ring hemiaminal compounds **35** and **36** (see Scheme 3.20).



Scheme 3.20

3.4. Transformation of the adducts. Synthesis of the 1,4-dicarbonyl compounds

At this point, we proceeded to explore methodologies that would enable the cleavage of the hydrazone moiety and thus access to 1,4-dicarbonyl compounds. We began by evaluating the possibility to perform this process on the hemiaminal adduct **32a**. In this sense, several experiments, using conditions for carrying out acid hydrolysis or oxidative cleavage, were attempted (shown in Scheme 3.21). We observed that subjecting the hemiaminal moiety to acidic conditions promoted in all cases the dehydration of the compound to yield the dihydropyridazine **37a**.



32a **37a**

Conditions:

A) $FeCl_3$, CH_2Cl_2	58%
B) PPTS, *i*-PrOH	85%
C) H_2SO_4, Dioxane	72%

Scheme 3.21

On the other hand, an attempt to carry out an ozonolytic cleavage of the hydrazone resulted in the unexpected formation of peroxide **38a** (see Scheme 3.22). Other methodologies described in the literature for the oxidative cleavage of hydrazones (*i.e.* the use of IBX[27] or other hypervalent organoiodine reagents[28]) did not result in any reaction.

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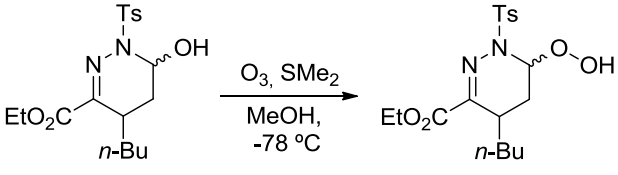
[27] Bose, D. S.; Srinivas, P. *Synlett* **1998**, 997.

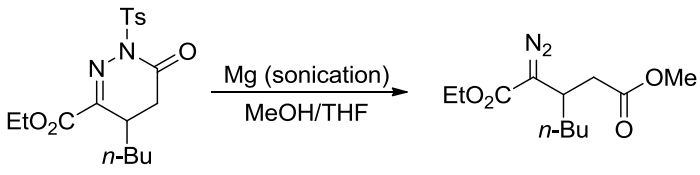
[28] a) Barton, D. H. R.; Jaszberenyi, J. C.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52*, 14673; b) Moriarty, R. M.; Berlung, B. A.; Chander Rao, M. S. *Synthesis* **1993**, 318.



32a **38a**
87%

Scheme 3.22

Considering the limited success we achieved with hemiaminal **32a**, we decided to examine the utility of pyridazinone **33a** in the reaction. The starting material was recovered unchanged after acidic hydrolysis treatment and was also inert towards the oxidative cleavage conditions attempted. On the contrary, when reductive conditions for hydrazone cleavage were tested, involving a magnesium-promoted detosylation, formation of the diazo-compound **39a** in moderate yield was detected (see Scheme 3.23).

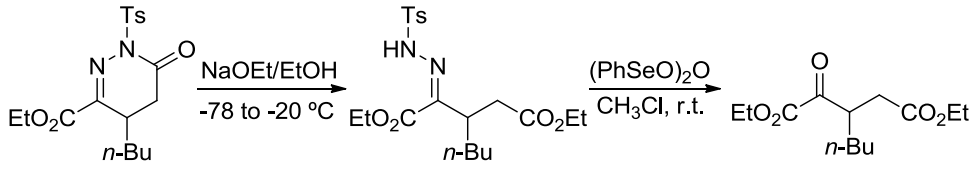


33a **39a**
46%

Scheme 3.23

At this stage, we thought that the poor reactivity presented by compounds **32a** and **33a** towards oxidative cleavage of the hydrazone moiety could be caused by their cyclic nature. Moreover, the oxidative processes for hydrazone cleavage tested in the previous examples are reported to be effective in those cases in which a free NH group is present at the hydrazone moiety. Thus, we decided to carry out a

ring opening ethanolysis on the tetrahydropyridazine **33a**, which would lead to an acyclic *N*-monosubstituted hydrazone product with a more appropriate structure for a subsequent oxidative cleavage process. In this sense, the reaction of **33a** with NaOEt/EtOH rendered the 1,5-diester **40a** as shown in the Scheme 3.24. Once the monosubstituted hydrazone was obtained, we examined whether the desired transformation could be undertaken with this acyclic product, initially finding that the acidic hydrolysis resulted unsuccessful. Once again, ozonolysis and hypervalent iodine-mediated oxidative cleavage processes failed to provide the desired β-acyl substituted compound. However, using benzeneleneninic anhydride (BSA), which is a reagent specifically described in literature for the cleavage of tosylhydrazones,[29] the synthesis of 1,4-dicarbonyl compound **41a** was finally achieved. In this sense, we could optimize the transformation in a two-step sequence.



33a **40a** 92% **41a** 93%

Scheme 3.24

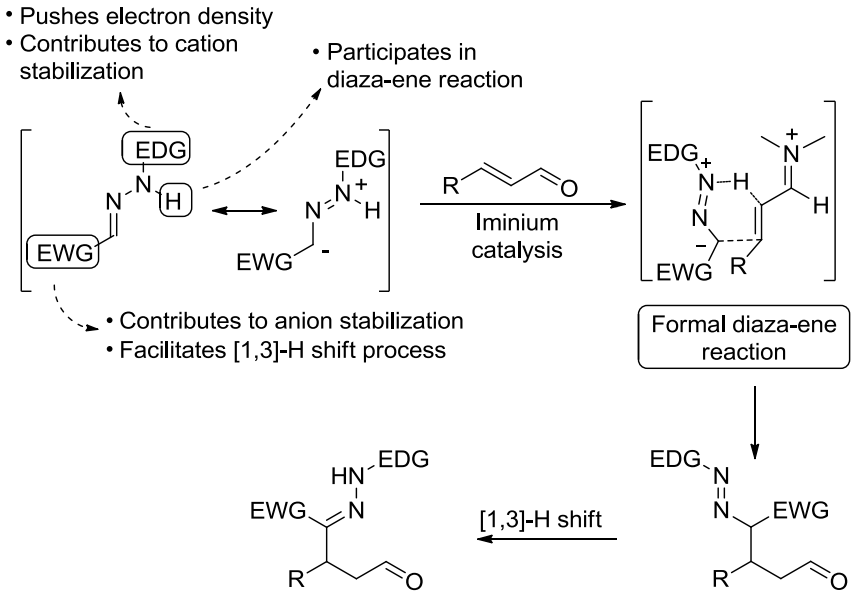
Finally, with an efficient methodology for the obtaining of 1,4-dicarbonyl compounds in hand, we proceeded to apply it to the cleavage of a series of oxidized tetrahydropyridazine compounds **33a**. However, to our surprise, we found that the overall conjugate addition/oxidation process could not be reproduced again for all adducts **32**, obtaining different values of ee for several sets of experiments performed under the optimized reaction conditions. For this reason, and having

[29] Barton, D. H. R., Okano, T.; Parekh, S. I. *Tetrahedron* **1991**, *47*, 1823.

failed to develop a robust and reproducible methodology for the conjugate addition of tosylhydrazones derived from ethyl glyoxylate, we decided to revise our hypothesis and re-evaluate the most appropriate structure of the hydrazone to be employed for the initial Michael-type reaction under iminium activation.

3.5. Revision of the hypothesis: *p*-methoxyphenyl hydrazone as the nucleophile

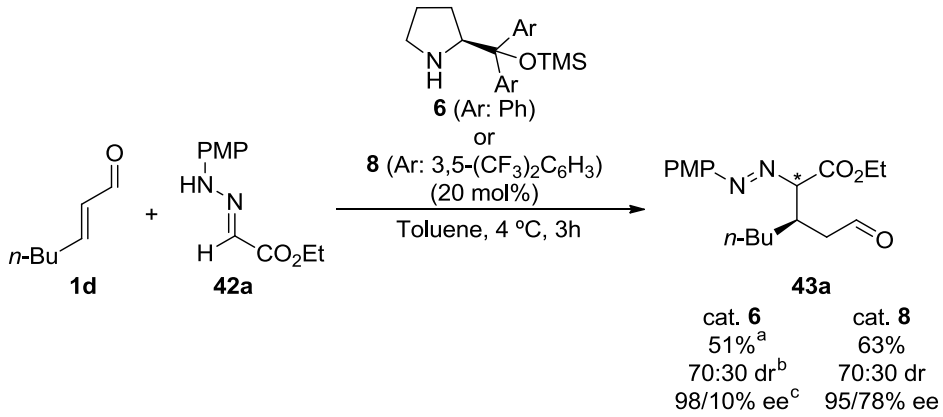
Our main hypothesis to explain the lack of reproducibility of our methodology is based on the tendency of the obtained adducts to racemize through an equilibrium process between our products and the corresponding enamine species (shown in Scheme 3.18). This idea was supported by observation of the obtained cyclic hemiaminals and oxidized compounds racemizing upon standing at room temperature for a few hours. On the contrary, acyclic 1,4-dicarbonyl compounds obtained after the oxidative cleavage were configurationally stable. In this sense, avoiding the hemiaminalization step would considerably diminish the possibility of racemization, since our initial strategy afforded compounds that possess a structure that favours this event. We thought that the use of a hydrazone with a protecting group that would lower the acidity of the N-H group might be less reactive towards a subsequent hemiaminalization process. However, we had already tested a series of groups with lower acidity to prove that none of them presented reactivity towards the conjugate addition. Thus, in further examination of the actual requirements needed for the generation of a partial negative charge at the azomethine position, we realized that a strongly electron-donating group would favour this situation by increasing electron density through the π system. This would enable the electron pair of the nitrogen to be more accesible to participate in a formal diaza-ene reaction, after which a [1,3]-hydride shift process would end up delivering the β-hydrazono substituted compounds. On the other hand, we thought that maintaining a strongly electron-withdrawing group at the azomethine position would still be beneficial to the reaction design, playing an important role with the stabilization of the charge at that position (see Scheme 3.25).



Scheme 3.25

With this new hypothesis in mind, we selected the *p*-methoxyphenyl group (PMP) as the electron-donating protecting group, maintaining the ethyl carboxylate at the azomethine position. Once the new nucleophile had been synthesized,[30] we began our studies by evaluating the viability of the postulated hypothesis. For this purpose, and in a similar way as for the previous work, we took the reaction between 2-heptenal **1d** and the *p*-methoxyphenyl hydrazone **42a** as a model system, according to the general reaction shown in the Scheme 3.26, and simultaneously evaluating the effect of two different catalysts.

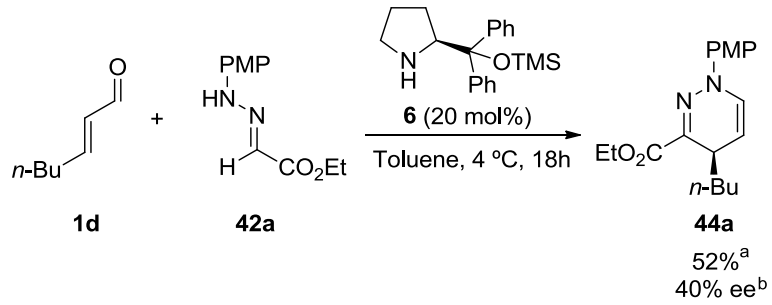
[30] Zhou, J.; Oh, L. M.; Ma, P.; Li, H.-Y. *PCT Int. Appl.* **2003**, WO 03049681.



Scheme 3.26[31]

As shown in the scheme, in our first attempt we were able to isolate the γ-azoaldehyde product **43a** after 3 hour reaction time, when using *O*-trimethylsilyl protected diphenylprolinol derivatives **6** and **8**. Both catalysts provided the aldehyde **43a** in moderate yield and as a 70:30 mixture of diastereoisomers. However, in regard to the stereocontrol, they behaved quite differently. While both catalysts **6** and **8** furnished the conjugate addition product **43a** with excellent enantioselectivity for the main diastereoisomer (98% and 95% respectively), only the latter was able to induce stereocontrol in the formation of the minor diastereoisomer (10% ee for **6** *vs*. 78% ee for **8**). More thorough monitoring of the reaction proved that in the initial 3 hours only the formation of the desired aldehyde **43a** product could be observed, whereas extended reaction times favoured subsequent hemiaminalization and dehydration, leading to the synthesis of the dihydropyridazine moiety **44a**, in similar yield, but lower enantioselectivity (as shown in Scheme 3.27).

31 [a] Yield of the pure product isolated after flash chromatography. [b] Calculated by NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase.

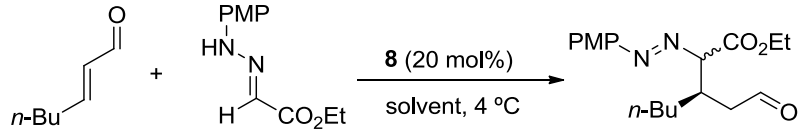


Scheme 3.27[32]

These experiments demonstrated the ability of the hydrazone reagent **42a** to behave as anticipated in Scheme 3.25. Once this had been confirmed, we moved to evaluate the optimal experimental conditions to obtain the best results in terms of yield and stereoselectivity. In this sense, we started evaluating the effect of the solvent on the reaction, using catalyst **8**, since it had provided better results in terms of stereoselectivity. From the results summarized in Table 3.8, we concluded that toluene was the most effiecient solvent in terms of conversion and stereolectivity. α,α,α-Trifluorotoluene provided slightly improved diastereoselectivity, however, the enantioselectivity of the minor diastereoisomer decreased (entry 2), which was similar to the results obtained in chloroform (entry 3). On the other hand, the use of polar solvent resulted in the formation of the desired compounds in very low conversion.

32 [a] Yield of the pure product isolated after flash chromatography. [b] Determined by HPLC analysis on a chiral stationary phase.

Table 3.8. Study of the influence of the solvent on the reaction.



1d **42a** **43a**

Entry	Solvent	Yield (%)[a]	dr[b]	ee (%)[c]
1	Toluene	63	70:30	95/78
2	$CF_3C_6H_5$	54	76:24	96/52
3	$CHCl_3$	59	70:30	95/60
4	THF	15	n.d.[d]	n.d.[d]
5	EtOH	<5	n.d.[d]	n.d.[d]
6	DMF	<5	n.d.[d]	n.d.[d]

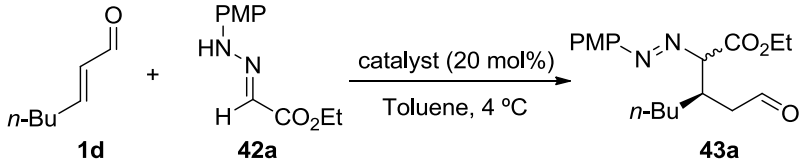
[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] n.d.: not determined.

The inclusion of different acids or bases as co-catalysts (*e.g.* benzoic or acetic acids, DABCO, etc.) was also investigated; however, these promoted the acceleration of the isomerization from the azo compound to the hydrazone, thus enhancing the rate of cyclization to the undesired dihydropyridazine **44a**. Hence, we concluded that optimal conditions for this reaction would avoid the use of additives.

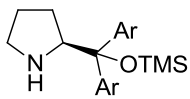
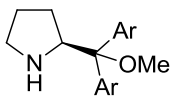
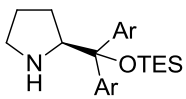
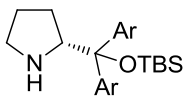
Once we had established that the best conditions required the use of toluene as solvent and no co-catalyst, we proceeded to evaluate a series of aminocatalysts in an effort to achieve higher stereocontrol during the reaction. In this sense, taking into consideration that both diastereoisomers of **43a** would converge into a single product after the projected [1,3]-hydride shift process, we focused on searching for the best conditions to obtain a highly enantioenriched material regardless the diastereomeric proportion. Considering previous results shown in Scheme 3.26,

which anticipated that the presence of larger aryl groups would be essential to promote a high degree of enantiocontrol for the minor diastereoisomer, we evaluated a family of related diarylprolinol catalysts incorporating substituents of different sizes on the oxygen atom. In this sense, the use of *O*-methyl-containing catalyst **9** provided poor results, with low conversion and decreased enantioselectivities. Increasing the steric bulk of the catalyst by incorporating a triethylsilyl group (catalyst **45**) did not influence the reaction substantially, so providing similar results to those obtained with the trimethylsilyl group (catalyst **8**). However, we observed that the enantioselectivity of the process improved notably when the steric bulk of the trialkylsilyl group was considerably increased (catalyst ***ent*-46**). In fact, this catalyst provided a satisfactory 86% ee for the minor diastereoisomer, while maintaining the results concerning the yield and the enantioselectivity of the major diastereoisomer. All the results are summarized in Table 3.9.

Table 3.9. Secondary amine catalyst screening.



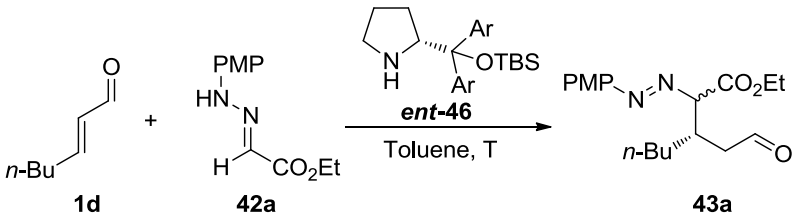
1d **42a** **43a**

			
Ar: 3,5-$(CF_3)_2C_6H_3$	Ar: 3,5-$(CF_3)_2C_6H_3$	Ar: 3,5-$(CF_3)_2C_6H_3$	Ar: 3,5-$(CF_3)_2C_6H_3$
8	**9**	**45**	***ent*-46**
63%[a]	20%	66%	64%
70:30 dr[b]	70:30 dr	70:30 dr	70:30 dr
95/78% ee[c]	74/12% ee	96/75% ee	-98/-86% ee

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase.

Having determined that the optimal catalyst for the reaction was the secondary amine ***ent*-46** and the most suitable solvent toluene, we decided to carry out a final set of experiments directed to improving the yield of the transformation (see Table 3.10). In this sense, simply by raising the reaction temperature the yield was significantly increased, while retaining the high levels of enantioselectivity (entry 2). With this result in hand, we decided to evaluate the possibility to lower the catalyst loading to 10 mol%. As we observe in the entry 3, this gave a satisfactory result, noticing just a slight decrease in the isolated yield while keeping identical levels of stereoselection.

Table 3.10. Optimization of the yield of the reaction.



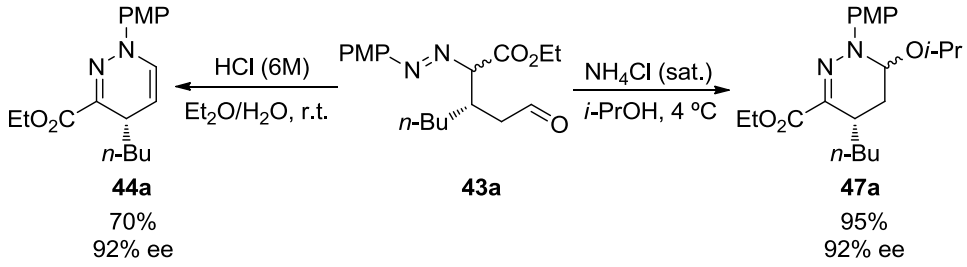
1d **42a** **43a**

Entry	Cat. (mol%)	T (ºC)	Yield (%)[a]	dr[b]	ee (%)[c]
1	20	4	64	70:30	98/86
2	20	r.t.	83	70:30	96/84
3	10	r.t.	79	70:30	96/84

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase.

Thus, conditions shown in entries 2 and 3 of the Table 3.10 were selected as the optimal to carry out the diaza-ene type reaction with *p*-methoxyphenyl hydrazones and enals – *i.e.* using the catalyst ***ent*-46** in toluene at room temperature.

Considering the overall reaction design proposed in Scheme 3.25, in order to achieve the γ-hydrazonoaldehydes, we next focussed on evaluating appropriate conditions to promote the [1,3]-hydride shift. With this purpose in mind we began by treating aldehyde **43a** with diluted hydrochloric acid, which promoted the projected [1,3]-hydride shift process smoothly. However, the isomerized compound had a pronounced tendency to undergo intramolecular hemiaminal formation and subsequent dehydration, to form the cyclic dihydropyridazine derivative **44a**. Nevertheless, we should mention that this was isolated without erosion of the enantiopurity on this occasion (Scheme 3.28). Other Brønsted acids such as TFA, *p*-TsOH or diphenylphosphoric acid (DPP) were also investigated, but all provided very similar results. Alternatively, treating the aldehyde **43a** with ammonium chloride and using *iso*-propanol as solvent, we managed to avoid the dehydration step by the formation of the *O*-protected hemiaminal **47a** as a mixture of α- and β-anomers. This compound was also obtained in excellent yields and high enantioselectivities (Scheme 3.28).



44a
70%
92% ee

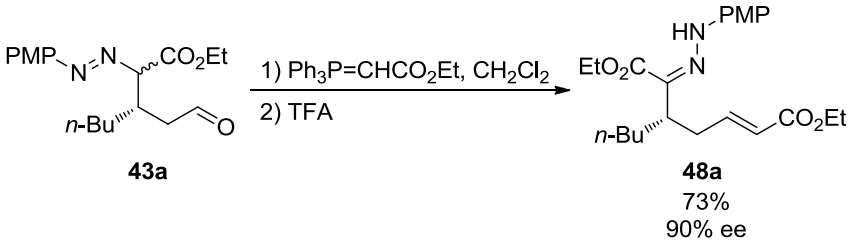
43a

47a
95%
92% ee

Scheme 3.28

Thus, we assumed that in order to avoid the cyclization process we needed to carry out a modification of the formyl moiety. We initially proceeded to modify the aldehyde moiety prior to promoting the [1,3]-hydride shift process, by subjecting product **43a** to a standard Wittig protocol. *In situ* addition of TFA led to the

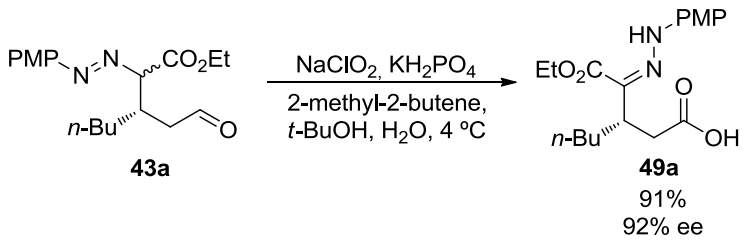
formation of α,β-unsaturated ε-hydrazonoester **48a** in high yield without erosion of the enantiopurity (Scheme 3.29).



43a **48a**
73%
90% ee

Scheme 3.29

Although the transformation shown in the Scheme 3.29 provided the hydrazone product in good yield and enantioselectivity, the products obtained did not correspond to that expected from a conjugate addition of a hydrazone. Thus, in an attempt to maintain a similarity to a β-hydrazono substituted carbonyl compound, we decided to investigate the oxidation of the aldehyde. To our delight, this transformation under standard conditions proceeded simultaneously with the [1,3]-hydride shift process, leading to the formation of the γ-hydrazono carboxylic acid **49a** in a single step and in an excellent yield and retention of enantioselectivity (Scheme 3.30).



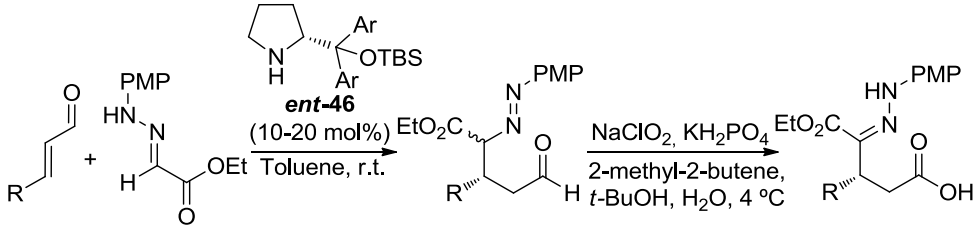
43a **49a**
91%
92% ee

Scheme 3.30

Once the best conditions for carrying out the conjugate addition reaction of the *p*-methoxyphenyl hydrazone **42a** had been established, and with a reliable protocol for the subsequent [1,3]-hydride shift, we next proceeded to extend the reaction to the use of α,β-unsaturated aldehydes with different substitution patterns at the β-position.

In an overall analysis of the results summarized in Table 3.11, we could say that the reaction sequence proceeded satisfactorily in most cases, furnishing the γ-hydrazonocarboxylic acids **49a-m** in high yields and excellent enantioselectivities. β-Substituted α,β-unsaturated aldehydes containing linear alkyl chains were tested initially (entries 1-5), to observe that they provided the products in excellent results and that the yield became only moderately affected when the length of the chain was considerably increased (entry 5). Aldehydes containing non-linear or unsaturated alkyl chains also performed well, providing excellent enantioselectivities (entries 6-8). As we could anticipate, we observed a substantial decrease in isolated yield for the *iso*-propyl containing enal (entry 7), since the size of the substituent was notably larger than in the previous cases. Furthermore, a series of compounds containing different functional groups on their structure were also tested (entries 9-11), providing the expected conjugate addition products in high yields and excellent enantioselectivities.

Table 3.11. Scope of the reaction using a series of differently substituted α,β-unsaturated aldehydes.



1a-v **42a** **43a-m** **49a-m**

Entry	R (1)	Prod.	Yield (%)[a]	dr[b]	Prod.	Yield (%)[a]	ee (%)[c]
1	*n*-Bu (**1d**)	**43a**	79	70:30	**49a**	91	92
2[d]	Me (**1b**)	**43b**	89	70:30	**49b**	86	92
3	Et (**1a**)	**43c**	83	70:30	**49c**	81	96
4	*n*-Pr (**1c**)	**43d**	86	60:40	**49d**	85	91
5	*n*-C_8H_{17} (**1h**)	**43e**	62	70:30	**49e**	93	94
6	*i*-Bu (**1t**)	**43f**	59	70:30	**49f**	98	92
7	*i*-Pr (**1j**)	**43g**	37	70:30	**49g**	94	99
8	*Z*-EtCH=CH$(CH_2)_2$ (**1i**)	**43h**	67	70:30	**49h**	85	96
9[d]	$(MeO)_2CH$ (**1l**)	**43i**	78	80:20	**49i**	76	94
10	$BnOCH_2$ (**1n**)	**43j**	69	95:5	**49j**	82	96
11	$PhCH_2CH_2$ (**1u**)	**43k**	57	70:30	**49k**	78	99
12	Ph (**1m**)	**43l**	38	70:30	**43l**	70	74
13	*p*-BrC_6H_4 (**1v**)	**43m**	62	60:40	**49m**	83	86

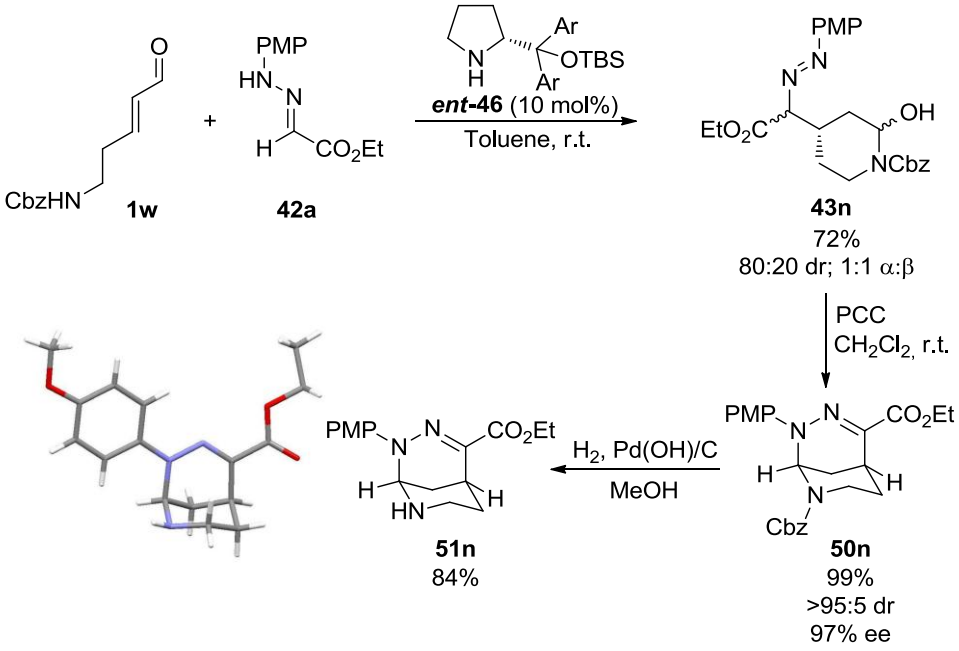
[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction performed at 0 ºC.

The behaviour of β-aryl substituted α,β-unsaturated aldehydes showed a high dependence on the electronic nature of the aryl group. Cinnamaldehyde **1m** presented lower reactivity and provided poorer enantioselectivity compared to the

aliphatic enals tested before (entry 12), whereas *p*-bromocinnamaldehyde **1v**, possessing electron-withdrawing properties, performed very well in the reaction. However, the introduction of more strongly electron-withdrawing groups on the phenyl ring resulted in the formation of the hemiaminal derivatives. These were difficult to isolate by flash column chromatography, making the determination of the yields and enantioselectivities impossible. On the other hand, aryl substituents containing electron-donating properties presented very poor reactivity towards the conjugate addition reaction, showing the formation of the desired compounds in yields below 10%.

Finally, we evaluated the use of a functionalized α,β-unsaturated δ-aminoaldehyde **1w**, which reacted efficiently with hydrazone **42a** under the optimized conditions. However, the pendant protected amine underwent an intramolecular reaction with the formyl group, leading to the formation of the corresponding hemiaminal **43n** in excellent yield and enantiopurity, and as a 1:1 mixture of α and β anomers (see Scheme 3.31). Thus, aiming to simplify the diastereomeric mixture of compounds for an easier characterization, a PCC mediated oxidation was attempted. However, the acidic nature of this oxidant promoted the formation of bicyclic aminal **50n**, resulting from an initial [1,3]-hydride shift followed by intramolecular reaction between the *in situ* generated iminium and the NHPMP of the hydrazone moiety. Deprotection of the Cbz group by hydrogenolysis yielded aminal **51n**, from which suitable monocrystal structures for single crystal X-ray analysis were obtained. The absolute stereochemical outcome showed a (1*S*,5*S*) absolute configuration. This was extended to adducts **43a-n** obtained after the catalytic enantioselective formal diaza-ene reaction catalyzed by amine ***ent*-46** and was also in good agreement with the expected

stereochemical outcome described for other conjugate addition reactions catalyzed by this type of *O*-silylated α,α-diarylprolinol derivatives.[33]

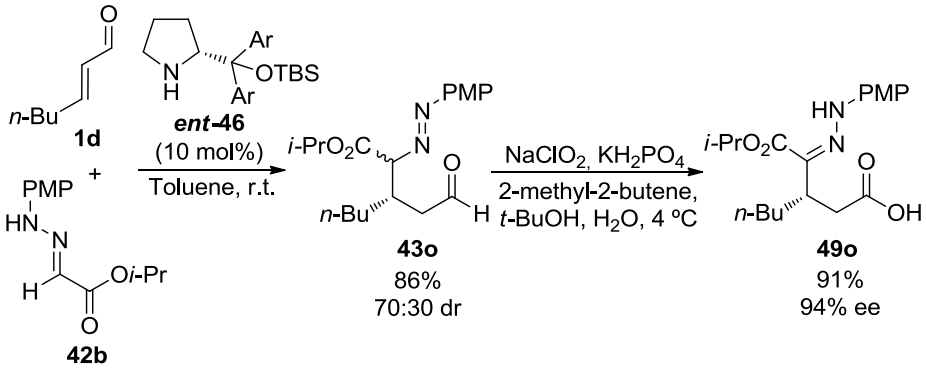


Scheme 3.31

Once a series of enals had been tested in the reaction, we next proceeded to evaluate the performance of other *N*-aryl substituted hydrazones towards the designed reaction. Initially, we evaluated the use of a glyoxylate *p*-methoxyphenyl hydrazone containing a more sterically demanding alkoxy group. In this sense, *iso*-propyl glyoxylate based hydrazone **42b** was tested, showing that the size of this

[33] For some reviews covering general aspects and uses of these catalysts, see: a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248; b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632.

group had no influenece on the course of the reaction. The oxidized compound **49o** was isolated in excellent yield and enantioselectivity (Scheme 3.32).

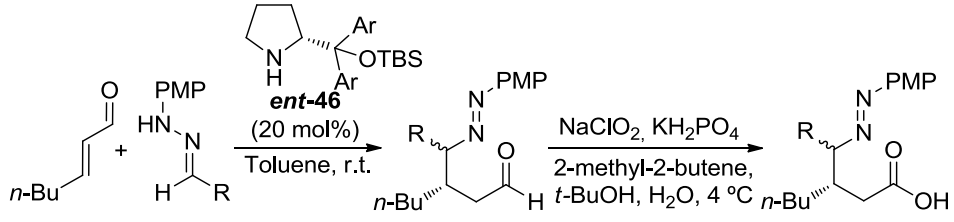


Scheme 3.32

We next proceeded to evaluate the influence that the nature of the group at the azomethine position may have on the reaction pathway, testing a series of hydrazones with non-carboxylate substituents. From the results compiled in Table 3.12, we noticed that groups with different electronic nature behaved in a slightly different manner. In this sense, whereas the strongly electron-withdrawing trifluoromethyl group provided the corresponding γ-azoaldehyde in good yield and diastereoselectivity (entry 1), decreasing the electron-withdrawal ability of the group at this position provided lower reactivity (entries 2 and 3). A particularly sluggish case involved the use of phenyl-substituted hydrazone, which only provided the desired compound in trace amounts (entry 4). Importantly, subsequent oxidation of the aldehydes obtained did not lead to the expected derivatives in which the [1,3]-hydride shift had occurred together with the oxidation. In this case, γ-azo carboxylic acids **52**, shown in the scheme of the Table 3.12, were isolated in variable yields. This event was rationalized by assuming that the proton located in α to the azo functionality needs to be highly acidic so that the [1,3]-hydride shift can occur

concomitantly with the oxidation process. Also, we considered that the process was even more favoured when using a carboxylate containing hydrazone, due to the ability of the final compounds to form an intramolecular hydrogen bond between the NHPMP and CO_2Et groups.

Table 3.12. Scope of the reaction using a series of differently substituted hydrazones.



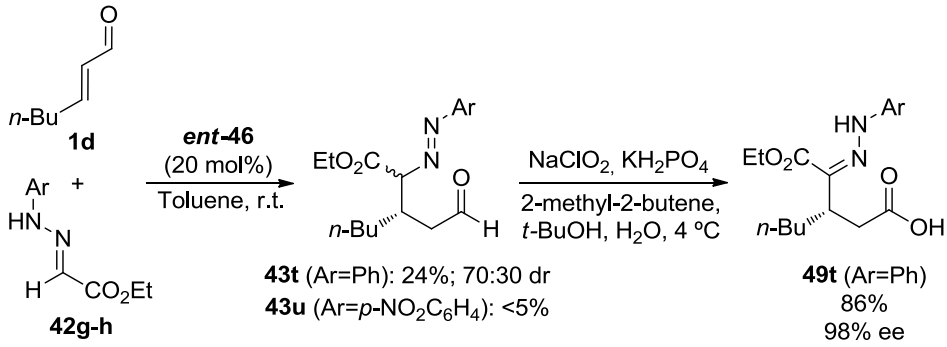
1d **42** **43p-s** **52p-s**

Entry	R (42)	Prod.	Yield (%)[a]	dr[b]	Prod.	Yield (%)[a]	ee (%)[c]
1	CF_3 (**42c**)	**43p**	62	90:10	**52p**	91	80
2	$(MeO)_2CH$ (**42d**)	**43q**	47	70:30	**52q**	35	70/92
3	Me (**42e**)	**43r**	48	60:40	**52r**	73	40/95
4	Ph (**42f**)	**43s**	<15	n.d.[d]	-	-	-

[a] Yield of the pure product isolated after flash chromatography. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase after esterification. [d] n.d.: not determined.

Finally, aiming to validate the hypothesis for our strategy as presented in Scheme 3.25, which postulated need for an electron-donating group at the nitrogen in order to obtain an efficient reaction, we decided the study the effect of changing the electronic properties of the aryl group at the nitrogen. In fact, we found that the electronic nature of this substituent was crucial for the efficiency of the reaction, observing that *N*-phenyl substituted hydrazone **42g** was able to provide us with the expected product, albeit in low conversion, whereas changing to a hydrazone with an electron-withdrawing *p*-nitrophenyl group **42h** did not offer the desired reactivity

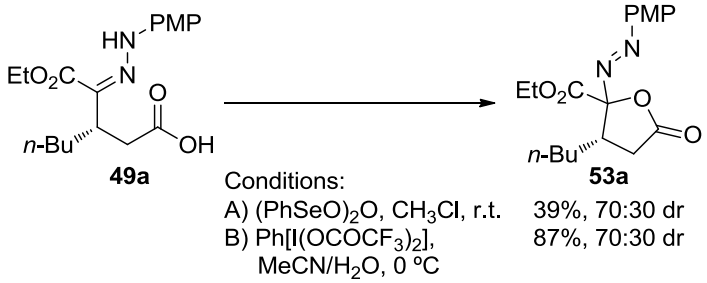
(Scheme 3.33). From our point of view, this was an indication of the important role played by the *p*-methoxyphenyl group, which favoured the stabilization of a partial negative charge on the azomethine position of the hydrazone.



Scheme 3.33

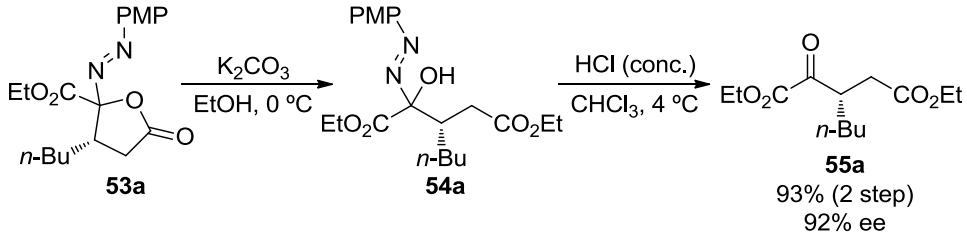
Having finally developed a successful methodology for the aminocatalyzed enantioselective conjugate addition of hydrazones to enals, we proceeded to address our final goal – *i.e.* the transformation of the obtained hydrazones into the corresponding 1,4-dicarbonyl compounds. With this purpose in mind, we started by evaluating the most utilized conditions for hydrolytic or oxidative cleavage of hydrazones. Widely used conditions for the acid hydrolysis of *N*,*N*'-dialkylhydrazones, like using oxalic or hydrochloric acid, resulted in the recovery of unreacted starting material so we decided to explore oxidative cleavage conditions. On the one hand, the use of benzeneseleninic anhydride (BSA) resulted in the formation of the azo-lactone **53a** in moderate yield, arising from the intramolecular attack of the carboxylic acid to the azomethine carbon. This intramolecular addition is favoured due to the increased electrophilicity of this carbon after the selenium reagent links to the hydrazone moiety. On the other hand, the treatment of the γ-hydrazonoacid **49a** with phenyliodoniumbis(trifluoroacetate) (PIFA) resulted in the

synthesis of the same azo-lactone product, albeit in a highly efficient manner (see Scheme 3.34).



Scheme 3.34

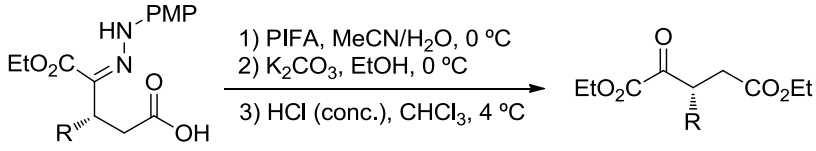
Considering the studies reported by Barton and co-workers regarding the oxidation of hydrazones employing hypervalent organoiodine reagents,[28a] and given the structure of the azo-lactone **53a**, which was cleanly obtained after treating the γ-hydrazonocarboxylic acid with PIFA, we proposed that an ethanolysis of this molecule should provide the corresponding α-hydroxy azo-compound, which would subsequently undergo hydrolysis in order to generate the desired γ-carbonyl moiety. In this sense, we subjected compound **53a** to ethanolysis conditions, which rendered the corresponding α-hydroxy azo intermediate **54a** smoothly, as detected by NMR, and could then be subjected to hydrolytic work-up. The desired α-keto-1,5-diester **55a** was isolated in an excellent overall yield and with retention of enantiopurity – as indicated by HPLC analysis on chiral stationary phase.



Scheme 3.35

Once a suitable methodology for the cleavage of the hydrazone functionality had been obtained, this was applied to a set of representative compounds **49**. The results are summarized in the Table 3.13. The designed sequence proceeded efficiently for all the γ-hydrazono carboxylic acids tested, providing high overall yields and without erosion of enantiopurity. Only with substrate **49b**, containing a methyl substituent at the stereogenic centre and where the keto-enol tautomerization is more likely to occur, a slight erosion in the enantioselectivity of the final product was noticed – from 92 to 86% ee (entry 2).

Table 3.13. Synthesis of 1,4-dicarbonyl compounds.



49 **55**

Entry	R (**49**)	Prod.	Yield (%)[a] (3 step)	ee (%)[b]
1	*n*-Bu (**49a**)	**55a**	81	92
2	Me (**49b**)	**55b**	83	86
3	*i*-Pr (**49g**)	**55g**	74	99
4	*Z*-EtCH=CH(CH_2)$_2$ (**49h**)	**55h**	70	94

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

4. CONCLUSIONS

Considering the results obtained during this chapter we could conclude the following:

- Iminium mediated organocatalysis is an efficient tool for the conjugate addition of hydrazones as useful synthetic acyl anion equivalents.

- *N*-Monosubstituted hydrazones are suitable reagents to carry out conjugate addition reaction to enals under iminium activation. However, the electronic nature of the substituents present on these hydrazones plays a crucial role in the performance of the reaction. Specifically, we have proven that hydrazones containing an electron-withdrawing group at the azomethine position are the most efficient towards the conjugate addition to α,β-unsaturated aldehydes.

- The conjugate addition using tosylhydrazones as acyl anion equivalents proceeds in an efficient way; however, it presents irreproducibility issues, presumably arisen from the configurational instability of the cyclic compounds that are formed. Even so, the hydrazone was proven to be a synthetic equivalent of a glyoxylate group, after benzeneseleninic anhydride-mediated oxidative cleavage of the initial Michael-type adducts.

- The conjugate addition of *p*-methoxyphenylhydrazones to enals works efficiently, leading to the formation of γ-azoaldehydes in high yields, which after oxidation/[1,3]-hydride shift sequence, are converted into highly enantioenriched γ-hydrazonocarboxylic acids. The reaction allows the use of a wide variety of enals, containing both alkyl and aryl groups.

- Finally, we have also developed a procedure that illustrates that *p*-methoxyphenyl hydrazones are useful acyl anion equivalents, which can be employed for the synthesis of 1,4-dicarbonyl compounds. The proposed PIFA-mediated intramolecular addition/ethanolysis/hydrolysis sequence is a very efficient methodology for the cleavage of the hydrazone moiety.

- Overall, we have developed a valuable enantioselective methodology for the indirect β-glyoxylation of α,β-unsaturated aldehydes.

4

4

Final conclusions

1. CONCLUSIONS

Throughout the present work it has been demonstrated that hydrazides and hydrazones are efficient and versatile reagents to be employed in secondary amine catalyzed conjugate addition reactions to α,β-unsaturated aldehydes. In this context, we determined that hydrazides could be employed as double *N*-donors for aza-Michael reactions, whereas hydrazones can behave as either *N*- or *C*-donors for both aza-Michael and Michael reactions respectively. From the developed methodologies, we could conclude the following:

a) Hydrazides and hydrazones as *N*-donors in aminocatalytic aza-Michael initiated cascade reactions. Two new aminocatalytic aza-Michael initiated cascade reactions have been developed, using appropriately functionalized hydrazides or hydrazones and a variety of substituted α,β-unsaturated aldehydes as Michael acceptors. The first case, using *N*-Boc-*N'*-(*p*-nitrobenzenesulfonyl)hydrazide, led to an aza-Michael reaction/1,2-intramolecular addition sequence, whereas in the second example, the bifunctional tosylhydrazone derived from pyruvaldehyde, was able to engage in an aza-Michael/aldol condensation domino process. Diaryl prolinol derivative **8** was shown to be the most efficient catalyst to promote both processes in high yields and stereoselectivities. Furthermore, the pyrazolidin-3-ol products generated from the aza-Michael/1,2-addition reaction of enals with hydrazides are excellent precursors for the synthesis of other related molecules of interest, such as pyrazolines, pyrazolidinones or 1,3-diamines. These transformations were achieved in excellent yields whilst maintaining the enantiomeric purity of the starting compounds.

b) Hydrazones as *C*-nucleophiles for the aminocatalytic conjugate addition of acyl anion equivalents. A novel aminocatalytic conjugate addition of *N*-monosubstituted hydrazones to enals has been developed, highlighting the ability of these hydrazone reagents to act as both *N*- and *C*-donors. In this case, the diaryl prolinol derivatives **6** (when using tosylhydrazones) or **46** (when employing *p*-methoxyphenyl hydrazones) catalyze the reaction in an efficient manner, providing the desired products in high yields and excellent enantioselectivities. The reaction with the tosylhydrazones displayed reproducibility issues due to the configurational instability of the cyclic adducts generated, whereas *p*-methoxyphenyl hydrazones, allowed the isolation of acyclic, and thus, configurationally stable compounds. Finally, simple and efficient methods for the cleavage of the hydrazone moiety has been presented, verifying that hydrazones are useful acyl anion equivalents that can be employed in the synthesis of 1,4-dicarbonyl compounds.

5

5

Experimental

5.3. Induction of the [1,3]-hydride shift

5.4. Oxidation of the aldehydes: synthesis of γ-hydrazono carboxylic acids **49a-t** and **52p-r**

5.5. Transformation of γ-hydrazono carboxylic acids: access to α-keto-1,5-diesters **55a-h**

1. GENERAL METHODS AND MATERIALS

NMR: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H-NMR and ^{13}C-NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and and 125.7 MHz ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e. NOESY, COSY and HSQC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals.[1]

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100, a Perkin-Elmer 1600 and a Perkin-Elmer Spectrum BX apparatus, in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case.

MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer under electronic impact (EI) or chemical ionization (CI) 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%).

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

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

Polarimetry: Optical rotations were measured at 20 ºC 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.

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

HPLC: High performance liquid chromatography on a chiral stationary phase was performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak AD-H, AS-H, IA and IC and Chiralcel OZ-3 columns (0.46 cm x 25 cm) were used; specific conditions are indicated for each case.

X-Ray: X-ray data collections were performed in an *Agilent Supernova* diffractometer equipped with an *Atlas* CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250 μm FWHM beam size). The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone-N inert oil and transferred to the diffractometer. Alternatively, an *Oxford Diffraction Xcalibur 2* diffractometer equipped with a *Sapphire 2* CCD area detector, and a MoKα sealed-tube source with graphite monochromator (λ = 0.71073Å, 0.5mm collimator) was used. The samples were kept at 100(1)K with a *Oxford Cryosystems Cryostream 700* cooler.

Miscellaneous: 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, phosphomolybdic acid or *p*-anisaldehyde dips.[2] For flash chromatography Merck 60, 230-400 mesh silica gel was used.[3]

Anhydrous solvents were purified and dried with activated molecular sieves prior to use. 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_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to utilizing in an oven at 140 ºC, and allowed to cool under a dehumidified atmosphere.[4]

Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator. High pressure Parr apparatus was used for hydrogenations and a Fisher Ozon-Generator 502 instrument for ozonolysis. Sonications were performed in a Branson 3510 apparatus.

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[2] E. Stahl, *Thin Layer Chromatography*, Springer-Verlag, Berlin, **1969**.
[3] Still, W. C., Kann, H. , Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.
[4] Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis vía Boranes*, John Wiley & Sons, Nueva York, 1975.

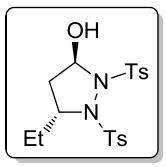
2. REACTION WITH HYDRAZIDES: AZA-MICHAEL/ HEMIAMINALIZATION

2.1 Synthesis of pyrazolidin-3-ols 4a-n.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **8** (0.02 mmol, 10 mol%), PhCOOH (0.05 mmol, 25 mol%) and toluene (2.0 mL). Then, hydrazide **2** (0.20 mmol) and α,β-unsaturated aldehyde **1a-l** (0.20 mmol) were added. The stirring was maintained at room temperature until the reaction was complete (24-72 h) and the reaction mixture was concentrated and charged directly onto silica gel and subjected to flash chromatography (FC). The racemic standards for HPLC separation conditions were prepared using D,L-proline (0.02 mmol, 10 mol%) instead of catalyst **8**, without PhCOOH and in CH_2Cl_2 (2.0 mL) at room temperature.

(3*R*,5*R*)-5-Ethyl-1,2-bis(*p*-toluenesulfonyl)pyrazolidin-3-ol (4a)



Following the general procedure, **4a** (46 mg, 0.11 mmol) was isolated by FC (*n*-hexane/EtOAc 1:1) as a white solid after 72 h reaction time, starting from *trans*-2-pentenal **1a** (21 μL, 0.20 mmol) and hydrazide **2a** (68 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (2 mg, 0.02 mmol), using toluene (2.0 mL) as solvent.

Yield: 54%.

dr: 91:9.

ee: 97% (determined by HPLC analysis after reduction to pyrazolidine **5a**).

^{1}H-NMR (δ, ppm): 7.78 (d, 2H, *J* = 8.1 Hz, C_{arom}-**H**), 7.69 (d, 2H, *J* = 8.1 Hz, C_{arom}-**H**), 7.29-7.24 (m, 4H, C_{arom}-**H**), 5.81-5.72 (m, 1H, C**H**OH), 4.15-4.01 (m, 1H, C**H**N), 3.21 (d, *J* = 3.9 Hz, 1H, CHO**H**), 2.42 (s, 6H, C_{arom}-C**H**$_3$), 1.97 (ddd, 1H, *J* = 13.4, 7.8, 2.3 Hz, C**H**$_a$H$_b$), 1.69-1.46 (m, 2H, C_{chain}**H**$_a$H$_b$, CH$_a$**H**$_b$), 1.17-0.99 (m, 1H, C_{chain}H$_a$**H**$_b$), 0.80 (t, 3H, *J* = 7.3 Hz, C**H**$_3$).

^{13}C-NMR (δ, ppm): 145.2 (**C**$_{arom}$-SO$_2$), 145.1 (**C**$_{arom}$-SO$_2$), 133.1 (**C**$_{arom}$-CH$_3$), 132.0 (**C**$_{arom}$-CH$_3$), 129.9 (**C**$_{arom}$-H), 129.5 (**C**$_{arom}$-H), 129.3 (**C**$_{arom}$-H), 129.2 (**C**$_{arom}$-H), 87.1 (**C**HOH), 64.3 (**C**HN), 39.8 (**C**H$_2$), 28.6 (**C**$_{chain}$H$_2$), 21.7 (C_{arom}-**C**H$_3$), 21.6 (C_{arom}-**C**H$_3$), 11.0 (**C**H$_3$).

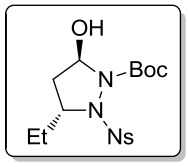
IR (film) cm^{-1}: 3495 (OH), 1357 (SO$_2$), 1166 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 110-112.

MS (EI) m/z (relative abundance): 252 (14), 223 (52), 155 (100), 139 (1), 117 (2), 91 (72), 65 (12).

HRMS: Calculated for $[C_{19}H_{24}N_2O_5NaS_2]^+$: 447.1024 $[M+Na]^+$; found: 447.1024.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-5-ethyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-ol (4b)



Following the general procedure, **4b** (70 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 48 h reaction time, starting from *trans*-2-pentenal **1a** (21 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 87%.

dr: 91:9.

ee: 93%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 42.62 min, τ_{minor} = 35.16 min.

$[\alpha]_D^{20}$: +44.9 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.36 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.18 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.84-5.77 (m, 1H, C**H**OH), 4.41-4.34 (m, 1H, C**H**N), 3.41 (d, *J* = 8.5 Hz, 1H, CHO**H**), 2.31–2.15 (m, 1H, C**H**$_a$CH$_b$), 2.15-2.00 (m, 1H, CH$_a$C**H**$_b$), 1.36–1.19 (m, 11H, C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.98 (t, *J* = 7.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 154.9 (**C**O), 150.8 (**C**$_{arom}$-NO$_2$), 142.2 (**C**$_{arom}$-SO$_2$), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.9 (**C**HOH), 82.8 (**C**(CH$_3$)$_3$), 63.0 (**C**HN), 41.1 (**C**H$_2$), 27.8 (C(**C**H$_3$)$_3$), 27.3 (**C**$_{chain}$H$_2$), 10.7 (**C**H$_3$).

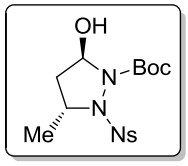
IR (Film) cm^{-1}: 3503 (OH), 1714 (CO), 1535 (NO_2), 1371 (NO_2), 1350 (SO_2), 1166 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 128-130.

MS (EI) m/z (relative abundance): 214 (2), 155 (6), 141 (8), 114 (25), 96 (98), 81 (100), 57 (64).

HRMS: Calculated for $[C_{16}H_{23}N_3O_7NaS]^+$: 424.1154 $[M+Na]^+$; found: 424.1163.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-5-methyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-ol (4c)



Following the general procedure, **4c** (72 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 24 h reaction time, starting from *trans*-crotonaldehyde **1b** (19 µL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent at 4 ºC.

Yield: 93%.

dr: 91:9.

ee: 85%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 26.59 min, τ_{minor} = 28.78 min.

$[\alpha]_D^{20}$: +24.1 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.16 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.85-5.79 (m, 1H, C**H**OH), 4.65-4.50 (m, 1H, C**H**N), 3.46 (d, *J* = 7.9 Hz, 1H, CHO**H**), 2.18-2.06 (m, 2H, C**H**$_2$), 1.30 (s, 9H, C(C**H**$_3$)$_3$), 1.16 (d, *J* = 6.8 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.0 (**C**O), 150.8 (**C**$_{arom}$-NO_2), 142.0 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.7 (**C**HOH), 82.9 (**C**$(CH_3)_3$), 57.1 (**C**HN), 42.4 (**C**H_2), 27.8 (C(**C**H_3)$_3$), 20.6 (**C**H_3).

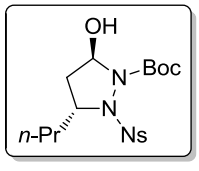
IR (Film) cm^{-1}: 3492 (OH), 1708 (CO), 1531 (NO_2), 1368 (NO_2), 1349 (SO_2), 1164 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 157-159.

MS (EI) m/z (relative abundance): 200 (6), 141 (8), 127 (16), 100 (42), 82 (65), 57 (100).

HRMS: Calculated for $[C_{15}H_{21}N_3O_7NaS]^+$: 410.0998 $[M+Na]^+$; found: 410.0996.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-propylpyrazolidin-3-ol (4d)



Following the general procedure, **4d** (82 mg, 0.20 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid in 48 h starting from *trans*-2-hexenal **1c** (26 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the

presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 99%.

dr: >95:5.

ee: 92%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min. τ_{major} = 67.44 min, τ_{minor} = 49.81 min.

$[\alpha]_D^{20}$: +40.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.34 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.16 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.82-5.75 (m, 1H, C**H**OH), 4.46-4.39 (m, 1H, C**H**N), 3.63 (d, *J* = 8.0 Hz, 1H, CHO**H**), 2.20-2.13 (m, 1H, C**H**$_a$CH$_b$), 2.07-1.98 (m, 1H, CH$_a$C**H**$_b$), 1.56-1.21 (m, 13H, 2 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.90 (t, *J* = 7.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.1 (**C**O), 150.7 (**C**$_{arom}$-NO_2), 142.2 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.8 (**C**HOH), 82.8 (**C**(CH$_3$)$_3$), 61.2 (**C**HN), 41.2 (**C**H$_2$), 36.1 (**C**$_{chain}$H$_2$), 27.8 (C(**C**H$_3$)$_3$), 19.4 (**C**$_{chain}$H$_2$), 13.4 (**C**H$_3$).

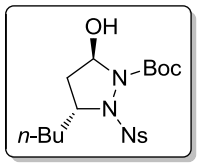
IR (Film) cm^{-1}: 3568 (OH), 1708 (CO), 1536 (NO_2), 1368 (NO_2), 1354 (SO_2), 1164 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 150-151.

MS (EI) m/z (relative abundance): 355 (6), 327 (6), 281 (51), 254 (26), 230 (2), 207 (100), 186 (46), 156 (13), 122 (88), 101 (18), 96 (7), 77 (56), 51 (29).

HRMS: Calculated for $[C_{17}H_{25}N_3O_7NaS]^+$: 438.1311 $[M+Na]^+$; found: 438.1309.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-5-butyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-ol (4e)



Following the general procedure, **4e** (78 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid in 48 h starting from *trans*-2-heptenal **1d** (26 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 91%.

dr: >95:5.

ee: 94%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 40.62 min, τ_{minor} = 29.30 min.

$[\alpha]_D^{20}$: +42.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.36 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 8.17 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 5.83-5.77 (m, 1H, C**H**OH), 4.49-4.40 (m, 1H, C**H**N), 3.43 (d, *J* = 8.5 Hz, 1H, CHO**H**), 2.25–2.18 (m, 1H, C**H**$_a$CH$_b$), 2.15-2.02 (m, 1H, CH$_a$C**H**$_b$), 1.37-1.17 (m, 15H, 3 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.89 (t, *J* = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 154.9 (**C**O), 150.8 (**C**$_{arom}$-NO_2), 142.2 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.9 (**C**HOH), 82.8 (**C**$(CH_3)_3$), 61.5 (**C**HN), 41.4 (**C**H_2), 33.8 (**C**$_{chain}H_2$), 28.3 (**C**$_{chain}H_2$), 27.8 (C(**C**$H_3)_3$), 22.1 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

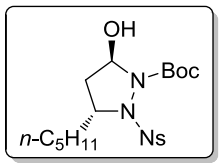
IR (Film) cm^{-1}: 3458 (OH), 1710 (CO), 1531 (NO_2), 1368 (NO_2), 1349 (SO_2), 1167 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 123-125.

MS (EI) m/z (relative abundance): 242 (2), 183 (4), 124 (12), 100 (24), 82 (100), 81 (56), 57 (38).

HRMS: Calculated for $[C_{18}H_{27}N_3O_7NaS]^+$: 452.1467 $[M+Na]^+$; found: 452.1470.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-pentylpyrazolidin-3-ol (4f)



Following the general procedure, **4f** (84 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-2-octenal **1e** (29 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 95%.

dr: >95:5.

ee: 93%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 37.92 min, τ_{minor} = 27.87 min.

$[\alpha]_D^{20}$: +41.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.17 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.82-5.76 (m, 1H, C**H**OH), 4.45-4.39 (m, 1H, C**H**N), 3.55 (d, *J* = 8.1 Hz, 1H, CHO**H**), 2.22-1.95 (m, 1H, C**H**$_a$CH$_b$), 2.10-1.92 (m, 1H, CH$_a$C**H**$_b$), 1.52-1.11 (m, 17H, 4 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.87 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.0 (**C**O), 150.7 (**C**$_{arom}$-NO_2), 142.2 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.8 (**C**HOH), 82.8 (**C**$(CH_3)_3$), 61.5 (**C**HN), 41.3 (**C**H_2), 34.0 (**C**$_{chain}H_2$), 31.1 (**C**$_{chain}H_2$), 27.8 (C(**C**$H_3)_3$), 25.8 (**C**$_{chain}H_2$), 22.5 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

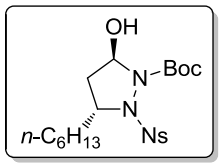
IR (Film) cm^{-1}: 3448 (OH), 1705 (CO), 1528 (NO_2), 1371 (NO_2), 1349 (SO_2), 1162 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 112-114.

MS (EI) m/z (relative abundance): 256 (2), 197 (7), 183 (6), 156 (7), 139 (17), 109 (12), 100 (34), 95 (46), 82 (100), 81 (54), 57 (70).

HRMS: Calculated for $[C_{19}H_{29}N_3O_7NaS]^+$: 466.1624 $[M+Na]^+$; found: 466.1631.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-5-hexyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-ol (4g)



Following the general procedure, **4g** (71 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-2-nonenal **1f** (33 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 78%.

dr: >95:5.

ee: 93%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 36.10 min, τ_{minor} = 25.75 min.

$[\alpha]_D^{20}$: +46.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.18 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.84-5.77 (m, 1H, C**H**OH), 4.51-4.36 (m, 1H, C**H**N), 3.46 (d, *J* = 8.4 Hz, 1H, CHO**H**), 2.24-2.17 (m, 1H, C**H**$_a$CH$_b$), 2.14-1.99 (m, 1H, CH$_a$C**H**$_b$), 1.48-1.20 (m, 19H, 5 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.87 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.0 (**C**O), 150.8 (**C**$_{arom}$-NO$_2$), 142.2 (**C**$_{arom}$-SO$_2$), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.9 (**C**HOH), 82.8 (**C**(CH$_3$)$_3$), 61.5 (**C**HN), 41.4

(**C**H_2), 34.1 (**C**$_{chain}H_2$), 31.7 (**C**$_{chain}H_2$), 28.6 (**C**$_{chain}H_2$), 27.8 (C(**C**H_3)$_3$), 26.1 (**C**$_{chain}H_2$), 22.5 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

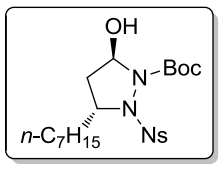
IR (Film) cm^{-1}: 3458 (OH), 1708 (CO), 1536 (NO_2), 1368 (NO_2), 1349 (SO_2), 1164 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 126-129.

MS (EI) m/z (relative abundance): 211 (4), 197 (2), 170 (4), 152 (14), 137 (4), 123 (8), 109 (12), 100 (20), 95 (44), 82 (100), 81 (50), 57 (42).

HRMS: Calculated for $[C_{20}H_{31}N_3O_7NaS]^+$: 480.1780 $[M+Na]^+$; found: 480.1792.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-5-heptyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-ol (4h)



Following the general procedure, **4h** (74 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-2-decenal **1g** (39 µL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 78%.

dr: >95:5.

ee: 92%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 34.65 min, τ_{minor} = 24.53 min.

$[\alpha]_D^{20}$: +47.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 8.17 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 5.83-5.76 (m, 1H, C**H**OH), 4.48-4.34 (m, 1H, C**H**N), 3.55 (d, *J* = 8.1 Hz, 1H, CHO**H**), 2.22-2.15 (m, 1H, C**H**$_a$CH$_b$), 2.09-2.00 (m, 1H, CH$_a$C**H**$_b$), 1.48-1.12 (m, 21H, 6 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.86 (t, *J* = 6.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.0 (**C**O), 150.7 (**C**$_{arom}$-NO_2), 142.2 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.8 (**C**HOH), 82.8 (**C**(CH$_3$)$_3$), 61.5 (**C**HN), 41.3 (**C**H$_2$), 34.1 (**C**$_{chain}$H$_2$), 31.7 (**C**$_{chain}$H$_2$), 29.2 (**C**$_{chain}$H$_2$), 28.9 (**C**$_{chain}$H$_2$), 27.8 (C(**C**H$_3$)$_3$), 26.2 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.0 (**C**H$_3$).

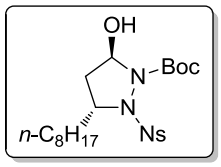
IR (Film) cm^{-1}: 3468 (OH), 1710 (CO), 1530 (NO_2), 1368 (NO_2), 1343 (SO_2), 1162 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 128-130.

MS (EI) m/z (relative abundance**)**: 225 (6), 210 (4), 184 (5), 167 (14), 137 (10), 137 (12), 100 (24), 95 (50), 82 (100), 81 (45), 57 (54).

HRMS: Calculated for $[C_{21}H_{33}N_3O_7NaS]^+$: 494.1937 $[M+Na]^+$; found: 494.1948.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-octylpyrazolidin-3-ol (4i)



Following the general procedure, **4i** (97 mg, 0.20 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-2-undecenal **1h** (40 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 99%.

dr: >95:5.

ee: 94%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 32.66 min, τ_{minor} = 22.93 min.

$[\alpha]_D^{20}$: +36.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.18 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.83-5.76 (m, 1H, C**H**OH), 4.47-4.40 (m, 1H, C**H**N), 3.49 (d, *J* = 8.3 Hz, 1H, CHO**H**), 2.27-2.14 (m, 1H, C**H**$_a$CH$_b$), 2.12-1.98 (m, 1H, CH$_a$C**H**$_b$), 1.50-1.12 (m, 23H, 7 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.87 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 155.0 (**C**O), 150.8 (**C**$_{arom}$-NO$_2$), 142.2 (**C**$_{arom}$-SO$_2$), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.9 (**C**HOH), 82.8 (**C**(CH$_3$)$_3$), 61.5 (**C**HN), 41.4

(**C**H_2), 34.1 (**C**$_{chain}H_2$), 31.8 (**C**$_{chain}H_2$), 29.5 (**C**$_{chain}H_2$), 29.2 (**C**$_{chain}H_2$), 29.0 (**C**$_{chain}H_2$), 27.8 (C(**C**$H_3)_3$), 26.2 (**C**$_{chain}H_2$), 22.6 (**C**$_{chain}H_2$), 14.1 (**C**H_3).

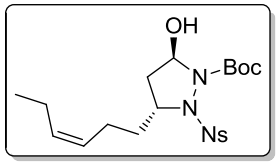
IR (Film) cm^{-1}: 3453 (OH), 1707 (CO), 1533 (NO_2), 1368 (NO_2), 1346 (SO_2), 1167 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 122-124.

MS (EI) m/z (relative abundance): 180 (14), 151 (8), 137 (12), 109 (8), 95 (52), 82 (100), 81 (38).

HRMS: Calculated for $[C_{22}H_{35}N_3O_7NaS]^+$: 508.2093 $[M+Na]^+$; found: 508.2090.

(3*R*,5*R*,3'*Z*)-2-*tert*-Butoxycarbonyl-5-(3-hexenyl)-1-(4-nitrophenylsulfonyl) pyrazolidin-3-ol (4jk)



Following the general procedure, **4j** (62 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-2-*cis*-6-nonadienal **1i** (34 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 68%.

dr: >95:5.

ee: 90%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 32.60 min, τ_{minor} = 23.03 min.

$[\alpha]_D^{20}$: +47.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.17 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.83-5.76 (m, 1H, C**H**OH), 5.47-5.34 (m, 1H, C**H**$_a$=CH$_b$), 5.33-5.20 (m, 1H, CH$_a$=C**H**$_b$), 4.48-4.41 (m, 1H, C**H**N), 3.52 (d, *J* = 8.1 Hz, 1H, CHO**H**), 2.27-1.94 (m, 6H, CH_2 + 2 x C_{chain}**H**$_2$), 1.39-1.26 (m, 11H, C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.96 (t, *J* = 6.4 Hz, 3H, C**H**$_3$).

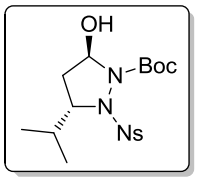
^{13}C-NMR (δ, ppm): 154.9 (**C**O), 150.8 (**C**$_{arom}$-NO$_2$), 142.2 (**C**$_{arom}$-SO$_2$), 133.2 (**C**H$_a$=CH$_b$), 131.1 (**C**$_{arom}$-H), 126.8 (CH$_a$=**C**H$_b$), 123.8 (**C**$_{arom}$-H), 85.9 (**C**HOH), 82.9 (**C**(CH$_3$)$_3$), 61.2 (**C**HN), 41.2 (**C**H$_2$), 34.2 (**C**$_{chain}$H$_2$), 27.8 (C(**C**H$_3$)$_3$), 23.9 (**C**$_{chain}$H$_2$), 20.6 (**C**$_{chain}$H$_2$), 14.3 (**C**H$_3$).

IR (Film) cm^{-1}: 3465 (OH), 1710 (CO), 1534 (NO_2), 1369 (NO_2), 1345 (SO_2), 1164 (SO_2).

MS (EI) m/z (relative abundance): 212 (4), 195 (3), 150 (12), 144 (8), 135 (16), 121 (48), 107 (6), 99 (24), 95 (10), 82 (100), 81 (90), 57 (42).

HRMS: Calculated for $[C_{20}H_{29}N_3O_7NaS]^+$: 478.1624 $[M+Na]^+$; found: 478.1616.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-*iso*-propyl pyrazolidin-3-ol (4k)



Following the general procedure, **4k** (83 mg, 0.20 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-4-methyl-2-pentenal **1j** (48 μL, 0.40 mmol) and hydrazide **2c** (126 mg, 0.40 mmol) in the presence of the catalyst **8** (24 mg, 0.04 mmol) and PhCOOH (12 mg, 0.10 mmol), using toluene (4.0 mL) as solvent.

Yield: 50%.

dr: >95:5.

ee: 97%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 37.67 min, τ_{minor} = 29.46 min.

$[\alpha]_D^{20}$: +22.8 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 8.18 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 5.78-5.72 (m, 1H, C**H**OH), 4.10 (t, *J* = 7.9 Hz, 1H, C**H**N), 3.54 (d, *J* = 7.9 Hz, 1H, CHO**H**), 2.43-2.28 (m, 1H, C**H**$_a$CH$_b$), 2.04-1.86 (m, 1H, CH$_a$C**H**$_b$), 1.53-1.42 (m, 1H, C**H**$(CH_3)_2$), 1.28 (s, 9H, C$(C\mathbf{H}_3)_3$), 0.97-0.91 (m, 6H, CH$(C\mathbf{H}_3)_2$).

^{13}C-NMR (δ, ppm): 154.5 (**C**O), 150.8 (**C**$_{arom}$-NO_2), 142.1 (**C**$_{arom}$-SO_2), 131.1 (**C**$_{arom}$-H), 123.8 (**C**$_{arom}$-H), 85.8 (**C**HOH), 82.9 (**C**$(CH_3)_3$), 67.2 (**C**HN), 38.3 (**C**H_2), 31.4 (**C**$H(CH_3)_2$), 27.8 (C(**C**$H_3)_3$), 19.2, 18.6 (CH(**C**$H_3)_2$).

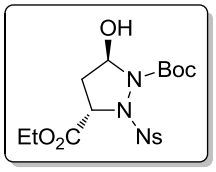
IR (Film) cm^{-1}: 3451 (OH), 1703 (CO), 1530 (NO_2), 1369 (NO_2), 1346 (SO_2), 1164 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 143-145.

MS (EI) m/z (relative abundance): 297 (4), 254 (100), 244 (6), 185 (84), 122 (80), 106 (6), 92 (10), 76 (14).

HRMS: Calculated for $[C_{17}H_{25}N_3O_7NaS]^+$: 438.1311 $[M+Na]^+$; found: 438.1309.

(3*R*,5*S*)-2-*tert*-Butoxycarbonyl-5-ethoxycarbonyl-1-(4-nitrophenylsulfonyl) pyrazolidin-3-ol (4l)



Following the general procedure, **4l** (58 mg, 0.13 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid after 72 h reaction time, starting from *trans*-4-oxobut-2-enoate **1k** (25 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 65%.

dr: 95:5.

ee: 89%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 68.93 min, τ_{minor} = 55.45 min.

$[\alpha]_D^{20}$: +9.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.37 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.21 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.95-5.89 (m, 1H, C**H**OH), 4.97 (dd, *J* = 8.5, 2.0 Hz, 1H, C**H**N), 4.29-4.06 (m, 2H, OC**H**$_2$CH$_3$), 3.44 (d, *J* = 7.4 Hz, 1H, CHO**H**), 2.72-2.65 (m, 1H, C**H**$_a$CH$_b$), 2.25-2.16 (m, 1H, CH$_a$C**H**$_b$), 1.35-1.15 (m, 12H, OCH$_2$C**H**$_3$ + CH(C**H**$_3$)$_3$).

^{13}C-NMR (δ, ppm): 168.8 (**C**O$_{ester}$), 154.2 (**C**O$_{Boc}$), 150.9 (**C**$_{arom}$-NO$_2$), 141.8 (**C**$_{arom}$-SO$_2$), 131.1 (**C**$_{arom}$-H), 123.9 (**C**$_{arom}$-H), 85.8 (**C**HOH), 83.1 (**C**(CH$_3$)$_3$), 62.2 (O**C**H$_2$CH$_3$), 61.1 (**C**HN), 38.8 (**C**H$_2$), 27.8 (C(**C**H$_3$)$_3$), 14.0 (OCH$_2$**C**H$_3$).

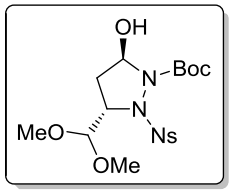
IR (Film) cm^{-1}: 3475 (OH), 1734 (CO$_{ester}$), 1708 (CO$_{Boc}$), 1531 (NO$_2$), 1368 (NO$_2$), 1345 (SO$_2$), 1169 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 102-104.

MS (EI) m/z (relative abundance): 258 (2), 199 (6), 185 (8), 158 (14), 140 (22), 130 (10), 112 (46), 95 (76), 84 (14), 57 (100).

HRMS: Calculated for [$C_{17}H_{23}N_3O_9NaS$]$^+$: 468.1053 [M+Na]$^+$; found: 468.1050.

(3*R*,5*S*)-2-*tert*-Butoxycarbonyl-5-dimethoxymethyl-1-(4-nitrophenylsulfonyl) pyrazolidin-3-ol (4m)



Following the general procedure, **4m** (85 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-fumaraldehyde **1l** (25 μL, 0.20 mmol) and hydrazide **2c** (63 mg, 0.20 mmol) in the presence of the catalyst **8** (12 mg, 0.02 mmol) and PhCOOH (6 mg, 0.05 mmol), using toluene (2.0 mL) as solvent.

Yield: 95%.

dr: >95:5.

ee: >99%.

HPLC: Chiralpak AS-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min. τ_{major} = 51.37 min, τ_{minor} = 27.04 min.

$[\alpha]_D^{20}$: +27.8 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.33 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 8.16 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 5.69-5.63 (m, 1H, C**H**OH), 4.38-4.30 (m, 2H, C**H**$(OCH_3)_2$ + C**H**N), 3.47-3.38 (m, 7H, CHO**H** + CH$(OC\mathbf{H}_3)_2$), 2.56-2.48 (m, 1H, C$\mathbf{H}_a$CH_b), 1.77-1.68 (m, 1H, CH_aC$\mathbf{H}_b$), 1.33 (s, 9H, C$(C\mathbf{H}_3)_3$).

^{13}C-NMR (δ, ppm): 154.8 (**C**O), 150.8 ($\mathbf{C}_{arom}$-NO_2), 141.6 ($\mathbf{C}_{arom}$-SO_2), 131.1 ($\mathbf{C}_{arom}$-H), 123.8 ($\mathbf{C}_{arom}$-H), 105.7 (**C**H$(OCH_3)_2$), 86.6 (**C**HOH), 82.6 (**C**$(CH_3)_3$), 61.6 (**C**HN), 57.0, 56.5 (CH$(O\mathbf{C}H_3)_2$), 35.0 (**C**H_2), 27.9 (C$(\mathbf{C}H_3)_3$).

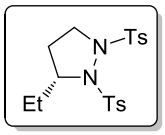
IR (Film) cm^{-1}: 3450 (OH), 1711 (CO), 1529 (NO_2), 1368 (NO_2), 1344 (SO_2), 1166 (SO_2).

MS (EI) m/z (relative abundance): 260 (2), 173 (4), 155 (4), 142 (4), 129 (28), 111 (100), 95 (8), 75 (8), 57 (50).

HRMS: Calculated for $[C_{17}H_{25}N_3O_9NaS]^+$: 470.1209 $[M+Na]^+$; found: 470.1215.

*Procedure for the preparation of reduced pyrazolidine **5a**:*

(5*R*)-5-Ethyl-1,2-bis(*p*-toluenesulfonyl)pyrazolidine (5a)



To a solution of pyrazolidin-3-ol **4a** (46 mg, 0.11 mmol) in CH_2Cl_2 (3.0 mL), Et_3SiH (46 µL, 0.36 mmol) and $BF_3{\cdot}Et_2O$ (53 µL, 0.33 mmol) were added under an argon atmosphere. The reaction was stirred at room temperature until completion (18h). The solvent was evaporated and the residual material was charged onto silica gel and subjected to flash chromatography (*n*-hexane/EtOAc gradient from 9:1 to 1:1) to obtain the pyrazolidine **5a** (23 mg, 0.06 mmol) as a white solid.

Yield: 51%.

ee: 97%.

HPLC: Chiralpak IA column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 15.00 min, τ_{minor} = 17.35 min.

$[\alpha]_D^{20}$: +87.3 (c = 0.5, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.79 (d, 2H, *J* = 8.2 Hz, C_{arom}-**H**), 7.72 (d, 2H, *J* = 8.2 Hz, C_{arom}-**H**), 7.37-7.26 (m, 4H, C_{arom}-**H**), 3.95-3.73 (m, 2H, C**H**$_2$N), 2.51-2.34 (m, 7H, C_{arom}-C**H**$_3$ + C**H**N), 1.98-1.79 (m, 2H, C**H**$_2$), 1.69-1.53 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.52-1.38 (m, 1H, C_{chain}H$_a$**H**$_b$), 0.90 (t, 3H, *J* = 7.4 Hz, C**H**$_3$).

^{13}C-NMR (δ, ppm): 145.0 (**C**$_{arom}$-SO_2), 144.8 (**C**$_{arom}$-SO_2), 133.1 (**C**$_{arom}$-CH_3), 132.2 (**C**$_{arom}$-CH_3), 129.8(**C**$_{arom}$-H), 129.6(**C**$_{arom}$-H), 129.5(**C**$_{arom}$-H), 129.4 (**C**$_{arom}$-H), 65.9 (**C**HN), 48.9 (**C**H$_2$N), 32.4 (**C**H$_2$), 29.3 (**C**$_{chain}$H$_2$), 21.8 (C_{arom}-**C**H$_3$), 21.7 (C_{arom}-**C**H$_3$), 11.4 (**C**H$_3$).

IR (Film) cm^{-1}: 1360 (SO_2), 1167 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 128-130.

MS (EI) m/z (relative abundance): 253 (11), 252 (75), 188 (8), 187(10), 155 (32), 139 (23), 97 (60), 92 (23), 91 (100), 69 (17), 67 (10), 65 (27).

HRMS: Calculated for $[C_{19}H_{24}N_2O_4NaS]^+$: 431.1075 $[M+Na]^+$; found: 431.1075.

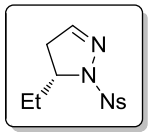
2.2 Deprotection and dehydration of pyrazolidinols 4b-i: synthesis of pyrazolines 21b-i.

General procedure:

To a solution of pyrazolidinol **4b-i** (0.20 mmol) in CH_2Cl_2 (2.0 mL), TFA (2.00 mmol) was added. The reaction was stirred at room temperature until completion (~5h). The reaction mixture was diluted with water (1.0 mL) and stirred for a few minutes prior to extraction in dichloromethane (3 x 5.0 mL). The

combined organic extracts were dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography (FC).

(5*R*)-5-Ethyl-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazole (21b)



Following the general procedure, **21b** (55 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4b** (79 mg, 0.20 mmol) and TFA (150 μL, 2.00 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 97%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 37.82 min, τ_{minor} = 40.53 min.

$[\alpha]_D^{20}$: -444.1 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.88–3.64 (m, 1H, C**H**N), 2.82 (dd, *J* = 18.3, 10.9 Hz, 1H, C**H**$_a$H$_b$), 2.57 (dd, *J* = 18.3, 8.8 Hz, 1H, CH$_a$**H**$_b$), 2.11-2.02 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.89-1.68 (m, 1H, C_{chain}H$_a$**H**$_b$), 0.94 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.7 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.3 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.1 (**C**$_{arom}$-H), 61.0 (**C**HN), 40.0 (**C**H$_2$), 28.1 (**C**$_{chain}$H$_2$), 9.2 (**C**H$_3$).

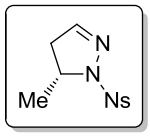
IR (Film) cm^{-1}: 1604 (C=N), 1531 (NO_2), 1349 (NO_2), 1308 (SO_2), 1174 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 119-121.

MS (EI) m/z (relative abundance): 283 (10), 254 (100), 186 (84), 122 (80), 106 (5), 92 (8), 76 (14), 64 (4), 54 (4).

HRMS: Calculated for $[C_{11}H_{14}N_3O_4S]^+$: 284.0705 $[M+H]^+$; found: 284.0704.

(5*R*)-5-Methyl-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazole (21c)



Following the general procedure, **21c** (46 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 1:1) as a white solid in 18h, starting from pyrazolidin-3-ol **4c** (77 mg, 0.20 mmol) and TFA (150 μL, 2.00 mmol) using CH_2Cl_2 (2.0 mL) as solvent at 4ºC.

Yield: 85%

ee: 85%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 41.11 min, τ_{minor} = 46.72 min.

$[\alpha]_D^{20}$: -254.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 6.97 (s, 1H, **H**C=N), 3.94-3.71 (m, 1H, C**H**N), 2.92 (ddd, *J* = 18.1,

10.6, 1.6 Hz, 1H, C**H**$_a$H$_b$), 2.51 (ddd, J = 18.1, 9.3, 1.6 Hz, 1H, CH$_a$**H**$_b$), 1.55 (d, J = 6.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.5 (H**C**=N), 150.2 (**C**$_{arom}$-NO$_2$), 141.3 (**C**$_{arom}$-SO$_2$), 129.8 (**C**$_{arom}$-H), 124.1 (**C**$_{arom}$-H), 56.2 (**C**HN), 42.9 (**C**H$_2$), 21.6 (**C**H$_3$).

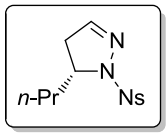
IR (Film) cm^{-1}: 1604 (C=N), 1523 (NO$_2$), 1354 (NO$_2$), 1307 (SO$_2$), 1177 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 158-160.

MS (EI) m/z (relative abundance): 269 (28), 254 (100), 186 (82), 122 (76), 106 (4), 92 (8), 83 (8), 76 (20).

HRMS: Calculated for [C$_{10}$H$_{12}$N$_3$O$_4$S]$^+$: 270.0549 [M+H]$^+$; found: 270.0544.

(5*R*)-1-(4-Nitrophenylsulfonyl)-5-propyl-4,5-dihydro-1*H*-pyrazole (21d)



Following the general procedure, **21d** (59 mg, 0.20 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4d** (83 mg, 0.20 mmol) and TFA (150 μL, 2.00 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 99%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 29.41 min, τ_{minor} = 35.95 min.

$[\alpha]_D^{20}$: -270.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.36 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 9.0 Hz, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.87-3.64 (m, 1H, C**H**N), 2.82 (ddd, *J* = 18.3, 10.8, 1.7 Hz, 1H, C**H**$_a$H$_b$), 2.56 (ddd, *J* = 18.3, 8.9, 1.7 Hz, 1H, CH$_a$**H**$_b$), 2.17-1.97 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.81-1.56 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.48-1.27 (m, 2H, C_{chain}**H**$_2$), 0.94 (t, *J* = 7.3 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.8 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.3 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-H), 59.9 (**C**HN), 40.6 (**C**H_2), 37.5 (**C**$_{chain}H_2$), 18.6 (**C**$_{chain}H_2$), 13.8 (**C**H_3).

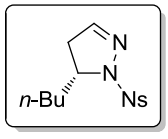
IR (Film) cm^{-1}: 1604 (C=N), 1529 (NO_2), 1352 (NO_2), 1309 (SO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 114-116.

MS (EI) m/z (relative abundance): 297 (8), 254 (100), 186 (84), 122 (72), 106 (5), 92 (7), 76 (14), 64 (4), 54 (4).

HRMS: Calculated for $[C_{12}H_{16}N_3O_4S]^+$: 298.0862 $[M+H]^+$; found: 298.0867.

(5*R*)-5-Butyl-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazole (21e)



Following the general procedure, **21e** (53 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4e** (73 mg, 0.17 mmol) and TFA (130 μL, 1.70 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 99%.

ee: 91%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 25.29 min, τ_{minor} = 30.87 min.

$[\alpha]_D^{20}$: -415.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.81-3.70 (m, 1H, C**H**N), 2.82 (dd, *J* = 18.3, 10.8 Hz, 1H, C**H**$_a$H$_b$), 2.56 (dd, *J* = 18.3, 8.9 Hz, 1H, CH$_a$**H**$_b$), 2.15-2.04 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.81-1.60 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.46-1.16 (m, 4H, 2 x C_{chain}**H**$_2$), 0.92 (t, *J* = 7.0 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.7 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.4 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-H), 60.1 (**C**HN), 40.6 (**C**H_2), 35.1 (**C**$_{chain}H_2$), 27.4 (**C**$_{chain}H_2$), 22.4 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

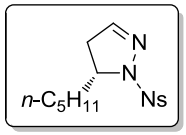
IR (Film) cm^{-1}: 1607 (C=N), 1533 (NO_2), 1354 (NO_2), 1312 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 132-138

MS (EI) m/z (relative abundance): 311 (2), 254 (100), 186 (82), 122 (70), 106 (5), 92 (6), 82 (4), 69 (18), 54 (4).

HRMS: Calculated for $[C_{13}H_{18}N_3O_4S]^+$: 312.1018 $[M+H]^+$; found: 312.1028.

(*5R*)-1-(4-Nitrophenylsulfonyl)-5-pentyl-4,5-dihydro-1H-pyrazole (21f)



Following the general procedure, **21f** (49 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4f** (76 mg, 0.17 mmol) and TFA (130 μL, 1.70 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 87%.

ee: 91%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 11.35 min, τ_{minor} = 11.90 min.

$[\alpha]_D^{20}$: -266.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.85-3.61 (m, 1H, C**H**N), 2.82 (dd, *J* = 18.3, 10.8 Hz, 1H, C**H**$_a$H$_b$), 2.56 (dd, *J* = 18.3, 8.9 Hz, 1H, CH$_a$**H**$_b$), 2.12-2.02 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.77-1.64 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.46-1.17 (m, 6H, 3 x C_{chain}**H**$_2$), 0.89 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.8 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.3 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-H), 60.1 (**C**HN), 40.6 (**C**H_2), 35.3 (**C**$_{chain}H_2$), 31.4 (**C**$_{chain}H_2$), 25.0 (**C**$_{chain}H_2$), 22.5 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

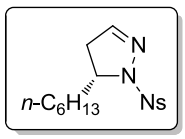
IR (Film) cm^{-1}: 1606.8 (C=N), 1531 (NO_2), 1354 (NO_2), 1312 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 88-90.

MS (EI) m/z (relative abundance): 325 (2), 254 (100), 186 (84), 139 (36), 122 (62), 106 (4), 92 (6), 69 (17), 55 (5).

HRMS: Calculated for $[C_{14}H_{20}N_3O_4S]^+$: 326.1175 $[M+H]^+$; found: 326.1179.

(5*R*)-5-Hexyl-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazole (21g)



Following the general procedure, **21g** (41 mg, 0.12 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4g** (63 mg, 0.14 mmol) and TFA (100 μL, 1.40 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 86%.

ee: 90%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 11.13 min, τ_{minor} = 11.71 min.

$[\alpha]_D^{20}$: -308.8 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 8.05 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.79-3.69 (m, 1H, C**H**N), 2.82 (ddd, *J* = 18.3, 10.8, 1.6 Hz, 1H, C**H**$_a$H$_b$), 2.56 (ddd, *J* = 18.3, 8.8, 1.6 Hz, 1H, CH$_a$**H**$_b$), 2.14-2.01 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.81-1.58 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.38-1.21 (m, 8H, 4 x C_{chain}**H**$_2$), 0.88 (t, *J* = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.7 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.4 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-H), 60.1 (**C**HN), 40.6 (**C**H_2), 35.4 (**C**$_{chain}H_2$), 31.7 (**C**$_{chain}H_2$), 29.0 (**C**$_{chain}H_2$), 25.2 (**C**$_{chain}H_2$), 22.5 (**C**$_{chain}H_2$), 14.0 (**C**H_3).

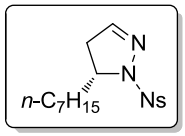
IR (Film) cm^{-1}: 1609 (C=N), 1540 (NO_2), 1366 (NO_2), 1310 (SO_2), 1172 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 104-106.

MS (EI) m/z (relative abundance): 254 (100), 186 (81), 170 (3), 153 (42), 140 (2), 122 (58), 106 (4), 92 (6), 69 (20), 55 (4).

HRMS: Calculated for $[C_{15}H_{22}N_3O_4S]^+$: 340.1331 $[M+H]^+$; found: 340.1346.

(5*R*)-5-Heptyl-1-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazole (21h)



Following the general procedure, **21h** (57 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4h** (75 mg, 0.16 mmol) and TFA (120 μL, 1.60 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 99%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 10.04 min, τ_{minor} = 10.70 min.

$[\alpha]_D^{20}$: -229.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.74 (qd, *J*=8.8, 3.7 Hz, 1H, C**H**N), 2.82 (ddd, *J* = 18.2, 10.8, 1.6 Hz, 1H, C**H**$_a$H$_b$), 2.56 (ddd, *J* = 18.2, 8.8, 1.6 Hz, 1H, CH$_a$**H**$_b$), 2.18-1.96 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.81-1.59 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.39-1.20 (m, 10H, 5 x C_{chain}**H**$_2$), 0.87 (t, *J* = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.8 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.3 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.1 (**C**$_{arom}$-H), 60.1 (**C**HN), 40.6 (**C**H$_2$), 35.4 (**C**$_{chain}$H$_2$), 31.7 (**C**$_{chain}$H$_2$), 29.3 (**C**$_{chain}$H$_2$), 29.2 (**C**$_{chain}$H$_2$), 25.3 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.1 (**C**H$_3$).

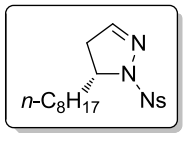
IR (Film) cm^{-1}: 1608 (C=N), 1526 (NO_2), 1354 (NO_2), 1310 (SO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 105-107.

MS (EI) m/z (relative abundance): 254 (100), 186 (76), 167 (48), 156 (2), 140 (1), 122 (50), 106 (4), 92 (5), 69 (21), 55 (4).

HRMS: Calculated for $[C_{16}H_{24}N_3O_4S]^+$: 354.1488 $[M+H]^+$; found: 354.1490.

(5*R*)-1-(4-Nitrophenylsulfonyl)-5-octyl-4,5-dihydro-1*H*-pyrazole (21i)



Following the general procedure, **21i** (44 mg, 0.12 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4i** (60 mg, 0.12 mmol) and TFA (100 μL, 1.20 mmol) using CH_2Cl_2 (2.0 mL) as solvent.

Yield: 99%.

ee: 90%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 8.82min, τ_{minor} = 9.68 min.

$[\alpha]_D^{20}$: -228.8 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.35 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.06 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 6.98 (s, 1H, **H**C=N), 3.74 (qd, *J* = 9.0, 3.6 Hz, 1H, C**H**N), 2.82 (ddd, *J* = 18.3, 10.7, 1.4 Hz, 1H, C**H**$_a$H$_b$), 2.56 (dd, *J* = 18.3, 9.0 Hz, 1H, CH$_a$**H**$_b$), 2.16-2.01 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.82-1.60 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.39-1.19 (m, 12H, 6 x C_{chain}**H**$_2$), 0.87 (t, *J* = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 150.7 (H**C**=N), 150.4 (**C**$_{arom}$-NO_2), 141.3 (**C**$_{arom}$-SO_2), 129.8 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-H), 60.1 (**C**HN), 40.6 (**C**H_2), 35.4 (**C**$_{chain}H_2$), 31.8 (**C**$_{chain}H_2$), 29.4 (**C**$_{chain}H_2$), 29.3 (**C**$_{chain}H_2$), 29.2 (**C**$_{chain}H_2$), 25.3 (**C**$_{chain}H_2$), 22.6 (**C**$_{chain}H_2$), 14.1 (**C**H_3).

IR (Film) cm^{-1}: 1609 (C=N), 1538 (NO_2), 1352 (NO_2), 1310 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 108-112.

MS (EI) m/z (relative abundance): 254 (100), 186 (74), 181 (56), 170 (2), 156 (4), 122 (46), 106 (4), 92 (5), 69 (23), 55 (5).

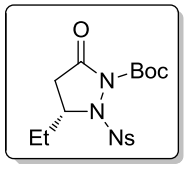
HRMS: Calculated for $[C_{17}H_{26}N_3O_4S]^+$: 368.1644 $[M+H]^+$; found: 368.1653.

2.2 Oxidation of pyrazolidinols 4b-i: synthesis of pyrazolidinones 22b-i.

General procedure:

To a solution of pyrazolidinol **4b-i** (0.18 mmol) in CH_2Cl_2 (5.0 mL), PCC (0.91 mmol) and molecular sieves (4Å) were added. The reaction was stirred at room temperature until completion (~16h) and the reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (FC).

(5*R*)-2-*tert*-Butoxycarbonyl-5-ethyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-one (22b)



Following the general procedure, **22b** (68 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4b** (73 mg, 0.18 mmol) and PCC (196 mg, 0.91 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 95%.

ee: 93%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 56.85 min, τ_{minor} = 53.09 min.

$[\alpha]_D^{20}$: +99.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.39 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.14 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 4.33-4.17 (m, 1H, C**H**N), 2.40 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.10 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.64-1.38 (m, 11H, C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 1.02 (t, *J* = 7.3 Hz, 3H, C**H**$_3$).

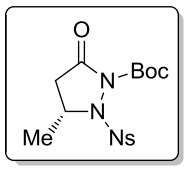
^{13}C-NMR (δ, ppm): 171.1 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 140.9 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.5 (**C**(CH$_3$)$_3$), 59.4 (**C**HN), 36.9 (**C**H$_2$), 27.7 (C(**C**H$_3$)$_3$), 27.5 (**C**$_{chain}$H$_2$), 10.0 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1770(CO$_{Boc}$), 1531 (NO$_2$), 1371 (NO$_2$), 1348 (SO$_2$), 1145 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 142-144.

HRMS: Calculated for [C$_{16}$H$_{21}$N$_3$O$_7$NaS]$^+$: 422.0998 [M+Na]$^+$; found: 422.0995.

(5*R*)-2-*tert*-Butoxycarbonyl-5-methyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-one (22c)



Following the general procedure, **22c** (69 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 1:1) as a white solid in 18 h, starting from pyrazolidin-3-ol **4c** (72 mg, 0.19 mmol) and PCC (205 mg, 0.95 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent at 4 ºC.

Yield: 94%.

ee: 84%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 52.07 min, τ_{minor} = 63.76 min.

$[\alpha]_D^{20}$: +73.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.40 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 8.16 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 4.61-4.52 (m, 1H, C**H**N), 2.55 (dd, *J* = 17.6, 7.9 Hz, 1H, C**H**$_a$H$_b$), 2.09 (d, *J* = 17.6 Hz, 1H, CH$_a$**H**$_b$), 1.45 (s, 9H, C(C**H**$_3$)$_3$), 1.33 (d, *J* = 6.8 Hz, 3H, C**H**$_3$).

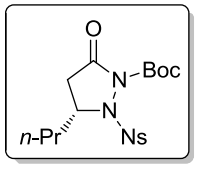
^{13}C-NMR (δ, ppm): 170.9 (**C**O), 151.2 (**C**O$_{Boc}$), 148.0 (**C**$_{arom}$-NO$_2$), 141.9 (**C**$_{arom}$-SO$_2$), 131.8 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.5 (**C**(CH$_3$)$_3$), 53.9 (**C**HN), 38.4 (**C**H$_2$), 27.8 (C(**C**H$_3$)$_3$), 20.5 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1774 (CO$_{Boc}$), 1536 (NO$_2$), 1368 (NO$_2$), 1352 (SO$_2$), 1145 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 134-136.

HRMS: Calculated for $[C_{15}H_{19}N_3O_7NaS]^+$: 408.0841 $[M+Na]^+$; found: 408.0844.

(5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-propylpyrazolidin-3-one (22d)



Following the general procedure, **22d** (68 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4d** (70 mg, 0.17 mmol) and PCC (205 mg, 0.95 mmol), in the presence of

molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 97%.

ee: 92%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 53.51 min, τ_{minor} = 49.51 min.

$[\alpha]_D^{20}$: +93.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.39 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.15 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.46-4.28 (m, 1H, C**H**N), 2.43 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.08 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.63-1.29 (m, 13H, 2 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.93 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

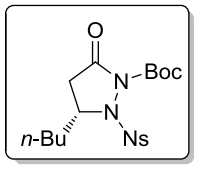
^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 140.9 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.4 (**C**(CH$_3$)$_3$), 57.8 (**C**HN), 37.7 (**C**H$_2$), 36.2 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 18.7 (**C**$_{chain}$H$_2$), 13.4 (**C**H$_3$).

IR (Film) cm^{-1}: 1794 (CO), 1772 (CO$_{Boc}$), 1537 (NO$_2$), 1371 (NO$_2$), 1349 (SO$_2$), 1143 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 121-123.

HRMS: Calculated for $[C_{17}H_{23}N_3O_7NaS]^+$: 433.1154 $[M+Na]^+$; found: 433.1166.

(5*R*)-2-*tert*-Butoxycarbonyl-5-butyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-one (22e)



Following the general procedure, **22e** (61 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4e** (68 mg, 0.16 mmol) and PCC (170 mg, 0.79 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 90%.

ee: 90%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 51.91 min, τ_{minor} = 45.86 min.

$[\alpha]_D^{20}$: +93.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.40 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 8.15 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 4.38-4.31 (m, 1H, C**H**N), 2.44 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.10 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.61-1.20 (m, 15H, 3 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.89 (t, *J* = 7.1 Hz, 3H, C**H**$_3$).

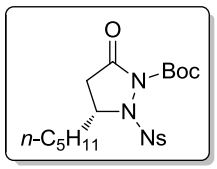
^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.5 (**C**(CH$_3$)$_3$), 58.0 (**C**HN), 37.3 (**C**H$_2$), 33.9 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 27.4 (**C**$_{chain}$H$_2$), 22.0 (**C**$_{chain}$H$_2$), 13.8 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1770 (CO$_{Boc}$), 1533 (NO$_2$), 1369 (NO$_2$), 1352 (SO$_2$), 1147 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 124-126.

HRMS: Calculated for $[C_{18}H_{25}N_3O_7NaS]^+$: 450.1311 $[M+Na]^+$; found: 450.1306.

(5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-pentylpyrazolidin-3-one (22f)



Following the general procedure, **22f** (57 mg, 0.13 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4f** (59 mg, 0.13 mmol) and PCC (140 mg, 0.67 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 97%.

ee: 91%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 36.26 min, τ_{minor} = 32.61 min.

$[\alpha]_D^{20}$: +83.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.39 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.15 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 4.37-4.30 (m, 1H, C**H**N), 2.42 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.09 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.67-1.16 (m, 17H, 4 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.87 (t, *J* = 6.4 Hz, 3H, C**H**$_3$).

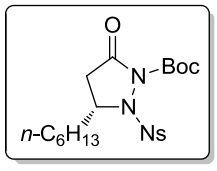
^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.4 (**C**(CH$_3$)$_3$), 58.1 (**C**HN), 37.2 (**C**H$_2$), 34.1 (**C**$_{chain}$H$_2$), 31.0 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 25.0 (**C**$_{chain}$H$_2$), 22.4 (**C**$_{chain}$H$_2$), 13.9 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1771 (CO$_{Boc}$), 1536 (NO$_2$), 1368 (NO$_2$), 1352 (SO$_2$), 1145 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 127-139.

HRMS: Calculated for [C$_{19}$H$_{27}$N$_3$O$_7$NaS]$^+$: 464.1467 [M+Na]$^+$; found: 464.1456.

(5*R*)-2-*tert*-Butoxycarbonyl-5-hexyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-one (22g)



Following the general procedure, **22g** (60 mg, 0.13 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4g** (65 mg, 0.14 mmol) and PCC (153 mg, 0.71 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 93%.

ee: 91%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 33.38 min, τ_{minor} = 28.93 min.

$[\alpha]_D^{20}$: +92.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.40 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.15 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.38-4.31 (m, 1H, C**H**N), 2.44 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.09 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.63-1.15 (m, 19H, 5 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.87 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

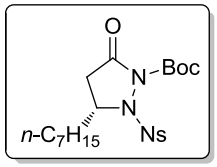
^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.4 (**C**(CH$_3$)$_3$), 58.1 (**C**HN), 37.3 (**C**H$_2$), 34.2 (**C**$_{chain}$H$_2$), 31.6 (**C**$_{chain}$H$_2$), 28.5 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 25.2 (**C**$_{chain}$H$_2$), 22.5 (**C**$_{chain}$H$_2$), 14.0 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1769 (CO$_{Boc}$), 1536 (NO$_2$), 1369 (NO$_2$), 1349 (SO$_2$), 1147 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 92-94.

HRMS: Calculated for $[C_{20}H_{29}N_3O_7NaS]^+$: 478.1624 $[M+Na]^+$; found: 478.1632.

(5*R*)-2-*tert*-Butoxycarbonyl-5-heptyl-1-(4-nitrophenylsulfonyl)pyrazolidin-3-one (22h)



Following the general procedure, **22h** (72 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4h** (75 mg, 0.16 mmol) and PCC (172 mg, 0.80 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 96%.

ee: 91%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 33.02 min, τ_{minor} = 28.26 min.

$[\alpha]_D^{20}$: +87.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.39 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.15 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.37-4.30 (m, 1H, C**H**N), 2.43 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.09 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.66-1.14 (m, 21H, 6 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

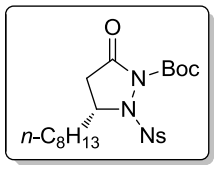
^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.4 (**C**(CH$_3$)$_3$), 58.0 (**C**HN), 37.2 (**C**H$_2$), 34.2 (**C**$_{chain}$H$_2$), 31.6 (**C**$_{chain}$H$_2$), 29.0 (**C**$_{chain}$H$_2$), 28.8 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 25.3 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.0 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1772 (CO$_{Boc}$), 1533 (NO$_2$), 1368 (NO$_2$), 1350 (SO$_2$), 1143 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 95-97.

HRMS: Calculated for $[C_{21}H_{31}N_3O_7NaS]^+$: 492.1780 $[M+Na]^+$; found: 492.1784.

(5*R*)-2-*tert*-Butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-octylpyrazolidin-3-one (22i)



Following the general procedure, **22i** (56 mg, 0.12 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a white solid, starting from pyrazolidin-3-ol **4i** (60 mg, 0.12 mmol) and PCC (133 mg, 0.62 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 94%.

ee: 90%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min; τ_{major} = 31.24 min, τ_{minor} = 26.88 min.

$[\alpha]_D^{20}$: +75.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.39 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.14 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.40-4.27 (m, 1H, C**H**N), 2.42 (dd, *J* = 17.7, 8.0 Hz, 1H, C**H**$_a$H$_b$), 2.08 (d, *J* = 17.7 Hz, 1H, CH$_a$**H**$_b$), 1.62-1.10 (m, 23H, 7 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 171.2 (**C**O), 151.2 (**C**O$_{Boc}$), 147.9 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-SO$_2$), 130.7 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 85.4 (**C**(CH$_3$)$_3$), 58.1 (**C**HN), 37.2 (**C**H$_2$), 34.2 (**C**$_{chain}$H$_2$), 31.8 (**C**$_{chain}$H$_2$), 29.3 (**C**$_{chain}$H$_2$), 29.1 (**C**$_{chain}$H$_2$), 28.9 (**C**$_{chain}$H$_2$), 27.7 (C(**C**H$_3$)$_3$), 25.3 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.0 (**C**H$_3$).

IR (Film) cm^{-1}: 1797 (CO), 1771 (CO_{Boc}), 1536 (NO_2), 1368 (NO_2), 1350 (SO_2), 1147 (SO_2).

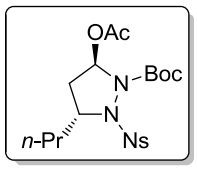
M.p. (*n*-hexane/EtOAc) (ºC): 85-87.

HRMS: Calculated for $[C_{22}H_{33}N_3O_7NaS]^+$: 506.1937 $[M+Na]^+$; found: 506.1936.

2.3 Other transformations.

Acetylation and p-chlorobenzoylation of pyrazolidinol **4d***:*

(3*R*,5*R*)-3-Acetoxy-2-*tert*-butoxycarbonyl-1-(4-nitrophenylsulfonyl)-5-propylpyrazolidine (23d)



To a solution of pyrazolidin-3-ol **4d** (82 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL), DMAP (25 mg, 0.02 mmol, 10 mol%) and Ac_2O (18 µL, 0.20 mmol) were added. The reaction was stirred at room temperature until completion and the reaction mixture was directly charged onto silica gel and subjected to flash chromatography (*n*-hexane/EtOAc gradient from 9:1 to 1:1) to obtain the product **23d** (91 mg, 0.20 mmol) as a white solid.

Yield: 99%.

dr: >95:5.

ee: 95%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 8.95 min, τ_{minor} = 12.79 min.

$[\alpha]_D^{20}$: +59.6 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.36 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 8.19 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.58 (dd, *J* = 7.1, 4.8 Hz, 1H, C**H**OAc), 4.34 (dd, *J* = 13.8, 6.3 Hz, C**H**N), 2.31-2.24 (m, 1H, CH_aH_b), 2.02-1.93 (m, 4H, CH_aCH_b + OCH_3), 1.40-1.31 (m, 13H, 2 x $C_{chain}H_2$ + $C(CH_3)_3$), 0.90 (t, *J* = 6.8 Hz, 3H, CH_3).

^{13}C-NMR (δ, ppm): 169.5 (CO_{Ac}) 154.2 (CO_{Boc}), 150.7 (C_{arom}-NO_2), 142.8 (C_{arom}-SO_2), 130.9 (C_{arom}-H), 123.8 (C_{arom}-H), 85.7 (**C**HOAc), 83.5 ($C(CH_3)_3$), 61.3 (**C**HN), 39.5 (CH_2), 36.4 ($C_{chain}H_2$), 27.8 ($C(CH_3)_3$), 21.0 (OCH_3), 19.3 ($C_{chain}H_2$), 13.4 (CH_3).

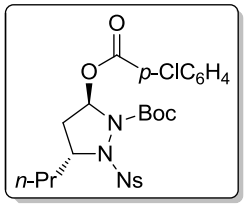
IR (Film) cm^{-1}: 1741 (CO_{Ac}), 1707 (CO_{Boc}), 1534 (NO_2), 1365 (NO_2), 1351 (SO_2), 1167 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 107-108.

MS (EI) m/z (relative abundance): 313 (2), 254 (100), 186 (75), 167(46), 122 (51), 109 (3), 95 (6), 82 (7), 69 (26), 55 (6).

HRMS: Calculated for $[C_{19}H_{27}N_3O_8NaS]^+$: 457.1517 $[M+Na]^+$; found: 457.1518.

(3*R*,5*R*)-2-*tert*-Butoxycarbonyl-3-(4-chlorobenzoyloxy)-1-(4-nitrophenylsulfonyl)-5-propylpyrazolidine (24d)



To a solution of pyrazolidin-3-ol **4d** (80 mg, 0.19 mmol) in CH_2Cl_2 (2.0 mL), Et_3N (27 µL, 0.19 mmol) and *p*-chlorobenzoyl chloride (24 µL, 0.19 mmol) were added. The reaction was stirred at room temperature until completion and the crude mixture was directly charged onto silica gel and subjected to flash chromatography (*n*-hexane/EtOAc gradient from 9:1 to 1:1) to obtain the product **24d** (95 mg, 0.17 mmol) as a white solid.

Yield: 89%.

dr: 90:10.

ee: 91%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 16.68 min, τ_{minor} = 32.14 min.

$[\alpha]_D^{20}$: +37.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 8.31 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 8.20 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 7.99 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 7.44 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 6.95 (dd, *J* = 5.7 Hz, *J* = 5.7 Hz, 1H, C**H**CO*p*ClPh), 4.53-4.46 (m, 1H, C**H**N), 2.45-2.39 (m, 1H, C**H**$_2$), 1.42-1.26 (m, 13H, 2 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.90 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.4 (**C**O_{Bz}), 153.7 (**C**O_{Boc}), 150.6 (**C**$_{arom}$-NO_2), 143.0 (**C**$_{arom}$-SO_2), 140.0 (**C**$_{arom}$-Cl), 131.2 (**C**$_{arom}$-H), 130.8 (**C**$_{arom}$-H), 128.9 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-CO), 123.9 (**C**$_{arom}$-H), 86.0 (**C**HOCO*p*ClPh), 83.5 (**C**$(CH_3)_3$), 61.1 (**C**HN), 40.0 (**C**H_2), 36.5 (**C**$_{chain}H_2$), 27.8 (C(**C**$H_3)_3$), 19.4 (**C**$_{chain}H_2$), 13.4 (**C**H_3).

IR (Film) cm^{-1}: 1743 (CO_{Bz}), 1710 (CO), 1531 (NO_2), 1370 (NO_2), 1356 (SO_2), 1166 (SO_2).

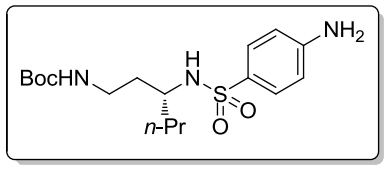
M.p. (*n*-hexane/EtOAc) (ºC): 89-91.

MS (EI) m/z (relative abundance): 297 (6), 254 (100), 186 (80), 170 (3), 122 (70), 106 (4), 92 (6), 76 (13), 64 (3), 51 (2).

HRMS: Calculated for $[C_{24}H_{28}N_3O_8NaSCl]^+$: 576.1183 $[M+Na]^+$; found: 576.1187.

Hydrogenation of pyrazolidin-3-ol **4d**. *Synthesis of 1,3-diamine* **25d**:

(*R*)-*tert*-Butyl [3-(4-aminophenylsulfonamido)hexyl] carbamate (25d)



To a solution of pyrazolidin-3-ol **4d** (278 mg, 0.67 mmol) in THF (10.0 mL), aqueous Raney-Ni (~420 mg) was added. The reaction was carried out at room temperature under 6 atm H_2 pressure for 24 h. After completion, 1M HCl (~15 mL) was added. The mixture was extracted with EtOAc (3 x 15.0 mL) and the collected organic fractions were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residual material was purified by FC (*n*-hexane/EtOAc gradient from

7:3 to 100% EtOAc), yielding the corresponding 1,3-diamine **25d** (250 mg, 0.67 mmol) as a colourless oil.

Yield: 99%.

ee: 94%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 64.77 min, τ_{minor} = 106.18 min.

$[\alpha]_D^{20}$: -19.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm;MeOD): 7.56 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 6.68 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 4.15-3.96 (m, 1H, C**H**N), 3.74 (bs, 1H, NC**H**$_a$H$_b$), 3.62-3.46 (m, 1H, NCH$_a$**H**$_b$), 1.81-1.45 (m, 2H, C**H**$_2$), 1.41-1.18 (m, 13H, 2 x C_{chain}**H**$_2$ + C(C**H**$_3$)$_3$), 0.93-0.76 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm;MeOD) (* denotes minor rotamer): 157.9, 157.7*, 157.2* (**C**O$_{Boc}$), 154.9*, 154.8 (**C**$_{arom}$-NH$_2$), 131.8*, 131.7 (**C**$_{arom}$-SO$_2$), 125.0, 124.9* (**C**$_{arom}$-H), 114.3 (**C**$_{arom}$-H), 82.7*, 82.5*, 81.8, 81.5* (**C**(CH$_3$)$_3$), 60.9*, 60.6*, 60.1 (**C**HN), 58.4, 58.3*, 57.8* (N**C**H$_2$), 36.0*, 35.7*, 35.8 (**C**$_{chain}$H$_2$), 35.1, 35.0* (**C**H$_2$), 28.6, 28.3* (C(**C**H$_3$)$_3$), 21.0*, 20.9 (**C**$_{chain}$H$_2$), 14.5 (**C**H$_3$).

IR (Film) cm^{-1}: 3472 (NH$_2$), 3367 (NH$_2$), 3244 (NH), 2961 (NH), 1704 (CO), 1366 (SO$_2$), 1148 (SO$_2$).

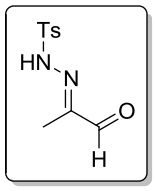
MS (EI) m/z (relative abundance): 207 (13), 181 (8), 155 (6), 125 (34), 112 (14), 101 (4), 83 (92), 69 (6), 57 (100).

HRMS: Calculated for $[C_{17}H_{29}N_3O_4NaS]^+$: 394.1776 $[M+Na]^+$; found: 394.1779.

3. HYDRAZONES AS BIFUNCTIONAL REAGENTS: AZA-MICHAEL/ALDOL CASCADE

3.1 Synthesis of hydrazone 26.

(*E*)-4-Methyl-*N'*-(1-oxopropan-2-ylidene)benzenesulfonohydrazide (26)



To a suspension of *p*-toluenesulfonyl hydrazide (5.0 g, 26.80 mmol) in ether (15.0 mL), a aqueous methyl glyoxal solution in water (40% *v*/*v*, 5.5 mL, 32.20 mmol) was added, followed by the addition of anhydrous Na_2SO_4. The reaction mixture was vigorously stirred at room temperature for 18 h. Solids were removed by filtration and triturated with ether. The filtrate was concentrated *in vacuo* and purified by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) yielding the corresponding hydrazone **26** (955 mg, 3.97 mmol) as a pale yellow solid.

Yield: 15%.

^{1}H-NMR (δ, ppm): 9.33 (s, 1H, C**H**O), 9.08 (s, 1H, N**H**), 7.87 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.35 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 2.44 (s, 3H, C_{arom}-C**H**$_3$), 1.87 (s, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 190.4 (**C**HO), 150.8 (**C**=N), 145.1 (**C**$_{arom}$-SO_2), 134.5 (**C**$_{arom}$-CH_3), 129.9 (**C**$_{arom}$-H), 128.0 (**C**$_{arom}$-H), 21.6 (C_{arom}-**C**H_3), 8.3 (**C**H_3).

IR (neat) cm^{-1}: 3220 (NH), 1696 (CHO), 1338 (SO_2), 1167 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 123-125.

MS (EI) m/z (relative abundance): 214 (2), 197 (3), 184 (4), 155 (25), 139 (100), 123 (40), 108 (4), 91 (56), 77 (14), 65 (15), 51 (3).

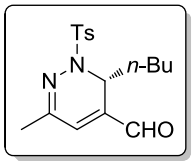
HRMS: Calculated for $[C_{10}H_{13}N_2O_3S]^+$: 240.0647 $[M+H]^+$; found: 240.0649.

3.2 Synthesis of dihydropyridazines 27a-m.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **8** (0.06 mmol, 20 mol%), PhCOOH (0.30 mmol) and toluene (6.0 mL). Then, α,β-unsaturated aldehyde **1a-r** (0.30 mmol) was added and the mixture was stirred for 10 minutes prior to the addition of hydrazone **26** (0.60 mmol). The stirring was maintained at room temperature until the reaction was complete (3-6 days). The reaction mixture was washed twice with a solution of saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography (FC) to afford dihydropyridazine **27a-m**. The racemic standard for HPLC separation conditions was prepared using a 1:1 ratio of (*R*)- and (*S*)-catalyst **8** (0.06 mmol, 20 mol%).

(*R*)-3-Butyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27a)



Following the general procedure, **27a** (84 mg, 0.25 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-2-heptenal **1d** (41 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 84%.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 12.64 min, τ_{minor} = 16.44 min.

$[\alpha]_D^{20}$: -428.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.77 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.26 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.37 (s, 1H, C**H**=C), 5.45 (t, *J* = 6.4 Hz, 1H, C**H**N), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.16 (s, 3H, C**H**$_3$-C=N), 1.44-1.32 (m, 2H, C_{chain}**H**$_2$), 1.29-1.09 (m, 3H, C_{chain}**H**$_2$ + C_{chain}**H**$_a$H$_b$), 1.08-0.97 (m, 1H, C_{chain}H$_a$**H**$_b$), 0.78 (t, *J* = 7.0 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 190.1 (**C**HO), 148.2 (**C**-CHO), 144.0 ($\mathbf{C}_{arom}$-SO_2), 138.0 (**C**=N), 136.3 ($\mathbf{C}_{arom}$-CH_3), 130.6 (**C**H=C), 129.5 ($\mathbf{C}_{arom}$-H), 127.7 ($\mathbf{C}_{arom}$-H),

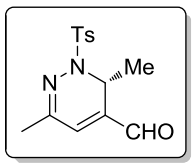
49.3 (**C**HN), 32.8 ($\mathbf{C}_{chain}H_2$), 26.0 ($\mathbf{C}_{chain}H_2$), 22.3 ($\mathbf{C}_{chain}H_2$), 21.6 (C_{arom}-$\mathbf{C}H_3$), 21.2 ($\mathbf{C}H_3$-C=N), 13.8 ($\mathbf{C}H_3$).

IR (neat) cm^{-1}: 1681 (CHO), 1598 (C=N), 1357 (SO_2), 1166 (SO_2).

MS (EI) m/z (relative abundance): 334 (20), 320 (2), 291 (7), 179 (100), 137.1 (76), 122 (8), 108 (14), 91 (25), 77 (12), 53 (6).

HRMS: Calculated for $[C_{17}H_{23}N_2O_3S]^+$: 335.1429 $[M+H]^+$; found: 335.1443.

(*R*)-3-Methyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27b)



Following the general procedure, **27b** (80 mg, 0.27 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 120 h reaction time, starting from *trans*-crotonaldehyde **1b** (29 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 91%.

ee: 89%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 18.16 min, τ_{minor} = 23.38 min.

$[\alpha]_D^{20}$: -274.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.84 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.29 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 6.40 (s, 1H, C**H**=C), 5.45 (q, *J* = 6.5 Hz, 1H, C**H**N), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 2.18 (s, 3H, C**H**$_3$-C=N), 0.97 (d, *J* = 6.5 Hz, 3H, C**H**$_3$).

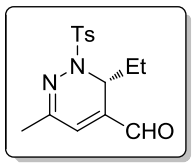
^{13}C-NMR (δ, ppm): 189.7 (**C**HO), 147.4 (**C**-CHO), 144.2 (**C**$_{arom}$-SO_2), 140.0 (**C**=N), 136.4 (**C**$_{arom}$-CH_3), 130.4 (**C**H=C), 129.6 (**C**$_{arom}$-H), 128.0 (**C**$_{arom}$-H), 45.4 (**C**HN), 21.6 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N), 17.2 (**C**H_3).

IR (neat) cm^{-1}: 1680 (CHO), 1597 (C=N), 1355 (SO_2), 1166 (SO_2).

MS (EI) m/z (relative abundance): 292 (20), 207 (3), 155 (2), 137 (100), 122 (2), 109 (16), 91 (14), 77 (7), 65 (9), 53 (5).

HRMS: Calculated for $[C_{14}H_{17}N_2O_3S]^+$: 293.0960 $[M+H]^+$; found: 293.0972.

(*R*)-3-Ethyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27c)



Following the general procedure, **27c** (68 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-2-pentenal **1a** (32 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 74%.

ee: 96%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 14.76 min, τ_{minor} = 21.21 min.

$[\alpha]_D^{20}$: -391.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.56 (s, 1H, C**H**O), 7.77 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.26 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.40 (s, 1H, C**H**=C), 5.42 (t, *J* = 6.4 Hz, 1H, C**H**N), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.15 (s, 3H, C**H**$_3$-C=N), 1.58-1.37 (m, 2H, $C_{chain}H_2$), 0.74 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

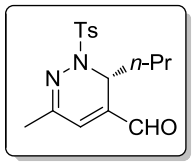
^{13}C-NMR (δ, ppm): 190.2 (**C**HO), 147.9 (**C**-CHO), 144.0 ($\mathbf{C}_{arom}$-SO_2), 137.6 (**C**=N), 136.2 ($\mathbf{C}_{arom}$-CH_3), 130.8 (**C**H=C), 129.5 ($\mathbf{C}_{arom}$-H), 127.7 ($\mathbf{C}_{arom}$-H), 50.3 (**C**HN), 26.3 ($\mathbf{C}_{chain}H_2$), 21.6 (C_{arom}-**C**H$_3$), 21.1 (**C**H$_3$-C=N), 8.6 (**C**H$_3$).

IR (neat) cm^{-1}: 1681 (CHO), 1598 (C=N), 1358 (SO_2), 1167 (SO_2).

MS (EI) m/z (relative abundance): 306 (16), 207 (2), 151 (100), 136 (5), 123 (9), 106 (12), 91 (21), 78 (11), 65 (13), 51 (5).

HRMS: Calculated for $[C_{15}H_{19}N_2O_3S]^+$: 307.1116 $[M+H]^+$; found: 307.1103.

(*R*)-6-Methyl-3-propyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27d)



Following the general procedure, **27d** (69 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-2-hexenal **1c** (36 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 72%.

ee: 96%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 12.87 min, τ_{minor} = 17.57 min.

$[\alpha]_D^{20}$: -359.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.77 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.26 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 6.37 (s, 1H, C**H**=C), 5.46 (t, *J* = 6.4 Hz, 1H, C**H**N), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.16 (s, 3H, C**H**$_3$-C=N), 1.44-1.36 (m, 2H, C_{chain}**H**$_2$), 1.34-1.19 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.19-1.01 (m, 1H, C_{chain}H$_a$**H**$_b$), 0.80 (t, *J* = 7.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 190.1 (**C**HO), 148.2 (**C**-CHO), 144.0 (**C**$_{arom}$-SO_2), 138.0 (**C**=N), 136.2 (**C**$_{arom}$-CH_3), 130.6 (**C**H=C), 129.5 (**C**$_{arom}$-H), 127.7 (**C**$_{arom}$-H),

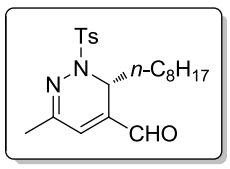
49.1 (**C**HN), 35.3 (**C**$_{chain}$H$_2$), 21.6 (C$_{arom}$-**C**H$_3$), 21.2 (**C**H$_3$-C=N), 17.3(**C**$_{chain}$H$_2$), 13.7 (**C**H$_3$).

IR (neat) cm^{-1}: 1682 (CHO), 1598 (C=N), 1356 (SO_2), 1168 (SO_2).

MS (EI) m/z (relative abundance): 320 (21), 291 (6), 207 (8), 165 (100), 151 (3), 137 (25), 122 (11), 108 (14), 91 (26), 65 (14), 51 (6).

HRMS: Calculated for $[C_{16}H_{21}N_2O_3S]^+$: 321.1273 $[M+H]^+$; found: 321.1286.

(*R*)-6-Methyl-3-octyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27e)



Following the general procedure, **27e** (74 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans*-2-undecenal **1h** (60 µL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 63%.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 9.22 min, τ_{minor} = 10.83 min.

$[\alpha]_D^{20}$: -274.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.56 (s, 1H, C**H**O), 7.77 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.27 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.37 (s, 1H, C**H**=C), 5.44 (t, *J* = 6.4 Hz, 1H, C**H**N), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.16 (s, 3H, C**H**$_3$-C=N), 1.48-1.07 (m, 14H, 7 x C_{chain}**H**$_2$), 0.86 (t, *J* = 7.3 Hz, 3H, C**H**$_3$).

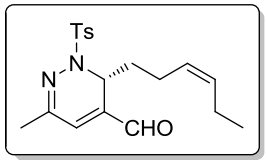
^{13}C-NMR (δ, ppm): 190.1 (**C**HO), 148.2 (**C**-CHO), 144.0 (**C**$_{arom}$-SO_2), 138.0 (**C**=N), 136.3 (**C**$_{arom}$-CH_3), 130.6 (**C**H=C), 129.5 (**C**$_{arom}$-H), 127.7 (**C**$_{arom}$-H), 49.3 (**C**HN), 33.1 (**C**$_{chain}H_2$), 31.8 (**C**$_{chain}H_2$), 29.3 (**C**$_{chain}H_2$), 29.3 (**C**$_{chain}H_2$), 29.2 (**C**$_{chain}H_2$), 23.9 (**C**$_{chain}H_2$), 22.6 (**C**$_{chain}H_2$), 21.6 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N), 14.1 (**C**H_3).

IR (Film) cm^{-1}: 1681 (CHO), 1596 (C=N), 1359 (SO_2), 1168 (SO_2).

MS (EI) m/z (relative abundance): 390 (14), 291 (7), 235 (100), 207 (12), 137 (45), 109 (10), 91 (15), 65 (6).

HRMS: Calculated for $[C_{21}H_{31}N_2O_3S]^+$: 391.2055 $[M+H]^+$; found: 391.2056.

(*R*,*Z*)-3-(Hex-3-en-1-yl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27f)



Following the general procedure, **27f** (74 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 72 h reaction time, starting from *trans-2-cis-6*-nonadienal **1i** (45 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 68%.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 16.54 min, τ_{minor} = 21.86 min.

$[\alpha]_D^{20}$: -236.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.77 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.26 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.39 (s, 1H, C**H**=C), 5.48 (t, *J* = 6.4 Hz, 1H, C**H**N), 5.37-5.26 (m, 1H, C**H**=CH), 5.19-5.07 (m, 1H, CH=C**H**), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.17 (s, 3H, C**H**$_3$-C=N), 2.03-1.79 (m, 4H, 2 x C_{chain}**H**$_2$), 1.49-1.39 (m, 2H, C_{chain}**H**$_2$), 0.91 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

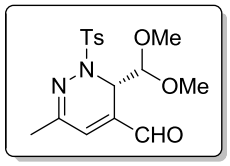
^{13}C-NMR (δ, ppm): 190.0 (**C**HO), 148.4 (**C**-CHO), 144.1 (**C**$_{arom}$-SO_2), 137.8 (**C**=N), 136.2 (**C**$_{arom}$-CH_3), 132.8 (**C**H=CH), 130.6, (**C**H=C), 129.5 (**C**$_{arom}$-H), 127.7 (**C**$_{arom}$-H), 127.1 (CH=**C**H), 49.1 (**C**HN), 33.2 (**C**$_{chain}H_2$), 22.0 (**C**$_{chain}H_2$), 21.6 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N), 20.5 (**C**$_{chain}H_2$), 14.2 (**C**H_3).

IR (neat) cm^{-1}: 1682 (CHO), 1596 (C=N), 1354 (SO_2), 1167 (SO_2).

MS (EI) m/z (relative abundance): 360 (2), 291 (100), 226 (1), 205 (92), 155 (3), 135 (52), 106 (46), 91 (25), 65 (13).

HRMS: Calculated for $[C_{19}H_{25}N_2O_3S]^+$: 361.1586 $[M+H]^+$; found: 361.1601.

(*S*)-3-Dimethoxymethyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27g)



Following the general procedure, **27g** (64 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 120 h reaction time, starting from *trans*-fumaraldehyde **1l** (38 μL, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 61%.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 17.42 min, τ_{minor} = 21.97 min.

$[\alpha]_D^{20}$: -545.1 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.57 (s, 1H, C**H**O), 7.80 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.27 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.48 (s, 1H, C**H**=C), 5.59 (d, *J* = 5.0 Hz, 1H, C**H**N), 4.15 (d, *J* = 5.0 Hz, 1H, C**H**$(OCH_3)_2$), 3.31 (s, 3H, CH(OC**H**$_3$)(OCH_3)), 3.25 (s, 3H, CH(OCH_3)(OC**H**$_3$)), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.15 (s, 3H, C**H**$_3$-C=N).

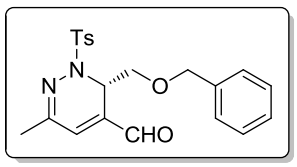
^{13}C-NMR (δ, ppm): 189.7 (**C**HO), 147.9 (**C**-CHO), 144.1 ($\mathbf{C}_{arom}$-SO_2), 136.0 (**C**=N), 133.4 ($\mathbf{C}_{arom}$-CH_3), 130.5 (**C**H=C), 129.4 ($\mathbf{C}_{arom}$-H), 127.9 ($\mathbf{C}_{arom}$-H), 104.0 (**C**H$(OCH_3)_2$), 56.0, 55.1(CH$(O\mathbf{C}H_3)_2$), 49.1 (**C**HN), 21.6 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N).

IR (neat) cm^{-1}: 1686 (CHO), 1354 (SO_2), 1169 (SO_2), 1120 (COC).

MS (EI) m/z (relative abundance): 278 (14), 214 (6), 185 (9), 171 (4), 155 (8), 139 (2), 123 (100), 106 (6), 91 (31), 79 (5), 65 (16), 51 (4).

HRMS: Calculated for $[C_{16}H_{21}N_2O_5S]^+$: 353.1171 $[M+H]^+$; found: 353.1176.

(*S*)-3-[(Benzyloxy)methyl]-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27h)



Following the general procedure, **27h** (82 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 96 h reaction time, starting from *trans*-4-(benzyloxy)but-2-enal **1n** (53 mg, 0.30 mmol) and hydrazone **26** (144 mg, 0.60 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 69%.

ee: 96%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 73.07 min, τ_{minor} = 62.73 min.

$[\alpha]_D^{20}$: -103.8 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.83 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.40-7.17 (m, 5H, C_{arom}-**H**), 7.14-7.07 (m, 2H, C_{arom}-**H**), 6.47 (s, 1H, C**H**=C), 5.63 (t, *J* = 4.4 Hz, 1H, C**H**N), 4.33-4.18 (m, 2H, OC**H**$_2$Ph), 3.48-3.31 (m, 2H, CHC**H**$_2$O), 2.37 (s, 3H, C_{arom}-C**H**$_3$), 2.11 (s, 3H, C**H**$_3$-C=N).

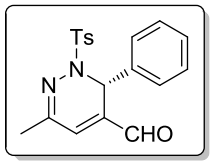
^{13}C-NMR (δ, ppm): 189.8 (**C**HO), 147.0 (**C**-CHO), 144.1 ($\mathbf{C}_{arom}$-SO_2), 137.6 (**C**=N), 136.2 ($\mathbf{C}_{arom}$-CH_3), 135.3 ($\mathbf{C}_{arom}$-CH_2O), 132.1 (**C**H=C), 129.4 ($\mathbf{C}_{arom}$-H), 128.2 ($\mathbf{C}_{arom}$-H), 128.0 ($\mathbf{C}_{arom}$-H), 127.5 ($\mathbf{C}_{arom}$-H), 127.3 ($\mathbf{C}_{arom}$-H), 73.0 (O**C**H$_2$Ph), 69.9 (CH**C**H$_2$O), 48.8 (**C**HN), 21.6 (C_{arom}-**C**H$_3$), 21.1 (**C**H$_3$-C=N).

IR (neat) cm^{-1}: 1680 (CHO), 1596 (C=N), 1354 (SO_2), 1166 (SO_2), 1091 (COC).

MS (EI) m/z (relative abundance): 398 (2), 355 (4), 281 (4), 241 (5), 207 (18), 171 (4), 121 (4), 107 (63), 91 (100), 77 (90), 65 (14), 51 (25).

HRMS: Calculated for $[C_{21}H_{23}N_2O_4S]^+$: 399.1379 $[M+H]^+$; found: 399.1375.

(*R*)-6-Methyl-3-phenyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27i)



Following the general procedure, **27i** (52 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 144 h reaction time, starting from *trans*-cinnamaldehyde **1m** (76 μL, 0.60 mmol) and hydrazone **26** (72 mg, 0.30 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 49%.

ee: 89%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min. τ_{major} = 84.87 min, τ_{minor} = 45.38 min.

$[\alpha]_D^{20}$: -33.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.40 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.23-7.14 (m, 1H, C_{arom}-**H**), 7.14-7.08 (m, 4H, C_{arom}-**H**), 7.03 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 6.51 (s, 1H, C**H**=C), 6.43 (s, 1H, C**H**N), 2.33 (s, 3H, C_{arom}-C**H**$_3$), 2.22 (s, 3H, C**H**$_3$-C=N).

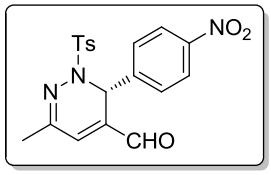
^{13}C-NMR (δ, ppm): 189.7 (**C**HO), 145.7 (**C**-CHO), 143.7 (**C**$_{arom}$-SO_2), 138.3 (**C**=N), 137.9 (**C**$_{arom}$-CH_3), 135.6 (**C**$_{arom}$-CH), 129.9 (**C**H=C), 128.9 (**C**$_{arom}$-H), 128.7 (**C**$_{arom}$-H), 128.5 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-H), 127.3 (**C**$_{arom}$-H), 52.8 (**C**HN), 21.5 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N).

IR (neat) cm^{-1}: 1688 (CHO), 1600 (C=N), 1360 (SO_2), 1169 (SO_2).

MS (EI) m/z (relative abundance): 354 (100), 327 (2), 281 (3), 226 (1), 199 (53), 171 (60), 155 (30), 144 (11), 115 (24), 91 (32), 65 (16).

HRMS: Calculated for $[C_{19}H_{19}N_2O_3S]^+$: 355.1116 $[M+H]^+$; found: 355.1117.

(*R*)-6-Methyl-3-(4-nitrophenyl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27j)



Following the general procedure, **27j** (62 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 96 h reaction time, starting from *trans*-4-nitrocinnamaldehyde **1o** (108 mg, 0.60 mmol) and hydrazone **26** (72 mg, 0.30 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 52%.

ee: 95%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min. τ_{major} = 103.45 min, τ_{minor} = 60.82 min.

$[\alpha]_D^{20}$: -96.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.95 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 7.50 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.29 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.10 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 6.57 (s, 1H, C**H**=C), 6.54 (s, 1H, C**H**N), 2.36 (s, 3H, C_{arom}-C**H**$_3$), 2.25 (s, 3H, C**H**$_3$-C=N).

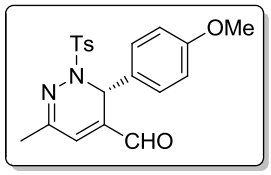
^{13}C-NMR (δ, ppm): 189.5 (**C**HO), 147.8 (**C**-CHO), 146.0 (**C**=N), 144.7 ($\mathbf{C}_{arom}$-NO_2), 144.6 ($\mathbf{C}_{arom}$-SO_2), 137.2 ($\mathbf{C}_{arom}$-CH), 135.3 ($\mathbf{C}_{arom}$-CH_3), 130.6 (**C**H=C), 129.3 ($\mathbf{C}_{arom}$-H), 128.0 ($\mathbf{C}_{arom}$-H), 127.8 ($\mathbf{C}_{arom}$-H), 123.7 ($\mathbf{C}_{arom}$-H), 51.2 (**C**HN), 21.5 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N).

IR (neat) cm^{-1}: 1681 (CHO), 1598 (C=N), 1521 (NO_2), 1346 (SO_2), 1304 (NO_2), 1167 (SO_2).

MS (EI) m/z (relative abundance): 399 (100), 327 (2), 281 (14), 253 (9), 241 (70), 227 (77), 198 (66), 171 (60), 169 (37), 139 (16), 115 (21), 91 (69), 65 (21).

HRMS: Calculated for $[C_{19}H_{18}N_3O_5S]^+$: 400.0967 $[M+H]^+$; found: 400.0984.

(*R*)-3-(4-Methoxyphenyl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27k)



Following the general procedure, **27k** (69 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 144 h reaction time, starting from *trans*-4-methoxycinnamaldehyde **1p** (98 mg, 0.60 mmol) and hydrazone **26** (72 mg, 0.30 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 60%.

ee: 85%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min. τ_{major} = 133.94 min, τ_{minor} = 77.78 min.

$[\alpha]_D^{20}$: +21.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm) : 9.53 (s, 1H, C**H**O), 7.41 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.04 (d, *J* = 8.4 Hz, 4H, C_{arom}-**H**), 6.61 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 6.51 (s, 1H, C**H**=C), 6.34 (s, 1H, C**H**N), 3.74 (s, 3H, OC**H**$_3$), 2.33 (s, 3H, C_{arom}-C**H**$_3$), 2.19 (s, 3H, C**H**$_3$-C=N).

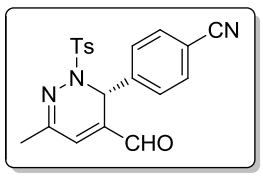
^{13}C-NMR (δ, ppm): 189.8 (**C**HO), 160.0 (**C**$_{arom}$-OCH$_3$), 145.5 (**C**-CHO), 143.5 (**C**$_{arom}$-SO$_2$), 138.5 (**C**=N), 135.7 (**C**$_{arom}$-CH$_3$), 130.2 (**C**$_{arom}$-CH), 129.6 (**C**H=C), 128.8 (**C**$_{arom}$-H), 128.8 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-H), 113.7 (**C**$_{arom}$-H), 55.3 (O**C**H$_3$), 52.4 (**C**HN), 21.5 (C_{arom}-**C**H$_3$), 21.2 (**C**H$_3$-C=N).

IR (neat) cm^{-1}: 1683 (CHO), 1608 (C=N), 1355 (SO$_2$), 1169 (SO$_2$), 1086 (COC).

MS (EI) m/z (relative abundance): 384 (100), 327 (2), 281 (6), 253 (5), 229 (50), 201 (44), 171 (15), 169 (37), 128 (11), 91 (35), 65 (14).

HRMS: Calculated for $[C_{20}H_{21}N_2O_4S]^+$: 385.1222 $[M+H]^+$; found: 385.1237.

(*R*)-3-(4-Cyanophenyl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27l)



Following the general procedure, **27l** (82 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 144 h reaction time, starting from *trans*-4-cyanocinnamaldehyde **1q** (94 mg, 0.60 mmol) and hydrazone **26** (72 mg, 0.30 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 72%.

ee: 94%.

HPLC: Chiralpak IC column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min. τ_{major} = 148.17 min, τ_{minor} = 81.53 min.

$[\alpha]_D^{20}$: -48.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.55 (s, 1H, C**H**O), 7.48 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.40 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.24 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.11 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.55 (s, 1H, C**H**=C), 6.48 (s, 1H, C**H**N), 2.38 (s, 3H, C_{arom}-C**H**$_3$), 2.22 (s, 3H, C**H**$_3$-C=N).

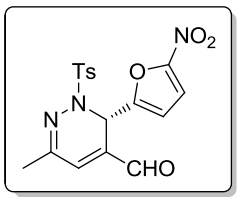
^{13}C-NMR (δ, ppm): 189.5 (**C**HO), 145.9 (**C**-CHO), 144.4 ($\mathbf{C}_{arom}$-SO_2), 142.8 (**C**=N), 137.2 ($\mathbf{C}_{arom}$-CN), 135.3 ($\mathbf{C}_{arom}$-CH_3), 132.3 ($\mathbf{C}_{arom}$-H), 130.5 (**C**H=C), 129.2 ($\mathbf{C}_{arom}$-H), 127.8 ($\mathbf{C}_{arom}$-H), 127.8 ($\mathbf{C}_{arom}$-H), 118.2 (**C**N), 112.4 ($\mathbf{C}_{arom}$-CH), 52.2 (**C**HN), 21.6 (C_{arom}-**C**H$_3$), 21.2 (**C**H$_3$-C=N).

IR (neat) cm^{-1}: 2228.3 (CN), 1678 (CHO), 1596 (C=N), 1358 (SO_2), 1166 (SO_2).

MS (EI) m/z (relative abundance): 379 (100), 281 (2), 224 (59), 196 (59), 155 (20), 127 (16), 91 (55), 65 (19).

HRMS: Calculated for $[C_{20}H_{18}N_3O_3S]^+$: 380.1069 $[M+H]^+$; found: 380.1063.

(*S*)-6-Methyl-3-(5-nitrofuran-2-yl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (27m)



Following the general procedure, **27m** (64 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) as a yellow oil after 144 h reaction time, starting from *trans*-3-(5-nitrofuran-2-yl)-acrolein **1r** (100 mg, 0.60 mmol) and hydrazone **26** (72 mg, 0.30 mmol) in the presence of **8** (36 mg, 0.06 mmol) and PhCOOH (34 mg, 0.30 mmol), using toluene (6.0 mL) as solvent.

Yield: 55%.

ee: 90%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 76.54 min, τ_{minor} = 59.32 min.

$[\alpha]_D^{20}$: +19.9 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 9.61 (s, 1H, C**H**O), 7.65 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.15 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.00 (d, *J* = 3.6 Hz, 1H, C_{furan}-**H**), 6.70 (s, 1H, C**H**=C), 6.50-6.46 (m, 2H, C**H**N + C_{furan}-**H**), 2.34 (s, 3H, C_{arom}-C**H**$_3$), 2.29 (s, 3H, C**H**$_3$-C=N).

^{13}C-NMR (δ, ppm): 188.6 (**C**HO), 151.7 (**C**-CHO), 151.6 ($\mathbf{C}_{furan}$-NO_2), 146.6 (**C**=N), 144.7 ($\mathbf{C}_{arom}$-SO_2), 134.4 ($\mathbf{C}_{furan}$-CH), 134.0 ($\mathbf{C}_{arom}$-CH_3), 131.8

(**C**H=C), 129.1 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-H), 52.8 (**C**HN), 21.5 (C_{arom}-**C**H_3), 21.2 (**C**H_3-C=N).

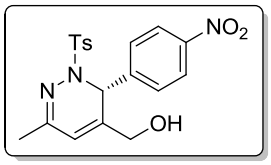
IR (neat) cm^{-1}: 1682 (CHO), 1532 (NO_2), 1501 (=CH_{furan}), 1348 (SO_2), 1310 (NO_2), 1162 (SO_2).

MS (EI) m/z (relative abundance): 389 (100), 234 (30), 188 (56), 155 (19), 132 (39), 91 (76), 65 (18).

HRMS: Calculated for $[C_{17}H_{16}N_3O_6S]^+$: 390.0760 $[M+H]^+$; found: 390.0757.

Determination of the absolute configuration:

(*R*)-[6-Methyl-3-(4-nitrophenyl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazin-4-yl]methanol (30j)



To a solution of the dihydropyridazine **27j** (42 mg, 0.10 mmol) in methanol (3.0 mL), $NaBH_4$ (~50 mg) was added at 0 ºC. The reaction mixture was stirred at this temperature for 20 minutes prior to the addition of a solution of saturated aqueous NH_4Cl (3.0 mL) and CH_2Cl_2 (5.0 mL). After 30 minutes stirring at room temperature, the mixture was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic fractions were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residual material was purified by FC (*n*-hexane/EtOAc gradient from 7:3 to 1:1) yielding the corresponding alcohol **30j** (32 mg, 0.08 mmol) as a yellow solid.

Yield: 76%.

ee: 93%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 70.74 min, τ_{minor} = 112.60 min.

$[\alpha]_D^{20}$: -47.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.96 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.42 (d, *J* = 8.3 Hz, 2, C_{arom}-**H**), 7.30 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.01 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 6.04 (s, 1H, C**H**=C), 5.93 (s, 1H, C**H**N), 4.19-4.01 (m, 2H, C**H**$_2$OH), 2.33 (s, 3H, C_{arom}-C**H**$_3$), 2.13 (s, 3H, C**H**$_3$-C=N).

^{13}C-NMR (δ, ppm): 148.4 (**C**-CH_2OH), 147.9 (**C**=N), 144.2 ($\mathbf{C}_{arom}$-CH), 143.9 ($\mathbf{C}_{arom}$-SO_2), 143.6 ($\mathbf{C}_{arom}$-NO_2), 135.6 ($\mathbf{C}_{arom}$-CH_3), 128.9 ($\mathbf{C}_{arom}$-H), 128.5 ($\mathbf{C}_{arom}$-H), 127.6 ($\mathbf{C}_{arom}$-H), 123.6 ($\mathbf{C}_{arom}$-H), 114.0 (**C**H=C), 62.1 (**C**H_2OH), 55.0 (**C**HN), 21.7 (C_{arom}-**C**H_3), 21.4 (**C**H_3-C=N).

IR (neat) cm^{-1}: 3418 (OH), 1597 (C=N), 1521 (NO_2), 1343 (SO_2), 1304 (NO_2), 1162 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 188-190.

MS (EI) m/z (relative abundance): 401 (2), 385 (49), 355 (12), 281 (11), 253 (20), 230 (72), 207 (90), 184 (100), 171 (19), 139 (22), 115 (19), 91 (91), 65 (22).

HRMS: Calculated for $[C_{19}H_{20}N_3O_5S]^+$: 402.1124 $[M+H]^+$; found: 402.1139.

4. CONJUGATE ADDITION REACTION OF *N*-TOSYLHYDRAZONES TO α,β-UNSATURATED ALDEHYDES

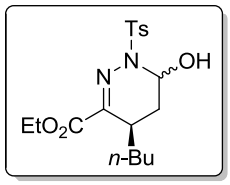
(Note: The stereochemical configuration for compounds **32** and **33** has been tentatively assigned according to the spected mechanism for the catalyst employed).

4.1 Conjugate addition/hemiaminalization sequence: synthesis of tetrahydropyridazines 32a-l.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **6** (0.10 mmol, 20 mol%), PhCOOH (0.50 mmol, 100 mol%), toluene (5.0 mL) and α,β-unsaturated aldehyde **1a-s** (0.50 mmol). The resulting mixture was stirred at room temperature for 10 minutes. The reaction was cooled to -20 ºC and stirred at this temperature for another 10 minutes prior to the addition of hydrazone **31a** (1.00 mmol) and water (0.50 mmol, 100 mol%). The stirring was maintained at -20 ºC until completion (~6 days). After this time, the reaction mixture was concentrated *in vacuo* and directly charged onto silica gel and subjected to flash chromatography (FC). Racemic standards were prepared using morpholine (0.10 mmol, 20 mol%) instead of catalyst **6**.

(4*R*)-Ethyl 4-butyl-6-hydroxy-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32a)



Following the general procedure, **32a** (136 mg, 0.36 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 144 h reaction time, starting from *trans*-2-heptenal **1d** (68 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 71%.

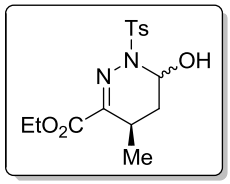
dr: 50:50.

ee: 92% (determined by HPLC analysis after oxidation to **33a**).

^{1}H-NMR (δ, ppm; *denotes diastereoisomer): 7.89-7.81 (m, 2H, C_{arom}-**H**), 7.33-7.29 (m, 2H, C_{arom}-**H**), 5.82 (s, 1H, C**H**OH), 5.60* (s, 1H, C**H**OH), 4.35-4.12 (m, 2H, OC**H**$_2$CH$_3$), 3.39 (s, 1H, CHO**H**), 3.26* (m, 1H, CHO**H**), 2.82-2.69 (m, 1H, C**H**), 2.43 (s, 3H, C_{arom}-C**H**$_3$), 2.26-2.06 (m, 1H, C**H**$_a$H$_b$), 1.84-1.09 (m, 10H, CH$_a$**H**$_b$ + OCH$_2$C**H**$_3$ + 3 x C_{chain}**H**$_2$), 0.93-0.76 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes diastereoisomer): 163.4, 163.2* (**C**=O), 147.8, 146.2* ($\mathbf{C}_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9, 134.7* ($\mathbf{C}_{arom}$-CH$_3$), 129.6, 129.5* ($\mathbf{C}_{arom}$-H), 128.3, 128.0* ($\mathbf{C}_{arom}$-H), 75.2, 74.6* (**C**HOH), 61.5, 61.3* (O**C**H$_2$CH$_3$), 31.0, 30.5* (**C**H), 29.7, 29.3* (**C**H$_2$), 28.7, 28.3* ($\mathbf{C}_{chain}$H$_2$), 28.0, 26.6* ($\mathbf{C}_{chain}$H$_2$), 22.4, 22.3* ($\mathbf{C}_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 13.9, 13.8* (**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-methyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32b)



Following the general procedure, **32b** (160 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 144 h reaction time, starting from *trans*-crotonaldehyde **1b** (42 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **8** (60 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 94%.

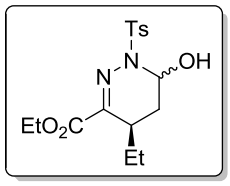
dr: 50:50.

ee: 26% (determined by HPLC analysis after oxidation to **33b**).

^{1}H-NMR (δ, ppm; *denotes diastereoisomer): 7.88-7.84 (m, 2H, C_{arom}-**H**), 7.32-7.27 (m, 2H, C_{arom}-**H**), 5.78 (s, 1H, C**H**OH), 4.34-4.17 (m, 2H, OC**H**$_2$CH$_3$), 3.45 (s, 1H, CHO**H**), 3.32* (s, 1H, CHO**H**), 2.96-2.70 (m, 1H, C**H**), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 2.22-1.99 (m, 1H, C**H**$_a$H$_b$), 1.77-1.49 (m, 1H, CH$_a$**H**$_b$), 1.36-1.30 (m, 3H, OCH$_2$C**H**$_3$), 1.25 (t, *J* = 7.2 Hz, 3H, C**H**$_3$), 1.18* (d, *J* = 7.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes diastereoisomer): 163.2, 163.0* (**C**=O), 147.5, 146.2* ($\mathbf{C}_{arom}$-SO$_2$), 144.6, 144.6* (**C**=N), 135.0, 134.9* ($\mathbf{C}_{arom}$-CH$_3$), 129.6, 129.6* ($\mathbf{C}_{arom}$-H), 128.3, 128.0* ($\mathbf{C}_{arom}$-H), 74.6, 74.4* (**C**HOH), 61.4, 61.3* (O**C**H$_2$CH$_3$), 33.8, 30.3* (**C**H), 23.6, 23.1* (**C**H$_2$), 21.6 (C_{arom}-**C**H$_3$), 17.8, 16.7* (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).

(4*R*)-Ethyl 4-ethyl-6-hydroxy-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32c)



Following the general procedure, **32c** (120 mg, 0.34 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 168 h reaction time, starting from *trans*-2-pentenal **1a** (51 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 68%.

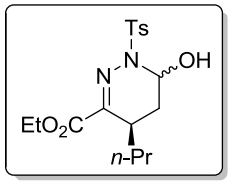
dr: 50:50.

ee: 20% (determined by HPLC analysis after oxidation to **33c**).

^{1}H-NMR (δ, ppm; *denotes diastereoisomer): 7.89-7.84 (m, 2H, C_{arom}-**H**), 7.33-7.29 (m, 2H, C_{arom}-**H**), 5.82* (m, 1H, C**H**OH), 5.56 (m, 1H, C**H**OH), 4.32-4.24 (m, 2H, OC**H**$_2$CH$_3$), 3.36 (m, 1H, CHO**H**), 3.22* (m, 1H, CHO**H**), 2.75-2.64 (m, 1H, C**H**), 2.42 (s, 3H, C_{arom}-C**H**$_3$), 2.32-1.99 (m, 1H, C**H**$_a$H$_b$), 1.86-1.37 (m, 2H, C_{chain}**H**$_2$), 1.36-1.31 (m, 4H, CH$_a$**H**$_b$ + OCH$_2$C**H**$_3$), 0.96 (t, *J* = 7.4 Hz, 3H, C**H**$_3$), 0.85* (t, *J* = 7.4 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes diastereoisomer): 163.5, 163.2* (**C**=O), 147.5, 146.1* ($\mathbf{C}_{arom}$-SO$_2$), 144.7, 144.6* (**C**=N), 134.9, 134.7* ($\mathbf{C}_{arom}$-CH$_3$), 129.6, 129.6* ($\mathbf{C}_{arom}$-H), 128.3, 128.0* ($\mathbf{C}_{arom}$-H), 75.2, 74.6* (**C**HOH), 61.5, 61.3* (O**C**H$_2$CH$_3$), 30.4, 29.2* (**C**H), 26.1 (**C**H$_2$), 23.8 , 23.4* ($\mathbf{C}_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 11.9, 10.6* (**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-propyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32d)



Following the general procedure, **32d** (141 mg, 0.38 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 168 h reaction time, starting from *trans*-2-hexenal **1c** (51 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 76%.

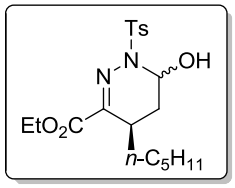
dr: 50:50.

ee: 76% (determined by HPLC analysis after oxidation to **33d**).

^{1}H-NMR (δ, ppm; *denotes diastereoisomer): 7.90-7.77 (m, 2H, C_{arom}-**H**), 7.32-7.28 (m, 2H, C_{arom}-**H**), 5.77* (s, 1H, C**H**OH), 5.66 (s, 1H, C**H**OH), 4.30-4.21 (m, 2H, OC**H**$_2$CH$_3$), 3.33 (s, 1H, CHO**H**), 3.29* (s, 1H, CHO**H**), 2.85-2.70 (m, 1H, C**H**), 2.42 (s, 3H, C_{arom}-C**H**$_3$), 2.26-2.10 (m, 1H, C**H**$_a$H$_b$), 1.80-1.40 (m, 3H, CH$_a$**H**$_b$ + C_{chain}**H**$_2$), 1.37-1.26 (m, 5H C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.91-0.85 (m, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes diastereoisomer): 163.5, 163.2* (**C**=O), 147.8, 146.2* (**C**$_{arom}$-SO$_2$), 144.5 (**C**=N), 134.6, 134.7* (**C**$_{arom}$-CH$_3$), 129.6, 129.6* (**C**$_{arom}$-H), 128.3, 128.0* (**C**$_{arom}$-H), 75.1, 74.6* (**C**HOH), 61.5, 61.3* (O**C**H$_2$CH$_3$), 33.0, 32.2* (**C**H), 31.0, 28.5* (**C**H$_2$), 27.9, 26.6* (**C**$_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 20.4, 19.5*(**C**$_{chain}$H$_2$), 14.1 (OCH$_2$**C**H$_3$), 13.9, 13.7* (**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-pentyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32e)



Following the general procedure, **32e** (169 mg, 0.43 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) after 144 h reaction time, starting from *trans*-2-octenal **1e** (79 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 85%.

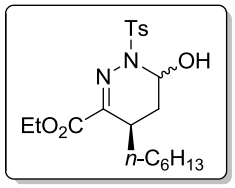
dr: 56:44.

ee: 99% (determined by HPLC analysis after oxidation to **33e**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.90-7.82 (m, 2H, C_{arom}-**H**), 7.35-7.26 (m, 2H, C_{arom}-**H**), 5.80* (s, 1H, C**H**OH), 5.62 (s, 1H, C**H**OH), 4.36-4.17 (m, 2H, OC**H**$_2$CH$_3$), 2.82-2.69 (m, 1H, C**H**), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 2.30-2.07 (m, 1H, C**H**$_a$H$_b$), 1.78-1.39 (m, 3H, CH$_a$**H**$_b$ + C_{chain}**H**$_2$), 1.36-1.22 (m, 9H, 3 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.93-0.77 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 163.4, 162.5* (**C**=O), 147.8*, 146.2 (**C**$_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9*, 134.7 (**C**$_{arom}$-CH$_3$), 129.7, 129.5* (**C**$_{arom}$-H), 128.3*, 128.1 (**C**$_{arom}$-H), 75.1, 74.6* (**C**HOH), 61.5, 61.4* (O**C**H$_2$CH$_3$), 31.5*, 31.4 (**C**H), 31.0*, 30.7 (**C**H$_2$), 30.0*, 28.7 (**C**$_{chain}$H$_2$), 28.0*, 26.8 (**C**$_{chain}$H$_2$), 26.6, 25.8* (**C**$_{chain}$H$_2$), 22.4, 22.3* (**C**$_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0*, 13.9 (**C**H$_3$).

(4*R*)-Ethyl 4-hexyl-6-hydroxy-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32f)



Following the general procedure, **32f** (136 mg, 0.33 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) after 144 h reaction time, starting from *trans*-2-nonenal **1f** (85 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 66%.

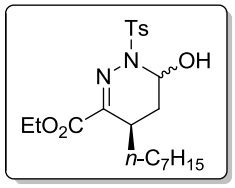
dr: 56:44.

ee: 93% (determined by HPLC analysis after oxidation to **33f**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.85 (d, J = 8.3 Hz, 2H, C_{arom}-**H**), 7.32-7.27 (m, 2H, C_{arom}-**H**), 5.83* (s, 1H, C**H**OH), 5.62 (s, 1H, C**H**OH), 4.36-4.15 (m, 2H, OC**H**$_2$CH$_3$), 2.85-2.69 (m, 1H, C**H**), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 2.32-2.06 (m, 1H, C**H**$_a$H$_b$), 1.78-1.40 (m, 3H, CH$_a$**H**$_b$ + C_{chain}**H**$_2$), 1.40-1.08 (m, 11H, 4 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.85 (t, J = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 163.5, 163.2* (**C**=O), 147.8*, 146.2 (**C**$_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9*, 134.7 (**C**$_{arom}$-CH$_3$), 129.6, 129.5* (**C**$_{arom}$-H), 128.3*, 128.1 (**C**$_{arom}$-H), 75.1, 74.6* (**C**HOH), 61.5, 61.4* (O**C**H$_2$CH$_3$), 31.6, 31.5* (**C**H), 31.1*, 30.8 (**C**H$_2$), 30.1, 29.0* (**C**$_{chain}$H$_2$), 28.9, 28.7* (**C**$_{chain}$H$_2$), 28.0*, 27.1 (**C**$_{chain}$H$_2$), 26.6, 26.1* (**C**$_{chain}$H$_2$), 22.6, 22.5* (**C**$_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0, 14.0* (**C**H$_3$).

(4*R*)-Ethyl 4-heptyl-6-hydroxy-1-(*p*-toluenesulfonyl) -1,4,5,6-tetrahydropyridazine-3-carboxylate (32g)



Following the general procedure, **32g** (134 mg, 0.32 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) after 144 h reaction time, starting from *trans*-2-decenal **1g** (96 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 63%.

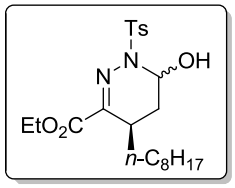
dr: 56:44.

ee: 99% (determined by HPLC analysis after oxidation to **33g**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.85 (d, J = 8.0 Hz, 2H, C_{arom}-**H**), 7.40-7.18 (m, 2H, C_{arom}-**H**), 5.79 (s, 1H, C**H**OH), 5.69* (s, 1H, C**H**OH), 4.38-4.15 (m, 2H, OC**H**$_2$CH$_3$), 2.76-2.70 (m, 1H, C**H**), 2.40 (s, 3H, C_{arom}-C**H**$_3$), 2.32-2.07 (m, 1H, C**H**$_a$H$_b$), 1.80-1.41 (m, 3H, CH$_a$**H**$_b$ + C_{chain}**H**$_2$), 1.39-1.00 (m, 13H, 5 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.85 (t, J = 6.3 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 163.5, 163.2* (**C**=O), 148.0*, 146.2 (**C**$_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9*, 134.7 (**C**$_{arom}$-CH$_3$), 129.6, 129.5* (**C**$_{arom}$-H), 128.3*, 128.1 (**C**$_{arom}$-H), 75.1, 74.5* (**C**HOH), 61.5, 61.3* (O**C**H$_2$CH$_3$), 31.8, 31.7* (**C**H), 31.1, 30.8* (**C**H$_2$), 30.1, 29.3* (**C**$_{chain}$H$_2$), 29.2, 29.1* (**C**$_{chain}$H$_2$), 29.0, 28.7* (**C**$_{chain}$H$_2$), 28.0, 27.2* (**C**$_{chain}$H$_2$), 26.6, 26.2* (**C**$_{chain}$H$_2$), 22.6, 22.6* (**C**$_{chain}$H$_2$), 21.6 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.1 (**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-octyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32h)



Following the general procedure, **32h** (205 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) after 168 h reaction time, starting from *trans*-2-undecenal **1h** (104 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 94%.

dr: 56:44.

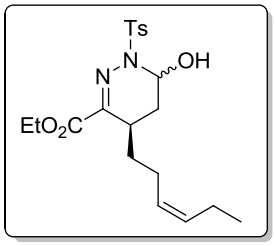
ee: 95% (determined by HPLC analysis after oxidation to **33h**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.85 (d, J = 8.3 Hz, 2H, C_{arom}-**H**), 7.33-7.26 (m, 2H, C_{arom}-**H**), 5.81 (s, 1H, C**H**OH), 5.64* (s, 1H, C**H**OH), 4.36-4.15 (m, 2H, OC**H**$_2$CH$_3$), 2.85-2.68 (m, 1H, C**H**), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 2.31-2.06 (m, 1H, C**H**$_a$H$_b$), 1.78-1.39 (m, 3H, CH$_a$**H**$_b$ + C_{chain}**H**$_2$), 1.35-1.23 (m, 15, 6 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.86 (t, J = 6.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 163.4, 163.2* (**C**=O), 147.8, 146.2* (**C**$_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9, 134.7* (**C**$_{arom}$-CH$_3$), 129.6, 129.5* (**C**$_{arom}$-H), 128.3, 128.0* (**C**$_{arom}$-H), 75.2, 74.6* (**C**HOH), 61.5, 61.3* (O**C**H$_2$CH$_3$), 31.8, 31.8* (**C**H), 31.1, 30.8* (**C**H$_2$), 30.1, 29.4* (**C**$_{chain}$H$_2$), 29.3, 29.2* (**C**$_{chain}$H$_2$), 29.2, 29.1* (**C**$_{chain}$H$_2$), 28.7, 28.6* (**C**$_{chain}$H$_2$), 28.0, 27.2* (**C**$_{chain}$H$_2$), 26.6,

26.5* (**C**$_{chain}$H$_2$), 22.6, 22.6* (**C**$_{chain}$H$_2$), 21.6 (C$_{arom}$-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.1 (**C**H$_3$).

(4*R*, 3'*Z*)-Ethyl 4-(3-hexenyl)-6-hydroxy-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32i)



Following the general procedure, **32i** (110 mg, 0.27 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) after 168 h reaction time, starting from *trans-2-cis-6*-nonadienal **1i** (84 µL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 µL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 54%.

dr: 50:50.

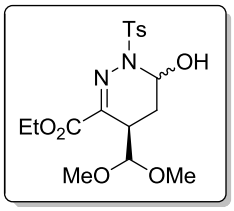
ee: 30% (determined by HPLC analysis after oxidation to **33i**).

^{1}H-NMR (δ, ppm; *denotes diastereoisomer): 7.86 (d, *J* = 8.2 Hz, 2H, C$_{arom}$-**H**), 7.32-7.28 (m, 2H, C$_{arom}$-**H**), 5.82 (s, 1H, C**H**OH), 5.66* (s, 1H, C**H**OH), 5.47-5.17 (m, 2H, C**H**=C**H**), 4.36-4.14 (m, 2H, OC**H**$_2$CH$_3$), 2.88-2.71 (m, 1H, C**H**), 2.41 (s, 3H, C$_{arom}$-C**H**$_3$), 2.34-1.88 (m, 4H, C**H**$_2$ + C$_{chain}$**H**$_2$), 1.86-1.44 (m, 4H, 2 x C$_{chain}$**H**$_2$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.02-0.84 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes diastereoisomer): 163.4, 163.2* (**C**=O), 147.5*, 145.8 (**C**$_{arom}$-SO$_2$), 144.6, 144.5* (**C**=N), 134.9*, 134.7 (**C**$_{arom}$-CH$_3$), 132.9*, 132.6

(**C**H=CH), 129.6, 129.5* (**C**$_{arom}$-H), 128.4, 128.3* (**C**$_{arom}$-H), 127.8, 127.3* (CH=**C**H), 74.9, 74.4* (**C**HOH), 61.5, 61.4* (O**C**H$_2$CH$_3$), 31.1*, 30.8 (**C**H), 29.8*, 28.2 (**C**H$_2$), 27.7*, 26.3 (**C**$_{chain}$H$_2$), 24.5, 23.8* (**C**$_{chain}$H$_2$), 21.6 (C$_{arom}$-**C**H$_3$), 20.5, 20.5* (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.2*, 14.1 (**C**H$_3$).

(4*S*)-Ethyl 4-(dimethoxymethyl)-6-hydroxy-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-4-carboxylate (32j)



Following the general procedure, **32j** (200 mg, 0.50 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 120 h reaction time, starting from *trans*-fumaraldehyde **1l** (65 μL, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 99%.

dr: 68:32.

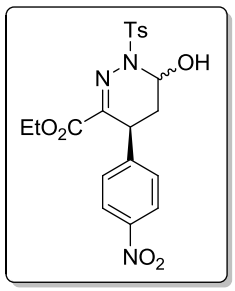
ee: 92% (determined by HPLC analysis after oxidation to **33j**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.89 (d, *J* = 8.3 Hz, 2H, C$_{arom}$-**H**), 7.85* (d, *J* = 8.3 Hz, 2H, C$_{arom}$-**H**), 7.29-7.25 (m, 2H, C$_{arom}$-**H**), 5.75-5.68 (m, 1H, C**H**OH), 4.83* (d, *J* = 3.7 Hz, 1H, C**H**(OCH$_3$)$_2$), 4.69 (d, *J* = 3.7 Hz, 1H, C**H**(OCH$_3$)$_2$), 4.25 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.42 (s, 3H, CH(OC**H**$_3$)(OCH$_3$)), 3.37* (s, 3H, CH(OC**H**$_3$)(OCH$_3$)), 3.22 (s, 3H, CH(OCH$_3$)(OC**H**$_3$)), 3.20* (s, 3H, CH(OCH$_3$)(OC**H**$_3$)), 3.16-2.95 (m, 1H, C**H**),

2.55 (d, J = 14.9 Hz, 1H, C**H**$_a$H$_b$), 2.39 (s, 3H, C$_{arom}$-C**H**$_3$), 2.18-1.82 (m, 1H, CH$_a$**H**$_b$), 1.40-1.29 (m, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 163.7, 163.4* (**C**=O), 144.5*, 144.1 (**C**$_{arom}$-SO$_2$), 138.5, 138.4* (**C**=N), 135.6, 134.8* (**C**$_{arom}$-CH$_3$), 129.5, 129.1* (**C**$_{arom}$-H), 128.7, 128.5* (**C**$_{arom}$-H), 104.3*, 103.7 (**C**H(OCH$_3$)$_2$), 75.0*, 71.8 (**C**HOH), 61.6, 61.4*(O**C**H$_2$CH$_3$), 56.9, 56.5*, 56.7, 56.3* (CH(OCH$_3$)$_2$), 33.0*, 32.9 (**C**H), 24.6*, 23.9 (**C**H$_2$), 21.6 (C$_{arom}$-**C**H$_3$), 14.2*, 14.1 (OCH$_2$**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-(4-nitrophenyl)-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32k)



Following the general procedure, **32k** (162 mg, 0.36 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) after 168 h reaction time, starting from *trans*-4-nitrocinnamaldehyde **1o** (89 mg, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 72%.

dr: 69:31.

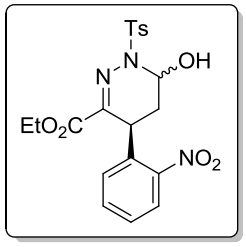
ee: 90% (determined by HPLC analysis after oxidation to **33k**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 8.12 (d, J = 8.6 Hz, 2H, C$_{arom}$-**H**), 7.90 (d, J = 8.1 Hz, 2H, C$_{arom}$-**H**), 7.36-7.21 (m, 4H, C$_{arom}$-**H**), 5.93 (s,

1H, C**H**OH), 5.84* (s, 1H, C**H**OH), 4.22-3.92 (m, 3H, C**H** + OC**H**$_2$CH$_3$), 2.50-2.33 (m, 4H, C_{arom}-C**H**$_3$ + C**H**$_a$H$_b$), 1.93-1.90 (m, 1H, CH$_a$**H**$_b$), 1.06 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 162.9*, 162.3 (**C**=O), 148.6, 147.6* ($\mathbf{C}_{arom}$-NO$_2$), 147.0, 146.7* ($\mathbf{C}_{arom}$-SO$_2$), 145.1*, 145.0 (**C**=N), 143.0, 141.2* ($\mathbf{C}_{arom}$-CH), 134.7, 133.7* ($\mathbf{C}_{arom}$-CH$_3$), 130.14*, 129.8 ($\mathbf{C}_{arom}$-H), 129.7, 128.7 ($\mathbf{C}_{arom}$-H), 128.4, 128.2 ($\mathbf{C}_{arom}$-H), 124.2, 123.6* ($\mathbf{C}_{arom}$-H), 73.8*, 73.7 (**C**HOH), 61.9*, 61.5 (O**C**H$_2$CH$_3$), 35.3, 33.8* (**C**H), 35.2, 32.0* (**C**H$_2$), 21.7 (C_{arom}-**C**H$_3$), 14.0*, 13.8 (OCH$_2$**C**H$_3$).

(4*R*)-Ethyl 6-hydroxy-4-(2-nitrophenyl)-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (32l)



Following the general procedure, **32l** (64 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) in 13 d starting from *trans*-2-nitrocinnamaldehyde **1s** (89 mg, 0.50 mmol) and hydrazone **31a** (270 mg, 1.00 mmol) in the presence of the catalyst **6** (32 mg, 0.10 mmol), PhCOOH (58 mg, 0.50 mmol) and water (9 μL, 0.50 mmol), using toluene (5.0 mL) as solvent at -20 ºC.

Yield: 29%.

dr: 85:15.

ee: 96% (determined by HPLC analysis after oxidation to **33l**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 8.12 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 7.90 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 7.36-7.21 (m, 4H, C_{arom}-**H**), 5.98 (s, 1H, C**H**OH), 5.82* (s, 1H, C**H**OH), 4.67-4.43 (m, 1H, C**H**), 4.23-3.80 (m, 2H, OC**H**$_2$CH$_3$), 2.81-2.51 (m, 1H, C**H**$_a$H$_b$), 2.42 (s, 3H, C_{arom}-C**H**$_3$), 2.05-1.97 (m, 1H, CH$_a$**H**$_b$), 0.99 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

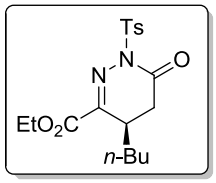
^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 162.0*, 161.9 (**C**=O), 149.5, 147.4* (**C**$_{arom}$-NO$_2$), 144.9, 143.6* (**C**$_{arom}$-SO$_2$), 136.0*, 134.9 (**C**=N), 133.8, 133.7* (**C**$_{arom}$-CH), 133.5, 132.9* (**C**$_{arom}$-CH$_3$), 131.2*, 130.7 (**C**$_{arom}$-H), 129.8, 129.7 (**C**$_{arom}$-H), 129.1, 128.9 (**C**$_{arom}$-H), 128.5, 128.4* (**C**$_{arom}$-H), 74.2*, 74.1 (**C**HOH), 61.7*, 61.4 (O**C**H$_2$CH$_3$), 34.5 (**C**H), 31.5, 31.2* (**C**H$_2$), 21.7 (C_{arom}-**C**H$_3$), 13.9*, 13.7 (OCH$_2$**C**H$_3$).

4.2 Determination of the enantiomeric purity: synthesis of tetrahydropyridazines 33a-l.

General procedure:

To a cooled suspension of PCC (2.50 mmol) and molecular sieves 4Å in CH_2Cl_2 (3.0 mL) was slowly added a solution of the tetrahydropyridazine **32** (0.50 mmol) in CH_2Cl_2 (2.0 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 minutes and then at room temperature until completion (~5 h). The reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (FC).

(4*R*)-Ethyl 4-butyl-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33a)



Following the general procedure, **33a** (80 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32a** (100 mg, 0.26 mmol) and PCC (280 mg, 1.30 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 76%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 18.77 min, τ_{minor} = 23.00 min.

$[\alpha]_D^{20}$: -7.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.33 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 4.46-4.28 (m, 2H, OC**H**$_2$CH$_3$), 3.29-3.15 (m, 1H, C**H**), 2.58-2.51 (m, 2H, C**H**$_2$), 2.43 (s, 3H, C_{arom}-C**H**$_3$), 1.65-1.46 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.39 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.25-1.10 (m, 5H, C_{chain}H$_a$**H**$_b$ + 2 x C_{chain}**H**$_2$), 0.82 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.6 (**C**=O), 149.2 (**C**$_{arom}$-SO$_2$), 145.7 (**C**=N), 134.4 (**C**$_{arom}$-CH$_3$), 129.6 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 33.5 (**C**H$_2$), 32.9 (**C**H), 29.8 (**C**$_{chain}$H$_2$), 28.2 (**C**$_{chain}$H$_2$), 22.3 (**C**$_{chain}$H$_2$), 21.7 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 13.7 (**C**H$_3$).

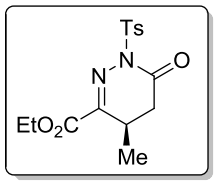
IR (Film) cm^{-1}: 1734 (CO), 1601 (C=N), 1380 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 104-106.

MS (EI) m/z (relative abundance): 335 (8), 316 (64), 260 (29), 243 (56), 155 (32), 127 (29), 91 (100).

HRMS: Calculated for $[C_{18}H_{25}N_2O_5S]^+$: 381.1484 $[M+H]^+$; found: 381.1498.

(4*R*)-Ethyl 4-methyl-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33b)



Following the general procedure, **33b** (115 mg, 0.34 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 1:1) as a white solid, starting from tetrahydropyridazine **32b** (161 mg, 0.47 mmol) and PCC (510 mg, 2.37 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 72%.

ee: 26%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 21.20 min, τ_{minor} = 26.63 min.

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.33 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 4.45-4.25 (m, 2H, OC**H**$_2$CH$_3$), 3.37-3.20 (m, 1H, C**H**), 2.60 (dd, *J* =

17.0, 6.8 Hz, 1H, C**H**$_a$H$_b$), 2.49-2.37 (m, 4H, CH$_a$**H**$_b$ + C$_{arom}$-C**H**$_3$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.13 (d, *J* = 7.4 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.5 (**C**=O), 162.3 (**C**=O), 149.5 (**C**$_{arom}$-SO$_2$), 145.7 (**C**=N), 134.4 (**C**$_{arom}$-CH$_3$), 129.6 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 35.7 (**C**H$_2$), 28.2 (**C**H), 21.7 (C$_{arom}$-**C**H$_3$), 16.1 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).

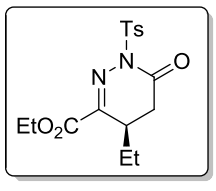
IR (Film) cm^{-1}: 1734 (CO), 1598 (C=N), 1382 (SO$_2$), 1178 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 107-109.

MS (EI) m/z (relative abundance): 293 (6), 274 (73), 201 (8), 155 (32), 127 (10), 109 (51), 91 (100).

HRMS: Calculated for [C$_{15}$H$_{19}$N$_2$O$_5$S]$^+$: 339.1015 [M+H]$^+$; found: 339.1020.

(4*R*)-Ethyl 4-ethyl-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33c)



Following the general procedure, **33c** (75 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32c** (105 mg, 0.30 mmol) and PCC (323 mg, 1.50 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 71%.

ee: 20%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 18.13 min, τ_{minor} = 21.64 min.

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.33 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 4.45-4.27 (m, 2H, OC**H**$_2$CH$_3$), 3.19-3.12 (m, 1H, C**H**), 2.61-2.52 (m, 2H, C**H**$_2$), 2.44 (s, 3H, C_{arom}-C**H**$_3$), 1.71-1.54 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.52-1.37 (m, 4H, C_{chain}H$_a$**H**$_b$ + OCH$_2$C**H**$_3$), 0.87 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.6 (**C**=O), 149.0 (**C**$_{arom}$-SO$_2$), 145.7 (**C**=N), 134.4 (**C**$_{arom}$-CH$_3$), 129.6 (**C**$_{arom}$-H), 129.1 (**C**$_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 34.4 (**C**H$_2$), 33.1 (**C**H), 23.5 (**C**$_{chain}$H$_2$), 21.7 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 10.8 (**C**H$_3$).

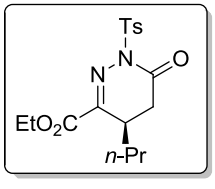
IR (Film) cm^{-1}: 1721 (CO), 1597 (C=N), 1381 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 81-83.

MS (EI) m/z (relative abundance): 307 (6), 288 (83), 260 (13), 243 (56), 155 (33), 127 (28), 99 (56), 91 (100).

HRMS: Calculated for $[C_{16}H_{21}N_2O_5S]^+$: 353.1171 $[M+H]^+$; found: 353.1180.

(4*R*)-Ethyl 6-oxo-4-propyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33d)



Following the general procedure, **33d** (95 mg, 0.26 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32d** (130 mg, 0.35 mmol) and PCC

(377 mg, 1.75 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 74%.

ee: 76%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 16.14 min, τ_{minor} = 20.02 min.

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.33 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 4.46-4.25 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.30-3.17 (m, 1H, C**H**), 2.58-2.51 (m, 2H, $C\mathbf{H}_2$), 2.43 (s, 3H, C_{arom}-$C\mathbf{H}_3$), 1.59-1.44 (m, 1H, $C_{chain}\mathbf{H}_aH_b$), 1.43-1.11 (m, 6H $C_{chain}H_a\mathbf{H}_b + C_{chain}\mathbf{H}_2 + OCH_2C\mathbf{H}_3$), 0.85 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.5 (**C**=O), 149.3 ($\mathbf{C}_{arom}$-SO_2), 145.7 (**C**=N), 134.4 ($\mathbf{C}_{arom}$-CH_3), 129.6 ($\mathbf{C}_{arom}$-H), 129.1 ($\mathbf{C}_{arom}$-H), 62.5 ($O\mathbf{C}H_2CH_3$), 33.5 ($\mathbf{C}H_2$), 32.7 (**C**H), 32.1 ($\mathbf{C}_{chain}H_2$), 21.7 (C_{arom}-$\mathbf{C}H_3$), 19.5 ($\mathbf{C}_{chain}H_2$), 14.0 ($OCH_2\mathbf{C}H_3$), 13.6 ($\mathbf{C}H_3$).

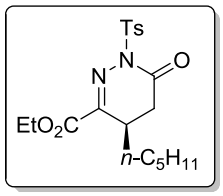
IR (Film) cm^{-1}: 1725 (CO), 1597 (C=N), 1383 (SO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 116-118.

MS (EI) m/z (relative abundance): 321 (7), 302 (66), 260 (61), 229 (15), 155 (33), 127 (30), 91 (100).

HRMS: Calculated for $[C_{17}H_{23}N_2O_5S]^+$: 367.1327 $[M+H]^+$; found: 367.1345.

(4*R*)-Ethyl 6-oxo-4-pentyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33e)



Following the general procedure, **33e** (86 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32e** (140 mg, 0.35 mmol) and PCC (377 mg, 1.75 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 62%.

ee: 99%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 14.29 min, τ_{minor} = 16.98 min.

$[\alpha]_D^{20}$: -6.1 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.96 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.32 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 4.43-4.27 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.28-3.15 (m, 1H, C**H**), 2.58-2.50 (m, 2H, $C\mathbf{H}_2$), 2.43 (s, 3H, C_{arom}-$C\mathbf{H}_3$), 1.59-1.10 (m, 11H, 4 x $C_{chain}\mathbf{H}_2$ + $OCH_2C\mathbf{H}_3$), 0.82 (t, *J* = 6.5 Hz, 3H, $C\mathbf{H}_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.5 (**C**=O), 149.2 ($\mathbf{C}_{arom}$-SO_2), 145.7 (**C**=N), 134.4 ($\mathbf{C}_{arom}$-CH_3), 129.6 ($\mathbf{C}_{arom}$-H), 129.0 ($\mathbf{C}_{arom}$-H), 62.5 ($O\mathbf{C}H_2CH_3$), 33.5 ($\mathbf{C}H_2$), 33.0 (**C**H), 31.3 ($\mathbf{C}_{chain}H_2$), 30.0 ($\mathbf{C}_{chain}H_2$), 25.8 ($\mathbf{C}_{chain}H_2$), 22.3 ($\mathbf{C}_{chain}H_2$), 21.7 (C_{arom}-$\mathbf{C}H_3$), 14.1 ($OCH_2\mathbf{C}H_3$), 13.9 ($\mathbf{C}H_3$).

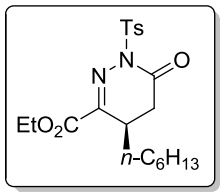
IR (Film) cm^{-1}: 1725 (CO), 1596 (C=N), 1384 (SO_2), 1177 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 111-113.

MS (EI) m/z (relative abundance): 349 (5), 330 (68), 260 (26), 257 (58), 155 (32), 127 (18), 109 (38), 91 (100).

HRMS: Calculated for $[C_{19}H_{27}N_2O_5S]^+$: 395.1640 $[M+H]^+$; found: 395.1656.

(4*R*)-Ethyl 4-hexyl-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33f)



Following the general procedure, **33f** (64 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32f** (112 mg, 0.27 mmol) and PCC (291 mg, 1.35 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 58%.

ee: 93%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 13.02 min, τ_{minor} = 15.44 min.

$[\alpha]_D^{20}$: -5.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.96 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.32 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 4.41-4.29 (m, 2H, OC**H**$_2$CH$_3$), 3.27-3.15 (m, 1H, C**H**), 2.55-2.53 (m,

2H, C**H**$_2$), 2.42 (s, 3H, C$_{arom}$-C**H**$_3$), 1.601.05 (m, 13H, 5 x C$_{chain}$**H**$_2$ + OCH$_2$C**H**$_3$), 0.84 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.5 (**C**=O), 149.2 (**C**$_{arom}$-SO$_2$), 145.6 (**C**=N), 134.4 (**C**$_{arom}$-CH$_3$), 129.6 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 33.5 (**C**H$_2$), 33.0 (**C**H), 31.4 (**C**$_{chain}$H$_2$), 30.1 (**C**$_{chain}$H$_2$), 28.8 (**C**$_{chain}$H$_2$), 26.0 (**C**$_{chain}$H$_2$), 22.5 (**C**$_{chain}$H$_2$), 21.7 (C$_{arom}$-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$).

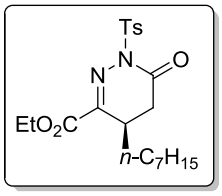
IR (Film) cm^{-1}: 1726 (CO), 1598 (C=N), 1385 (SO$_2$), 1175 (SO$_2$).

M.p. (*n*-hexane/EtOAc) (ºC): 104-106.

MS (EI) m/z (relative abundance): 363 (4), 344 (70), 271 (59), 260 (28), 155 (35), 109 (32), 91 (100).

HRMS: Calculated for [C$_{20}$H$_{29}$N$_2$O$_5$S]$^+$: 409.1797 [M+H]$^+$; found: 409.1812.

(4*R*)-Ethyl 4-heptyl-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33g)



Following the general procedure, **33g** (78 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32g** (125 mg, 0.30 mmol) and PCC (323 mg, 1.50 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 62%.

ee: 99%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 16.81 min, τ_{minor} = 20.82 min.

$[\alpha]_D^{20}$: -2.9 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.95 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 7.31 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 4.37-4.31 (m, 2H, OC**H**$_2$CH$_3$), 3.18-3.24 (m, 1H, C**H**), 2.53 (d, *J* = 4.4 Hz, 2H, C**H**$_2$), 2.41 (s, 3H, C_{arom}-C**H**$_3$), 1.61-0.95 (m, 15H, 6 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.84 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.5 (**C**=O), 149.2 ($\mathbf{C}_{arom}$-SO_2), 145.7 (**C**=N), 134.4 ($\mathbf{C}_{arom}$-CH_3), 129.6 ($\mathbf{C}_{arom}$-H), 129.0 ($\mathbf{C}_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 33.4 (**C**H$_2$), 32.9 (**C**H), 31.7 ($\mathbf{C}_{chain}H_2$), 30.1 ($\mathbf{C}_{chain}H_2$), 29.1 ($\mathbf{C}_{chain}H_2$), 28.9 ($\mathbf{C}_{chain}H_2$), 26.1 ($\mathbf{C}_{chain}H_2$), 22.6 ($\mathbf{C}_{chain}H_2$), 21.7 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$).

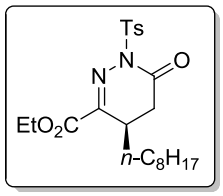
IR (Film) cm^{-1}: 1739 (CO), 1726 (CO), 1596 (C=N), 1388 (SO_2), 1160 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 107-109.

MS (EI) m/z (relative abundance): 377 (4), 358 (74), 285 (61), 260 (25), 155 (33), 109 (34), 91 (100).

HRMS: Calculated for $[C_{21}H_{31}N_2O_5S]^+$: 423.1954 $[M+H]^+$; found: 423.1953.

(4*R*)-Ethyl 6-oxo-4-octyl-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33h)



Following the general procedure, **33h** (84 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32h** (110 mg, 0.25 mmol) and PCC (269 mg, 1.25 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 77%.

ee: 95%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 16.07 min, τ_{minor} = 19.49 min.

$[\alpha]_D^{20}$: -4.5 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.32 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 4.41-4.30 (m, 2H, OC**H**$_2$CH$_3$), 3.27-3.16 (m, 1H, C**H**), 2.58-2.52 (m, 2H, C**H**$_2$), 2.43 (s, 3H, C_{arom}-C**H**$_3$), 1.61-1.05 (m, 17H, 7 x C_{chain}**H**$_2$ + OCH$_2$C**H**$_3$), 0.86 (t, *J* = 6.8 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**=O), 162.5 (**C**=O), 149.2 (**C**$_{arom}$-SO$_2$), 145.6 (**C**=N), 134.4 (**C**$_{arom}$-CH$_3$), 129.6 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 62.5 (O**C**H$_2$CH$_3$), 33.4 (**C**H$_2$), 33.0 (**C**H), 31.8 (**C**$_{chain}$H$_2$), 30.1 (**C**$_{chain}$H$_2$), 29.2 (**C**$_{chain}$H$_2$), 29.2 (**C**$_{chain}$H$_2$), 29.1 (**C**$_{chain}$H$_2$), 26.1 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 21.7 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$).

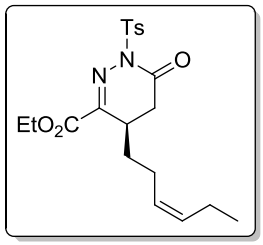
IR (Film) cm^{-1}: 1724 (CO), 1597 (C=N), 1384 (SO_2), 1157 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 108-109.

MS (EI) m/z (relative abundance): 391 (4), 372 (72), 299 (63), 260 (27), 155 (31), 91 (100).

HRMS: Calculated for $[C_{22}H_{33}N_2O_5S]^+$: 437.2110 $[M+H]^+$; found: 437.2128.

(4*R*, 3'*Z*)-Ethyl 4-(3-hexenyl)-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33i)



Following the general procedure, **33i** (58 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a white solid, starting from tetrahydropyridazine **32i** (80 mg, 0.20 mmol) and PCC (215 mg, 1.00 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 71%.

ee: 30%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 13.47 min, τ_{minor} = 16.22 min.

^{1}H-NMR (δ, ppm): 7.97 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.32 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 5.45-5.32 (m, 1H, C**H**=CH), 5.22-5.14 (m, 1H, CH=C**H**), 4.42-4.29 (m, 2H, OC**H**$_2$CH$_3$), 3.28-3.17 (m, 1H, C**H**), 2.57-2.54 (m, 2H, C**H**$_2$), 2.43 (s, 3H,

C_{arom}-C**H**$_3$), 2.05-1.87 (m, 4H, 2 x C_{chain}**H**$_2$), 1.65-1.63 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.49-1.32 (m, 4H $C_{chain}H_a$**H**$_b$ +OCH_2C**H**$_3$), 0.91 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.6 (**C**=O), 162.4 (**C**=O), 149.1 (**C**$_{arom}$-SO_2), 145.7 (**C**=N), 134.4 (**C**$_{arom}$-CH_3), 133.6 (**C**H=CH), 129.6 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 126.4 (CH=**C**H), 62.5 (O**C**H_2CH_3), 33.2 (**C**H_2), 32.5 (**C**H), 29.7 (**C**$_{chain}H_2$), 23.7 (**C**$_{chain}H_2$), 21.7 (C_{arom}-**C**H_3), 20.6 (**C**$_{chain}H_2$), 14.2 (OCH_2**C**H_3), 14.1 (**C**H_3).

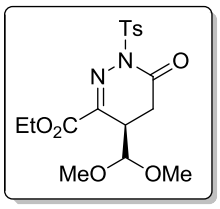
IR (Film) cm^{-1}: 1720 (CO), 1596 (C=N), 1382 (SO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 77-79.

MS (EI) m/z (relative abundance): 361 (2), 333 (22), 323 (26), 251 (38), 181 (33), 169 (98), 155 (26), 135 (33), 91 (100).

HRMS: Calculated for $[C_{20}H_{27}N_2O_5S]^+$: 407.1640 $[M+H]^+$; found: 406.1651.

(4*S*)-Ethyl 4-(dimethoxymethyl)-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33j)



Following the general procedure, **33j** (116 mg, 0.29 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a colourless oil, starting from tetrahydropyridazine **32j** (190 mg, 0.48 mmol) and PCC (517 mg, 2.40 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 60%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min; τ_{major} = 33.35 min, τ_{minor} = 15.43 min.

$[\alpha]_D^{20}$: +14.6 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.94 (d, *J* = 8.0 Hz, 2H, C_{arom}-**H**), 7.30 (d, *J* = 8.0 Hz, 2H, C_{arom}-**H**), 4.39-4.32 (m, 3H, OC**H**$_2$CH$_3$ + C**H**(OCH$_3$)$_2$), 3.45 (d, *J* = 7.9 Hz, 1H, C**H**), 3.24 (s, 3H, CH(OC**H**$_3$)(OCH$_3$)), 3.11 (s, 3H, CH(OCH$_3$)(OC**H**$_3$)), 2.77 (d, *J* = 16.8 Hz, 1H, C**H**$_a$H$_b$), 2.60-2.32 (m, 4H, CH$_a$**H**$_b$ + C_{arom}-C**H**$_3$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

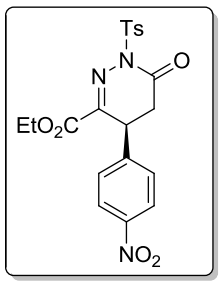
^{13}C-NMR (δ, ppm): 163.7 (**C**=O), 163.0 (**C**=O), 145.3 (**C**$_{arom}$-SO$_2$), 142.6 (**C**=N), 134.9 (**C**$_{arom}$-CH$_3$), 129.4 (**C**$_{arom}$-H), 129.0 (**C**$_{arom}$-H), 105.0 (**C**H(OCH$_3$)$_2$), 62.5 (O**C**H$_2$CH$_3$), 56.3, 56.3 (CH(O**C**H$_3$)$_2$), 38.2 (**C**H), 28.7 (**C**H$_2$), 21.7 (C_{arom}-**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$).

IR (Film) cm^{-1}: 1738 (CO), 1723 (CO), 1597 (C=N), 1378 (SO_2), 1177 (SO_2).

MS (EI) m/z (relative abundance): 367 (3), 325 (5), 243 (44), 183 (62), 155 (78), 91 (100).

HRMS: Calculated for $[C_{16}H_{19}N_2O_6S]^+$: 367.0964 $[M+H-CH_3OH]^+$; found: 367.0960.

(4*R*)-Ethyl 4-(4-nitrophenyl)-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33k)



Following the general procedure, **33k** (68 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a pale yelow solid, starting from tetrahydropyridazine **32k** (152 mg, 0.34 mmol) and PCC (366 mg, 1.70 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 45%.

ee: 90%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min; τ_{major} = 45.15 min, τ_{minor} = 52.75 min.

^{1}H-NMR (δ, ppm): 8.09-7.98 (m, 4H, C_{arom}-**H**), 7.37 (d, *J* = 8.0 Hz, 2H, C_{arom}-**H**), 7.14 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 4.61 (d, *J* = 7.6 Hz, 1H, C**H**), 4.44-4.20 (m, 2H, OC**H**$_2$CH$_3$), 3.00 (dd, *J* = 17.0, 8.1 Hz, 1H, C**H**$_a$H$_b$), 2.79 (d, *J* = 17.0 Hz, 1H, CH$_a$**H**$_b$), 2.48 (s, 3H, C_{arom}-C**H**$_3$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 163.0 (**C**=O), 162.0 (**C**=O), 147.6 (**C**$_{arom}$-NO$_2$), 146.3 (**C**$_{arom}$-SO$_2$), 145.1(**C**$_{arom}$-CH), 143.4 (**C**=N), 134.0 (**C**$_{arom}$-CH$_3$), 129.8 (**C**$_{arom}$-H), 129.1 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-H), 124.5 (**C**$_{arom}$-H), 63.0 (O**C**H$_2$CH$_3$), 38.8 (**C**H), 35.7 (**C**H$_2$), 21.8 (C_{arom}-**C**H$_3$), 14.0 (OCH$_2$**C**H$_3$).

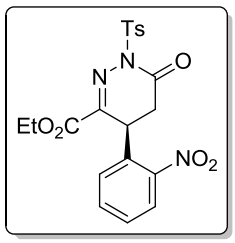
IR (Film) cm^{-1}: 1724 (CO), 1597 (C=N), 1524 (NO_2), 1380 (SO_2), 1348 (NO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 152-154.

MS (EI) m/z (relative abundance): 278 (41), 155 (25), 139 (100), 123 (35), 91 (63).

HRMS: Calculated for $[C_{13}H_{12}N_3O_5]^+$: 290.0777 $[M\text{-}Ts]^+$; found: 290.0798.

(4*R*)-Ethyl 4-(2-nitrophenyl)-6-oxo-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (33l)



Following the general procedure, **33l** (30 mg, 0.07 mmol) was isolated by FC (*n*-hexane/EtOAc 7:3) as a pale yelow solid, starting from tetrahydropyridazine **32l** (60 mg, 0.13 mmol) and PCC (140 mg, 0.65 mmol), in the presence of molecular sieves and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 52%.

ee: 96%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min; τ_{major} = 31.88 min, τ_{minor} = 44.21 min.

^{1}H-NMR (δ, ppm): 8.11-7.97 (m, 3H, C_{arom}-**H**), 7.53-7.34 (m, 4H, C_{arom}-**H**), 6.84 (dd, *J* = 7.4, 1.7 Hz, 1H, C_{arom}-**H**), 5.03 (dd, *J* = 8.6, 3.1 Hz, 1H, C**H**), 4.33-4.13 (m, 2H, OC**H**$_2$CH$_3$), 3.06 (dd, *J* = 17.3, 8.6 Hz, 1H, C**H**$_a$H$_b$), 2.94 (dd, *J* = 17.3, 3.1 Hz, 1H, CH$_a$**H**$_b$), 2.48 (s, 3H, C_{arom}-C**H**$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 163.0 (**C**=O), 161.6 (**C**=O), 148.3 ($\mathbf{C}_{arom}$-NO_2), 146.1 ($\mathbf{C}_{arom}$-SO_2), 145.0 ($\mathbf{C}_{arom}$-CH), 134.2 (**C**=N), 134.1 ($\mathbf{C}_{arom}$-CH_3), 131.3 ($\mathbf{C}_{arom}$-H), 129.8 ($\mathbf{C}_{arom}$-H), 129.5 ($\mathbf{C}_{arom}$-H), 129.2 ($\mathbf{C}_{arom}$-H), 128.0 ($\mathbf{C}_{arom}$-H), 126.1 ($\mathbf{C}_{arom}$-H), 62.8 (O**C**$H_2$$CH_3$), 36.0 (**C**H), 35.9 (**C**H_2), 21.8 (C_{arom}-**C**H_3), 13.9 (OCH_2**C**H_3).

IR (Film) cm^{-1}: 1727 (CO), 1596 (C=N), 1528 (NO_2), 1380 (SO_2), 1348 (NO_2), 1178 (SO_2).

M.p. (*n*-hexane/EtOAc) (ºC): 156-158.

MS (EI) m/z (relative abundance): 278 (46), 155 (25), 139 (100), 123 (36), 91 (69).

HRMS: Calculated for $[C_{13}H_{12}N_3O_{75}]^+$: 290.0777 $[M\text{-}Ts]^+$; found: 290.0778.

5. CONJUGATE ADDITION REACTION OF *N*-(*p*-METHOXYPHENYL)HYDRAZONES TO α,β-UNSATURATED ALDEHYDES

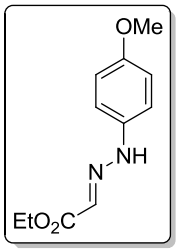
5.1 Synthesis of hydrazones 42a-h.

General procedure for the preparation of the hydrazones **42a-b***:*

A suspension of 4-methoxyphenyl hydrazine hydrochloride (5.0 g, 28.65 mmol) in anhydrous THF (40.0 mL) was treated with triethylamine (4.0 mL, 28.65 mmol) before the corresponding glyoxylate (28.65 mmol) 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 20.0 mL) and water (2 x 20.0 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting solids were triturated with diethyl ether to obtain the desired hydrazone **42**.

(*E*)-Ethyl 2-[2-(4-methoxyphenyl)hydrazono]acetate (42a)



Following the general procedure, **42a** (5.7 g, 25.65 mmol) was isolated as a brown solid, starting from ethyl glyoxylate (50% *w/v* solution in toluene, 5.7 mL, 28.65 mmol), triethylamine (4.0 mL, 28.65 mmol) and 4-methoxyphenylhydrazine hydrochloride (5.0 g, 28.65 mmol) in anhydrous tetrahydrofuran (40.0 mL).

Yield: 90%.

^{1}H-NMR (δ, ppm): 8.79 (s, 1H, N**H**), 7.18-6.99 (m, 3H, C_{arom}-**H** + =C**H**), 6.81 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.28 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.75 (s, 3H, OC**H**$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.7 (**C**O), 155.4 (**C**$_{arom}$-OMe), 136.3 (**C**$_{arom}$-NH), 124.4 (**C**=N), 115.5 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.8 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 14.3 (OCH$_2$**C**H$_3$).

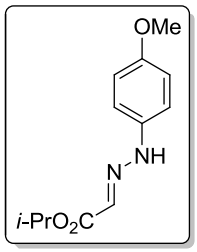
IR (neat) cm^{-1}: 3254 (NH), 1692 (CO), 1541 (C=N).

M.p. (Et_2O) (ºC): 124-126.

MS (EI) m/z (relative abundance): 222 (46), 148 (21), 122 (100), 95 (11).

HRMS: Calculated for $[C_{11}H_{15}N_2O_3]^+$: 223.1083 $[M+H]^+$; found: 223.1084.

(*E*)-*iso*-Propyl 2-[2-(4-methoxyphenyl)hydrazono]acetate (42b)



Following the general procedure, **42b** (5.5 g, 23.28 mmol) was isolated as a brown solid, starting from *iso*-propryl glyoxylate (3.33 g, 28.65 mmol), triethylamine (4.0 mL, 28.65 mmol) and 4-methoxyphenylhydrazine hydrochloride (5.0 g, 28.65 mmol) in anhydrous tetrahydrofuran (40.0 mL).

Yield: 81%.

^{1}H-NMR (δ, ppm): 8.57 (s, 1H, N**H**), 7.09 (d, *J* = 9.6 Hz, 2H, C_{arom}-**H**), 7.02 (s, 1H, =C**H**), 6.82 (d, *J* = 9.6 Hz, 2H, C_{arom}-**H**), 5.24-5.08 (m, 1H, OC**H**$(CH_3)_2$), 3.76 (s, 3H, OC**H**$_3$), 1.31 (d, *J* = 6.3 Hz, 6H, OCH(C**H**$_3)_2$).

^{13}C-NMR (δ, ppm): 164.1 (**C**O), 155.4 (**C**$_{arom}$-OMe), 136.3 (**C**$_{arom}$-NH), 124.9 (**C**=N), 115.5 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 68.2 (O**C**H$(CH_3)_2$), 55.6 (O**C**H$_3$), 21.9 (O**C**H$(CH_3)_2$).

IR (neat) cm^{-1}: 3250 (NH), 1689 (CO), 1549 (C=N).

M.p. (Et_2O) (ºC): 126-128.

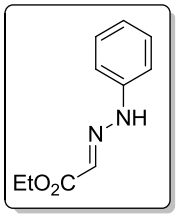
MS (EI) m/z (relative abundance): 236 (45), 194 (26), 148 (18), 122 (100), 95 (8).

HRMS: Calculated for $[C_{12}H_{17}N_2O_3]^+$: 237.1239 $[M+H]^+$; found: 237.1243.

General procedure for the preparation of the hydrazones **42g-h***:*

To a suspension of hydrazine (5.0 g) in anhydrous THF (40.0 mL) a solution of ethyl glyoxylate (50% *w/v* in toluene solution, 5.7 mL, 28.65 mmol) was added dropwise at 0 ºC. The mixture was stirred at this temperature for 30 minutes and then for 12 h at room temperature. Solvents were removed *in vacuo* and the resulting solids were triturated with diethyl ether to obtain the desired hydrazone **42**.

(*E*)-Ethyl 2-(2-phenylhydrazono)acetate (42g)



Following the general procedure, **42g** (4.3 g, 22.40 mmol) was isolated as a yellow solid starting from ethyl glyoxylate (50% *w/v* solution in toluene, 6.0 mL, 30.00 mmol) and phenylhydrazine (3.3 g, 30.00 mmol) in anhydrous tetrahydrofuran (45.0 mL).

Yield: 75%.

^{1}H-NMR (δ, ppm): 8.63 (s, 1H, N**H**), 7.37-7.23 (m, 2H, C_{arom}-**H**), 7.21-7.12 (m, 2H, C_{arom}-**H**), 7.09 (s, 1H, =C**H**), 6.97 (dd, *J* = 10.3, 4.2 Hz, 1H, C_{arom}-**H**), 4.31 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.4 (**C**O), 142.5 (**C**$_{arom}$-NH), 129.4 (**C**$_{arom}$-H), 125.7 (**C**=N), 122.4 (**C**$_{arom}$-H), 122.4 (**C**$_{arom}$-H), 114.0 (**C**$_{arom}$-H), 60.9 (O**C**H$_2$CH$_3$), 14.3 (OCH$_2$**C**H$_3$).

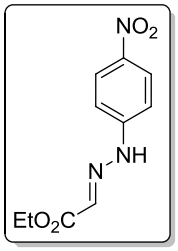
IR (neat) cm^{-1}: 3243 (NH), 1700 (CO), 1549 (C=N).

M.p. (Et$_2$O) (ºC): 132-133.

MS (EI) m/z (relative abundance): 192 (100), 118 (84), 91 (94), 77 (16), 65 (34).

HRMS: Calculated for $[C_{10}H_{13}N_2O_2]^+$: 193.0977 $[M+H]^+$; found: 193.0976.

(*E*)-Ethyl 2-[2-(4-nitrophenyl)hydrazono]acetate (42h)



Following the general procedure, **42h** (2.5 g, 10.55 mmol) was isolated as a brown solid, starting from ethyl glyoxylate (50% *w/v* solution in toluene, 3.2 mL, 16.30 mmol) and 4-nitrophenylhydrazine (2.5 g, 16.30 mmol) in anhydrous tetrahydrofuran (10.0 mL).

Yield: 65%.

^{1}H-NMR (δ, ppm;DMSO-d_6): 11.85 (s, 1H, N**H**), 8.20 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 7.34 (s, 1H, =C**H**), 7.22 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 4.23 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm;DMSO-d_6): 163.5 (**C**O), 149.6 (**C**$_{arom}$-NO$_2$), 141.0 (**C**$_{arom}$-NH), 130.7 (**C**=N), 126.5 (**C**$_{arom}$-H), 113.3 (**C**$_{arom}$-H), 60.9 (O**C**H$_2$CH$_3$), 14.6 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3248 (NH), 1703 (CO), 1560 (NO$_2$), 1549 (C=N), 1333 (NO$_2$).

M.p. (Et$_2$O) (ºC): 211-213.

MS (EI) m/z (relative abundance): 237 (96), 163 (100), 136 (64), 90 (16), 63 (17), 30 (15).

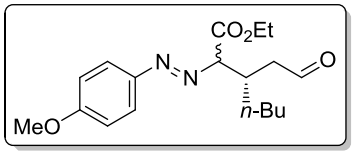
HRMS: Calculated for $[C_{10}H_{12}N_3O_4]^+$: 238.0828 $[M+H]^+$; found: 238.0839.

5.2 Diaza-ene type reaction: synthesis of γ-azoaldehydes 43a-t.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst ***ent*-46** (0.10 mmol, 10 mol%) and toluene (5.0 mL). Then, α,β-unsaturated aldehyde **1** (2.00 mmol) was added and the mixture was stirred for 10 minutes at room temperature prior to the addition of hydrazone **42** (1.00 mmol). The stirring was maintained at that temperature until the reaction was complete (30 minuted to 5 hours). The reaction mixture was charged onto silica gel and subjected to flash chromatography (FC). The racemic standards for HPLC separation conditions were prepared using 1:1 ratio of (*R*)- and (*S*)-catalyst **8** (0.10 mmol, 10 mol%).

(3*S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-(2-oxoethyl)heptanoate (43a)



Following the general procedure, **43a** (263 mg, 0.79 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 79%.

dr: 70:30.

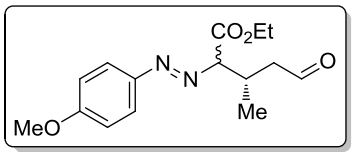
ee: 92% (determined by HPLC analysis after oxidation to **49a**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.75 (s, 1H, C**H**O), 7.76-7.62 (m, 2H, C_{arom}-**H**), 6.94 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.41* (d, *J* = 5.7 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.37 (d, *J* = 5.7 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.27-4.16 (m, 2H, OC**H**$_2CH_3$), 3.84 (s, 3H, OC**H**$_3$), 3.09-2.71 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.61-2.43 (m, 1H, CH$_a$**H**$_b$), 1.48-1.21 (m, 9H, 3 x C_{chain}**H**$_2$ + OCH_2C**H**$_3$), 0.86 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.5, 201.4* (**C**HO), 170.2, 169.8* ($\mathbf{C}_{arom}$-N_2), 162.3, 162.2* (**C**O), 145.9*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.7, 124.6* ($\mathbf{C}_{arom}$-H), 114.1 ($\mathbf{C}_{arom}$-H), 81.6, 81.4* (**C**H$CO_2CH_2CH_3$), 61.2, 61.1* (O**C**H_2CH_3), 55.6 (O**C**H_3), 45.3, 45.2* (**C**H_2), 36.0*, 35.7 (**C**H), 31.4, 31.1* ($\mathbf{C}_{chain}H_2$), 29.1*, 28.7 ($\mathbf{C}_{chain}H_2$), 22.7*, 22.6 ($\mathbf{C}_{chain}H_2$), 14.2*, 14.2 (OCH_2**C**H_3), 13.9 (**C**H_3).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-methyl-5-oxopentanoate (43b)



Following the general procedure, **43b** (259 mg, 0.89 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 30 minutes reaction time, starting from *trans*-crotonaldehyde **1b** (193 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent at 4 ºC.

Yield: 89%.

dr: 70:30.

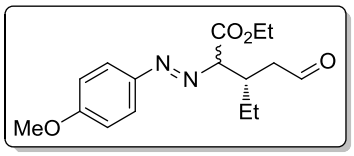
ee: 92% (determined by HPLC analysis after oxidation to **49b**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.72 (s, 1H, C**H**O), 7.77-7.60 (m, 2H, C_{arom}-**H**), 6.92 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.32-4.12 (m, 3H, C**H**$CO_2CH_2CH_3$ + OC**H**$_2CH_3$), 3.82 (s, 3H, OC**H**$_3$), 3.20-2.96 (m, 1H, C**H**), 2.86-2.60 (m, 1H, C**H**$_a$H$_b$), 2.55-2.30 (m, 1H, CH$_a$**H**$_b$), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.15* (d, *J* = 6.9 Hz, 3H, C**H**$_3$), 1.08 (d, *J* = 6.9 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.1, 200.9* (**C**HO), 169.8, 169.7* (**C**$_{arom}$-N_2), 162.3, 162.2* (**C**O), 145.9*, 145.8 (**C**$_{arom}$-OCH_3), 124.7, 124.6* (**C**$_{arom}$-H), 114.1 (**C**$_{arom}$-H), 83.7, 82.7* (**C**H$CO_2CH_2CH_3$), 61.1 (O**C**H_2CH_3), 55.5 (O**C**H_3), 47.2 (**C**H_2), 30.9*, 30.8 (**C**H), 17.5, 16.71* (**C**H_3), 14.2 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*S*)-Ethyl 3-ethyl-2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxopentanoate (43c)



Following the general procedure, **43c** (254 mg, 0.83 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 3 h reaction time, starting from *trans*-2-pentenal **1a** (213 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 83%.

dr: 70:30.

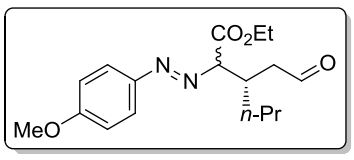
ee: 96% (determined by HPLC analysis after oxidation to **49c**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.76 (s, 1H, C**H**O), 7.76-7.64 (m, 2H, C_{arom}-**H**), 6.99-6.90 (m, 2H, C_{arom}-**H**), 4.42* (d, *J* = 5.7 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.38 (d, *J* = 5.7 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.21 (q, *J* = 7.1 Hz, 2H, OC**H**$_2CH_3$), 3.84 (s, 3H, OC**H**$_3$), 3.05-2.68 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.66-2.44 (m, 1H, CH$_a$**H**$_b$), 1.55-1.38 (m, 2H, C_{chain}**H**$_2$), 1.29-1.24 (m, 3H, OCH_2C**H**$_3$), 1.02-0.87 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.5, 201.4* (**C**HO), 170.2, 169.8* ($\mathbf{C}_{arom}$-N_2), 162.3, 162.2* (**C**O), 146.0*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.7, 124.6* ($\mathbf{C}_{arom}$-H), 114.1 ($\mathbf{C}_{arom}$-H), 81.3*, 81.2 (**C**H$CO_2CH_2CH_3$), 61.2, 61.1* (O**C**H_2CH_3), 55.6 (O**C**H_3), 45.0, 44.8* (**C**H_2), 37.5*, 37.3 (**C**H), 24.6, 24.3* ($\mathbf{C}_{chain}H_2$), 14.2 (OCH_2**C**H_3), 11.4*, 11.1 (**C**H_3).

IR (neat) cm^{-1}: 1724 (CO), 1510 (N=N).

(3*S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-(2-oxoethyl)hexanoate (43d)



Following the general procedure, **43d** (277 mg, 0.86 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-2-hexenal **1c** (260 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 86%.

dr: 60:40.

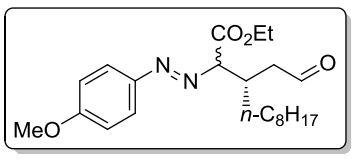
ee: 91% (determined by HPLC analysis after oxidation to **49d**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.74 (s, 1H, C**H**O), 7.69 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.93 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.40* (d, *J* = 5.6 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.35 (d, *J* = 5.6 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.20 (q, *J* = 7.1 Hz, 2H, OC**H**$_2CH_3$), 3.83 (s, 3H, OC**H**$_3$), 3.16-2.70 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.64-2.41 (m, 1H, CH$_a$**H**$_b$), 1.50-1.20 (m, 7H, 2 x C_{chain}**H**$_2$ + OCH_2C**H**$_3$), 0.99-0.82 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.5, 201.4* (**C**HO), 170.2, 169.8* (C_{arom}-N_2), 162.3, 162.2* (**C**O), 146.0*, 145.9 (C_{arom}-OCH_3), 124.7, 124.6* (C_{arom}-H), 114.1 (C_{arom}-H), 81.6, 81.4* (**C**H$CO_2CH_2CH_3$), 61.2, 61.1* (O**C**H_2CH_3), 55.6 (O**C**H_3), 45.3, 45.2* (**C**H_2), 35.8*, 35.6 (**C**H), 33.9, 33.6* ($C_{chain}H_2$), 20.1*, 19.7 ($C_{chain}H_2$), 14.2*, 14.2 (OCH_2**C**H_3), 14.1*, 14.0 (**C**H_3).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(*3S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-(2-oxoethyl)undecanoate (43e)



Following the general procedure, **43e** (242 mg, 0.62 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 1.5 h reaction time, starting from *trans*-2-undecenal **1h** (400 µL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 62%.

dr: 70:30.

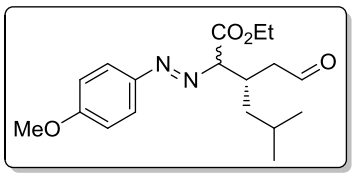
ee: 94% (determined by HPLC analysis after oxidation to **49e**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.75 (s, 1H, C**H**O), 7.69 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.94 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.41* (d, *J* = 5.8 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.37 (d, *J* = 5.8 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.21 (q, *J* = 6.8 Hz, 2H, OC**H**$_2CH_3$), 3.84 (s, 3H, OC**H**$_3$), 3.02-2.86 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.64-2.43 (m, 1H, CH$_a$**H**$_b$), 1.46-1.13 (m, 17H, 7 x C_{chain}**H**$_2$ + OCH_2C**H**$_3$), 0.85 (t, *J* = 6.8 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.4, 201.3* (**C**HO), 170.1, 169.8* ($\mathbf{C}_{arom}$-N_2), 162.3, 162.2* (**C**O), 146.0*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.7, 124.6* ($\mathbf{C}_{arom}$-H), 114.1 ($\mathbf{C}_{arom}$-H), 81.5, 81.4* (**C**H$CO_2CH_2CH_3$), 61.2, 61.0* (O**C**H_2CH_3), 55.5 (O**C**H_3), 45.3, 45.2* (**C**H_2), 36.1*, 35.8 (**C**H), 31.8 ($\mathbf{C}_{chain}H_2$), 31.7, 31.4* ($\mathbf{C}_{chain}H_2$), 29.6*, 29.5 ($\mathbf{C}_{chain}H_2$), 29.4*, 29.3 ($\mathbf{C}_{chain}H_2$), 29.2 ($\mathbf{C}_{chain}H_2$), 26.9*, 26.5 ($\mathbf{C}_{chain}H_2$), 22.6 ($\mathbf{C}_{chain}H_2$), 14.2*, 14.2 (OCH_2**C**H_3), 14.1 (**C**H_3).

IR (neat) cm^{-1}: 1727 (CO), 1509 (N=N).

(3*S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-5-methyl-3-(2-oxoethyl)hexanoate (43f)



Following the general procedure, **43f** (198 mg, 0.59 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-5-methyl-2-hexenal **1t** (224 mg, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 59%.

dr: 70:30.

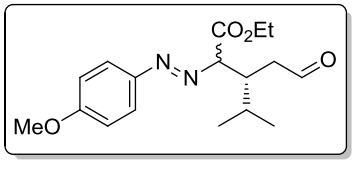
ee: 92% (determined by HPLC analysis after oxidation to **49f**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.75 (s, 1H, C**H**O), 9.73* (s, 1H, C**H**O), 7.72-7.66 (m, 2H, C_{arom}-**H**), 6.94 (d, J = 9.0 Hz, 2H, C_{arom}-**H**), 4.41* (d, J = 5.3 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.34 (d, J = 5.3 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.32-4.16 (m, 2H, OC**H**$_2CH_3$), 3.85 (s, 3H, OC**H**$_3$), 3.15-2.72 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.64-2.40 (m, 1H, CH$_a$**H**$_b$), 1.73-1.62 (m, 2H, C**H**$_2$CH(CH$_3$)$_2$), 1.42-1.18 (m, 4H, CH$_2$C**H**(CH$_3$)$_2$ + OCH$_2$C**H**$_3$), 1.02- 0.83 (m, 6H, CH$_2$CH(C**H**$_3$)$_2$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.5, 201.4* (**C**HO), 170.2, 169.8* (C_{arom}-N$_2$), 162.3, 162.2* (**C**O), 146.0 (C_{arom}-OCH$_3$), 124.7 (C_{arom}-H), 114.9*, 114.1 (C_{arom}-H), 81.6, 81.3* (**C**HCO$_2$CH$_2$CH$_3$), 61.2, 61.1* (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 45.5, 45.4* (**C**H$_2$), 40.9, 40.8* (**C**H), 34.1*, 33.8 (**C**H$_2$CH(CH$_3$)$_2$), 25.3*, 24.9 (CH$_2$**C**H(CH$_3$)$_2$), 22.9*, 22.7 (CH$_2$CH(**C**H$_3$)$_2$), 22.3, 22.2* (CH$_2$CH(**C**H$_3$)$_2$), 14.2*, 14.2 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*R*)-Ethyl 3-*iso*-propyl-2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxopentanoate (43g)



Following the general procedure, **43g** (120 mg, 0.37 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 3 h reaction time, starting

from *trans*-4-methyl-2-pentenal **1j** (240 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 37%.

dr: 70:30.

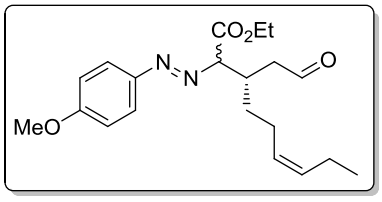
ee: 99% (determined by HPLC analysis after oxidation to **49g**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): δ 9.75* (s, 1H, C**H**O), 9.72 (s, 1H, C**H**O), 7.70* (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 7.66 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.93 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.49-4.44 (m, 1H, C**H**$CO_2CH_2CH_3$), 4.27-4.14 (m, 2H, OC**H**$_2CH_3$), 3.84 (s, 3H, OC**H**$_3$), 3.08-2.89 (m, 1H, C**H**), 2.79-2.65 (m, 1H, C**H**$_a$H$_b$), 2.58-2.50 (m, 1H, CH$_a$**H**$_b$), 1.83-1.72 (m, 1H, C**H**$(CH_3)_2$), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.00* (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3)_2$), 0.97 (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3)_2$), 0.91 (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3)_2$), 0.87* (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3)_2$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.7, 201.5* (**C**HO), 170.1, 170.0* ($\mathbf{C}_{arom}$-N_2), 162.3, 162.2* (**C**O), 145.9*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.7, 124.7* ($\mathbf{C}_{arom}$-H), 114.1 ($\mathbf{C}_{arom}$-H), 81.3 (**C**$HCO_2CH_2CH_3$), 61.2 (O**C**H_2CH_3), 55.6 (O**C**H_3), 42.3, 42.0* (**C**H_2), 41.4, 41.1* (**C**H), 29.2, 28.5* (**C**$H(CH_3)_2$), 21.1*, 20.7 ($CH(\mathbf{C}H_3)_2$), 18.6, 18.3* ($CH(\mathbf{C}H_3)_2$), 14.2, 14.1* ($OCH_2\mathbf{C}H_3$).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*S*,*Z*)-ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-(2- oxoethyl)non-6-enoate (43h)



Following the general procedure, **43h** (242 mg, 0.67 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans-2-cis-6*-nonadienal **1i** (194 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 67%.

dr: 80:20.

ee: 96% (determined by HPLC analysis after oxidation to **49h**).

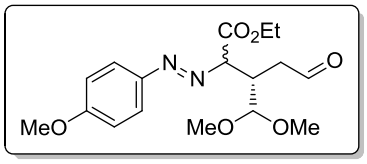
^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.75 (s, 1H, C**H**O), 9.73* (s, 1H, C**H**O), 7.74-7.65 (m, 2H, C_{arom}-**H**), 6.94 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.44- 5.20 (m, 2H, C**H**=C**H**), 4.43* (d, *J* = 5.6 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.40 (d, *J* = 5.6 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.27-4.16 (m, 2H, OC**H**$_2CH_3$), 3.84 (s, 3H, OC**H**$_3$), 3.11- 2.72 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.67-2.44 (m, 1H, CH$_a$**H**$_b$), 2.17-1.92 (m, 4H, 2 x C_{chain}**H**$_2$), 1.50-1.37 (m, 2H, C_{chain}**H**$_2$), 1.26 (td, *J* = 7.1, 3.2 Hz, 3H, OCH_2C**H**$_3$), 0.92 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.3, 201.2* (**C**HO), 170.1, 169.7* (**C**$_{arom}$-N_2), 162.3, 162.2* (**C**O), 145.9*, 145.9 (**C**$_{arom}$-OCH_3), 132.7, 132.6*, 127.8*, 127.6, 124.7, 124.6* (**C**$_{arom}$-H), 114.1 (**C**$_{arom}$-H), 81.3*, 81.2 (**C**H$CO_2CH_2CH_3$), 61.2, 61.1* (O**C**H_2CH_3), 55.6 (O**C**H_3), 45.2, 45.1* (**C**H_2), 35.6*,

35.4 (**C**H), 31.6, 31.4* (**C**$_{chain}$H$_2$), 24.5*, 24.1 (**C**$_{chain}$H$_2$), 20.5 (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.2*, 14.2 (**C**H$_3$).

IR (neat) cm^{-1}: 1726 (CO), 1510 (N=N).

(3*S*)-Ethyl 3-(dimethoxymethyl)-2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxopentanoate (43i)



Following the general procedure, **43i** (276 mg, 0.78 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 45 minutes reaction time, starting from *trans*-fumaraldehyde **1l** (253 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent at 4 ºC.

Yield: 78%.

dr: 80:20.

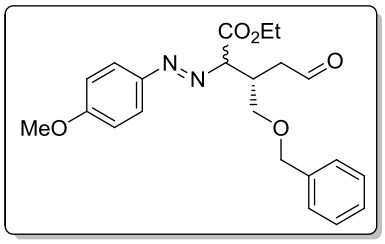
ee: 94% (determined by HPLC analysis after oxidation to **49i**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.76-9.75* (m, 1H, C**H**O), 9.70-9.64 (m, 1H, C**H**O), 7.72-7.66 (m, 2H, C$_{arom}$-**H**), 6.94 (dd, *J* = 9.0, 2.7 Hz, 2H, C$_{arom}$-**H**), 4.59-4.48 (m, 1H, C**H**(OCH$_3$)$_2$ + 1H*, C**H**CO$_2$CH$_2$CH$_3$), 4.33-4.27 (m, 1H, C**H**CO$_2$CH$_2$CH$_3$), 4.20 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.84 (s, 3H, OC**H**$_3$), 3.78-3.73 (m, 1H, C**H**), 3.46-3.40 (m, 3H, CH(OC**H**$_3$)(OCH$_3$)), 3.37-3.34 (m, 3H, CH(OCH$_3$)(OC**H**$_3$)), 2.74-2.66 (m, 1H, C**H**$_a$H$_b$), 2.65-2.59 (m, 1H, CH$_a$**H**$_b$), 1.36* (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 200.7, 200.6* (**C**HO), 169.6, 169.4* ($\mathbf{C}_{arom}$-N_2), 162.4, 162.3* (**C**O), 145.9*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.7, 124.6* ($\mathbf{C}_{arom}$-H), 114.1*, 114.1 ($\mathbf{C}_{arom}$-H), 105.3*, 105.2 (**C**H(OCH_3)$_2$), 78.7*, 78.6 (**C**H$CO_2CH_2CH_3$), 61.3, 61.1* (O**C**H_2CH_3), 55.6*, 55.6 (O**C**H_3), 55.4*, 55.2, 55.2, 54.8* (CH(O**C**H_3)$_2$), 41.0*, 40.7 (**C**H_2), 39.8*, 39.3 (**C**H), 14.2 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*S*)-Ethyl 3-(benzyloxymethyl)-2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxopentanoate (43j)



Following the general procedure, **43j** (274 mg, 0.69 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 1.5 h reaction time, starting from *trans*-4-(benzyloxy)but-2-enal **1n** (352 mg, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 69%.

dr: 95:5.

ee: 96% (determined by HPLC analysis after oxidation to **49j**).

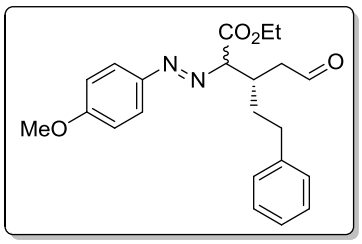
^{1}H-NMR (δ, ppm): 9.75 (s, 1H, C**H**O), 7.70 (d, *J* = 8.9 Hz, 2H, $\mathbf{C}_{arom}$-**H**), 7.40-7.18 (m, 5H, $\mathbf{C}_{arom}$-**H**), 6.95 (d, *J* = 8.9 Hz, 2H, $\mathbf{C}_{arom}$-**H**), 4.57 (d, *J* = 6.4 Hz,

1H, C**H**$CO_2CH_2CH_3$), 4.54-4.41 (m, 2H, OC**H**$_2$Ph), 4.19 (q, J = 7.1 Hz, 2H, OC**H**$_2CH_3$), 3.86 (s, 3H, OC**H**$_3$), 3.63-3.45 (m, 2H, C**H**$_2OCH_2$Ph), 3.45-3.29 (m, 1H, C**H**), 2.84 (dd, J = 17.3, 5.1 Hz, 1H, C**H**$_a$H$_b$), 2.74-2.59 (m, 1H, CH$_a$**H**$_b$), 1.24 (t, J = 7.1 Hz, 3H, OCH_2C**H**$_3$).

^{13}C-NMR (δ, ppm): 200.9 (**C**HO), 169.7 (**C**$_{arom}$-N$_2$), 162.4 (**C**O), 145.9 (**C**$_{arom}$-OCH_3), 137.9 (**C**$_{arom}$-**C**H_2), 128.4(**C**$_{arom}$-H), 127.6 (**C**$_{arom}$-H), 124.7 (**C**$_{arom}$-H), 114.1 (**C**$_{arom}$-H), 79.4 (**C**H$CO_2CH_2CH_3$), 73.2 (O**C**H_2Ph), 70.2 (**C**H_2OCH_2Ph), 61.3 (O**C**H_2CH_3), 55.6 (O**C**H_3), 42.9 (**C**H_2), 36.4 (**C**H), 14.2 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1728 (CO), 1690 (CO), 1509 (N=N).

(3*S*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxo-3-phenethylpentanoate (43k)



Following the general procedure, **43k** (218 mg, 0.57 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 2.5 h reaction time, starting from *trans*-5-phenylpent-2-enal **1u** (320 mg, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 57%.

dr: 70:30.

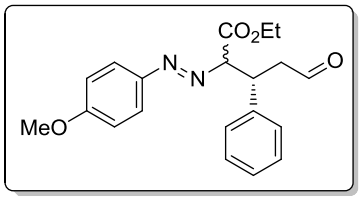
ee: 99% (determined by HPLC analysis after oxidation to **49k**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.77 (s, 1H, C**H**O), 9.75* (s, 1H, C**H**O), 7.72 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 7.33-7.11 (m, 5H, C_{arom}-**H**), 6.97 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.51-4.47 (m, 1H, C**H**$CO_2CH_2CH_3$), 4.32-4.17 (m, 2H, OC**H**$_2CH_3$), 3.87 (s, 3H, OC**H**$_3$), 3.19-2.51 (m, 5H, C**H** + C**H**$_2$ + CH_2C**H**$_2Ph$), 1.91-1.64 (m, 2H, C**H**$_2CH_2Ph$), 1.40-1.21 (m, 3H, OCH_2C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.2, 201.1* (**C**HO), 170.0, 169.7* (C_{arom}-N_2), 162.4, 162.3* (**C**O), 146.0*, 145.9 (C_{arom}-OCH_3), 141.5*, 141.4 (C_{arom}-**C**H_2), 128.5 (C_{arom}-H), 128.3 (C_{arom}-H), 126.0 (C_{arom}-H), 124.7, 124.7* (C_{arom}-H), 114.1 (C_{arom}-H), 81.2*, 81.2 (**C**H$CO_2CH_2CH_3$), 61.3, 61.2* (O**C**H_2CH_3), 55.6 (O**C**H_3), 45.3, 45.2* (**C**H_2), 35.7*, 35.5 (**C**H), 33.6, 33.4* (**C**H_2CH_2Ph), 33.3*, 32.9 (CH_2**C**H_2Ph), 14.3*, 14.2 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1725 (CO), 1509 (N=N).

(3*R*)-Ethyl 2-(*E*)-(4-methoxyphenyldiazenyl)-5-oxo-3- phenylpentanoate (43l)



Following the general procedure, **43l** (136 mg, 0.38 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 5 h reaction time, starting from *trans*-cinnamaldehyde **1m** (253 μL, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 38%.

dr: 70:30.

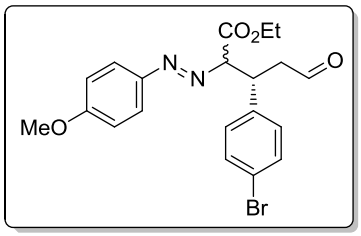
ee: 74% (determined by HPLC analysis after oxidation to **49l**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.65* (s, 1H, C**H**O), 9.62 (s, 1H, C**H**O), 7.81-7.68 (m, 2H, C_{arom}-**H**), 7.67-7.62* (m, 2H, C_{arom}-**H**), 7.40-7.15 (m, 5H, C_{arom}-**H**), 7.02- 6.88 (m, 2H, C_{arom}-**H**), 4.65-4.60 (m, 1H, C**H**$CO_2CH_2CH_3$), 4.45-4.25 (m, 1H, C**H**), 4.13* (q, *J* = 7.1 Hz, 2H, OC**H**$_2CH_3$), 4.01 (q, *J* = 7.1 Hz, 2H, OC**H**$_2CH_3$), 3.86 (s, 3H, OC**H**$_3$), 3.84* (s, 3H, OC**H**$_3$), 3.08-2.80 (m, 2H, C**H**$_2$), 1.16* (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.03 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 200.4, 200.2* (**C**HO), 169.3*, 168.9 ($\mathbf{C}_{arom}$-N_2), 162.5, 162.3* (**C**O), 146.0*, 145.8 ($\mathbf{C}_{arom}$-OCH_3), 139.6, 139.2* ($\mathbf{C}_{arom}$-**C**H), 128.8*, 128.8 ($\mathbf{C}_{arom}$-H), 128.5*, 128.4 ($\mathbf{C}_{arom}$-H), 127.5, 127.3* ($\mathbf{C}_{arom}$-H), 124.8, 124.6* ($\mathbf{C}_{arom}$-H), 114.2, 114.0* ($\mathbf{C}_{arom}$-H), 84.4, 82.7* (**C**H$CO_2CH_2CH_3$), 61.2*, 61.1 (O**C**H_2CH_3), 55.6, 55.6* (O**C**H_3), 46.6, 45.9* (**C**H), 42.1*, 42.0 (**C**H_2), 14.1*, 13.9 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1726 (CO), 1509 (N=N).

(3*R*)-Ethyl 3-(4-bromophenyl)-2-(*E*)-(4- methoxyphenyldiazenyl)-5-oxopentanoate (43m)



Following the general procedure, **43m** (268 mg, 0.62 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 4 h reaction time, starting from *trans*-cinnamaldehyde **1v** (422 mg, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00

mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 62%.

dr: 60:40.

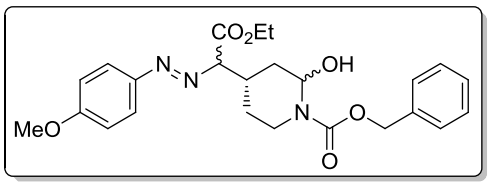
ee: 86% (determined by HPLC analysis after oxidation to **49m**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.64* (s, 1H, C**H**O), 9.61 (s, 1H, C**H**O), 7.71 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 7.64* (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 7.44-7.38 (m, 2H, C_{arom}-**H**), 7.21-7.15 (m, 2H, C_{arom}-**H**), 7.00-6.84 (m, 2H, C_{arom}-**H**), 4.60* (d, *J* = 9.2 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.56 (d, *J* = 9.2 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.40-4.19 (m, 1H, C**H**), 4.12* (q, *J* = 7.2 Hz, 2H, OC**H**$_2CH_3$), 4.03 (q, *J* = 7.2 Hz, 2H, OC**H**$_2CH_3$), 3.85 (s, 3H, OC**H**$_3$), 3.84* (s, 3H, OC**H**$_3$), 3.06-2.80 (m, 2H, C**H**$_2$), 1.16* (t, *J* = 7.2 Hz, 3H, OCH_2C**H**$_3$), 1.07 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 199.8, 199.6* (**C**HO), 169.0*, 168.7 ($\mathbf{C}_{arom}$-N_2), 162.6, 162.4* (**C**O), 145.9*, 145.8 ($\mathbf{C}_{arom}$-OCH_3), 138.8, 138.4* ($\mathbf{C}_{arom}$-**C**H), 131.8, 131.6* ($\mathbf{C}_{arom}$-H), 130.7*, 130.2 ($\mathbf{C}_{arom}$-H), 124.8, 124.6* ($\mathbf{C}_{arom}$-H), 121.4, 121.2* ($\mathbf{C}_{arom}$-H), 114.2, 114.1* ($\mathbf{C}_{arom}$-H), 83.8, 82.1* (**C**H$CO_2CH_2CH_3$), 61.4*, 61.3 (O**C**H_2CH_3), 55.6 (O**C**H_3), 46.4, 45.9* (**C**H), 41.4*, 41.2 (**C**H_2), 14.1*, 14.0 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 1722 (CO), 1505 (N=N).

(4*S*)-Benzyl 4-[2-ethoxy-1-(*E*)-(4- methoxyphenyldiazenyl)-2-oxoethyl]-2-hydroxypiperidine-1-carboxylate (43n)



Following the general procedure, **43n** (330 mg, 0.72 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 2 h reaction time, starting from *trans*-benzyl (5-oxopent-3-en-1-yl)carbamate **1w** (466 mg, 2.00 mmol) and hydrazone **42a** (222 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 72%.

dr: 80:20; **α/β**: 50:50.

ee: 97% (determined by HPLC analysis after transformation to **50n**).

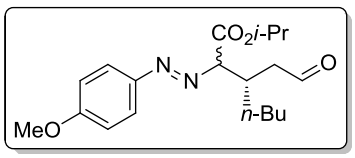
^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.72 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 7.41-7.28 (m, 5H, C_{arom}-**H**), 6.95 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.60-5.55 (m, 1H, C**H**OH), 5.21-5.07 (m, 2H, OC**H**$_2$Ph), 4.67* (d, *J* = 8.2 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.58 (d, *J* = 8.2 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.32-4.17 (m, 2H, OC**H**$_2CH_3$), 3.86 (s, 3H, OC**H**$_3$), 3.80-3.58 (m, 1H, C**H**$_a$H$_b$CHOH), 3.48-3.24 (m, 1H, CH$_a$**H**$_b$CHOH), 2.88-2.71 (m, 1H, C**H**), 2.10-1.85 (m, 2H, NC**H**$_2$), 1.80-1.53 (m, 2H, C**H**$_2$), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 170.0*, 169.8 (**C**$_{arom}$-N$_2$), 162.5, 162.2* (**C**O), 156.1 (N**C**O), 145.9, 145.7* (**C**$_{arom}$-OCH_3), 136.4, 136.3* (**C**$_{arom}$-**C**H_2), 128.6 (**C**$_{arom}$-H), 128.1 (**C**$_{arom}$-H), 128.0 (**C**$_{arom}$-H), 124.8, 124.6*

(**C**$_{arom}$-H), 114.2, 114.1* (**C**$_{arom}$-H), 82.5 (**C**HCO$_2$CH$_2$CH$_3$), 76.0 (**C**HOH), 67.3*, 67.3 (O**C**H$_2$Ph), 61.3, 61.2* (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 37.2 (N**C**H$_2$), 32.0*, 31.8 (CH), 31.7*, 30.9 (**C**H$_2$CHOH), 26.1, 24.8* (**C**H$_2$), 14.4*, 14.2 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 1732 (CO), 1683 (CO), 1509 (N=N).

(3*S*)-*iso*-Propyl 2-(*E*)-(4-methoxyphenyldiazenyl)-3-(2-oxoethyl)heptanoate (43o)



Following the general procedure, **43o** (298 mg, 0.86 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42b** (236 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (64 mg, 0.10 mmol) and using toluene (5.0 mL) as solvent.

Yield: 86%.

dr: 70:30.

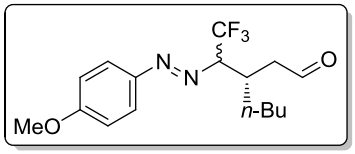
ee: 94% (determined by HPLC analysis after oxidation to **49o**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.75 (s, 1H, C**H**O), 7.72-7.64 (m, 2H, C$_{arom}$-**H**), 6.93 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-**H**), 5.17-5.02 (m, 1H, OC**H**(CH$_3$)$_2$), 4.38* (d, *J* = 5.7 Hz, 1H, C**H**CO$_2$CH(CH$_3$)$_2$), 4.33 (d, *J* = 5.7 Hz, 1H, C**H**CO$_2$CH(CH$_3$)$_2$), 3.83 (s, 3H, OC**H**$_3$), 3.08-2.70 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.61-2.33 (m, 1H, CH$_a$**H**$_b$), 1.54-1.17 (m, 12H, 3 x C$_{chain}$**H**$_2$ + OCH(C**H**$_3$)$_2$), 0.88-0.84 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.4, 201.3* (**C**HO), 169.6, 169.3* ($\mathbf{C}_{arom}$-N_2), 162.2, 162.1* (**C**O), 146.0*, 145.9 ($\mathbf{C}_{arom}$-OCH_3), 124.6, 124.5* ($\mathbf{C}_{arom}$-H), 114.0 ($\mathbf{C}_{arom}$-H), 81.6, 81.4* (**C**HCO_2 $CH(CH_3)_2$), 68.8, 68.7* (O**C**H$(CH_3)_2$), 55.5 (O**C**H_3), 45.3, 45.2* (**C**H_2), 36.0*, 35.7 (**C**H), 31.4, 31.1* ($\mathbf{C}_{chain}H_2$), 29.1*, 28.6 ($\mathbf{C}_{chain}H_2$), 22.6*, 22.6 ($\mathbf{C}_{chain}H_2$), 21.8*, 21.7 (OCH(**C**$H_3)_2$), 21.7 (OCH(**C**$H_3)_2$), 13.9 (**C**H_3).

IR (neat) cm^{-1}: 1727 (CO), 1510 (N=N).

(3*S*)-3-[2,2,2-Trifluoro-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl]heptanal (43p)



Following the general procedure, **43p** (206 mg, 0.62 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) as a yellow oil after 5 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42c** (218 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 62%.

dr: 90:10.

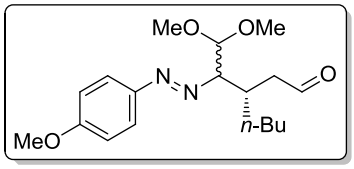
ee: 80% (determined by HPLC analysis after oxidation to **52p**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.74 (s, 1H, C**H**O), 9.72* (s, 1H, C**H**O), 7.74 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.97 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.10 (qd, *J* = 8.5, 3.3 Hz, 1H, C**H**CF_3), 3.86 (s, 3H, O**C**$\mathbf{H}_3$), 3.07-2.85 (m, 2H, C**H** + C$\mathbf{H}_a$$H_b$), 2.50 (dd, *J* = 17.3, 7.1 Hz, 1H, $CH_a$$\mathbf{H}_b$), 1.43-1.20 (m, 6H, 3 x $\mathbf{C}_{chain}H_2$), 0.87 (t, *J* = 6.8 Hz, 3H, C$\mathbf{H}_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 200.7, 200.6* (**C**HO), 162.8, 162.7* (**C**$_{arom}$-N_2), 145.85 (**C**$_{arom}$-OCH_3), 125.0, 124.9* (**C**$_{arom}$-H), 114.2 (**C**$_{arom}$-H), 78.4 (q, *J* = 24.7 Hz, **C**HCF_3), 55.6 (O**C**H_3), 44.6*, 44.4 (**C**H_2), 32.8 (**C**H), 31.5, 29.1* (**C**$_{chain}H_2$), 28.7 (**C**$_{chain}H_2$), 22.6*, 22.4 (**C**$_{chain}H_2$), 13.8 (**C**H_3).

IR (neat) cm^{-1}: 1726 (CO), 1509 (N=N).

(3*S*)-3-[2,2-Dimethoxy-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl]heptanal (43q)



Following the general procedure, **43q** (157 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 3 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42d** (224 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 47%.

dr: 70:30.

ee: 70/92% (determined by HPLC analysis after transformation to **52q-ester**).

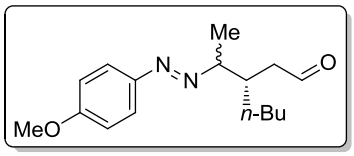
^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.76* (s, 1H, C**H**O), 9.73 (s, 1H, C**H**O), 7.69 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-**H**), 6.95 (d, *J* = 8.9 Hz, 2H, C$_{arom}$-**H**), 5.06 (d, *J* = 7.3 Hz, 1H, C**H**CH$(OCH_3)_2$), 4.93* (d, *J* = 7.3 Hz, 1H, C**H**CH$(OCH_3)_2$), 3.85 (s, 3H, O**C**H_3), 3.78 (dd, *J* = 7.2, 4.2 Hz, 1H, C**H**$(OCH_3)_2$), 3.44 (s, 3H, CH(O**C**H_3)(OCH_3)), 3.40* (s, 3H, CH(O**C**H_3)(OCH_3)), 3.26 (s, 3H, CH(OCH_3)(O**C**H_3)), 2.92* (dd, *J* = 16.5, 5.0 Hz, 2H, CH_2), 2.75-2.68 (m, 1H,

C**H**), 2.60-2.28 (m, 2H, C**H**$_2$), 1.77-1.71 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.46-1.15 (m, 5H, $C_{chain}H_a$**H**$_b$ + 2 x C_{chain}**H**$_2$), 0.87 (t, *J* = 7.4 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 202.5, 202.1* (**C**HO), 161.8*, 161.8 (**C**$_{arom}$-N$_2$), 146.2 (**C**$_{arom}$-OCH$_3$), 124.4, 124.3* (**C**$_{arom}$-H), 114.0* (**C**$_{arom}$-H), 102.8, 102.6* (**C**H(OCH$_3$)$_2$), 80.4, 79.5* (**C**HCH(OCH$_3$)$_2$), 55.5 (O**C**H$_3$), 53.7*, 53.6, 53.5, 53.3* (CH(O**C**H$_3$)$_2$), 45.6, 44.9* (**C**H$_2$), 34.4, 34.2* (**C**H), 31.9*, 30.0 (**C**$_{chain}$H$_2$), 29.5, 28.9* (**C**$_{chain}$H$_2$), 22.8, 22.6* (**C**$_{chain}$H$_2$), 14.0 (**C**H$_3$).

IR (neat) cm^{-1}: 1722 (CO), 1512 (N=N).

(3*S*)-3-[1-(*E*)-(4-Methoxyphenyldiazenyl)ethyl]heptanal (43r)



Following the general procedure, **43r** (132 mg, 0.48 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42e** (164 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 48%.

dr: 60:40.

ee: 40/95% (determined by HPLC analysis after transformation to **52r-ester**).

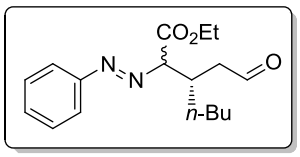
^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.76* (d, *J* = 2.0 Hz, 1H, C**H**O), 9.71 (t, *J* = 2.1 Hz, 1H, C**H**O), 7.64 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.95 (d, *J*

= 8.9Hz, 2H, C_{arom}-**H**), 3.91-3.63 (m, 4H, OC**H**$_3$ + C**H**CH_3), 2.84-2.30 (m, 3H, C**H** + C**H**$_2$), 1.60-1.14 (m, 9H, CHC**H**$_3$ + 3 x C_{chain}**H**$_2$), 0.99-0.77 (m, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 202.5, 202.4* (**C**HO), 161.6, 161.6* (**C**$_{arom}$-N_2), 146.2*, 146.1 (**C**$_{arom}$-OCH_3), 124.1 (**C**$_{arom}$-H), 114.0, 114.0* (**C**$_{arom}$-H), 74.5, 74.2* (**C**HCH_3), 55.5 (O**C**H_3), 45.3, 45.0* (**C**H_2), 38.4, 37.6* (**C**H), 31.4, 31.3* (**C**$_{chain}H_2$), 29.4*, 28.9 (**C**$_{chain}H_2$), 22.8, 22.2* (**C**$_{chain}H_2$), 17.0, 16.4* (CH**C**H_3), 14.2*, 14.0 (**C**H_3).

IR (neat) cm^{-1}: 1722 (CO), 1513 (N=N).

(3*S*)-Ethyl 3-(2-oxoethyl)-2-(*E*)-phenyldiazenylheptanoate (43t)



Following the general procedure, **43t** (72 mg, 0.24 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil after 2 h reaction time, starting from *trans*-2-heptenal **1d** (272 μL, 2.00 mmol) and hydrazone **42g** (192 mg, 1.00 mmol) in the presence of catalyst ***ent*-46** (128 mg, 0.20 mmol) and using toluene (5.0 mL) as solvent.

Yield: 24%.

dr: 70:30.

ee: 98% (determined by HPLC analysis after oxidation to **49t**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 9.78 (s, 1H, C**H**O), 7.81-7.64 (m, 2H, C_{arom}-**H**), 7.53-7.44 (m, 3H, C_{arom}-**H**), 4.47* (d, *J* = 5.5 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.44 (d, *J* = 5.5 Hz, 1H, C**H**$CO_2CH_2CH_3$), 4.23 (q, *J* = 7.1 Hz,

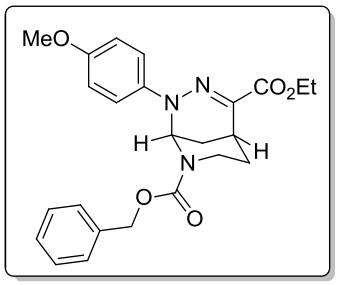
2H, OC**H**$_2$CH$_3$), 3.15-2.84 (m, 2H, C**H** + C**H**$_a$H$_b$), 2.69-2.47 (m, 1H, CH$_a$**H**$_b$), 1.48-1.17 (m, 9H, 3 x C$_{chain}$**H**$_2$ + OCH$_2$C**H**$_3$), 0.88 (t, *J* = 7.0 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 201.4 (**C**HO), 169.9 (**C**O), 151.6 (**C**$_{arom}$-N$_2$), 131.4 (**C**$_{arom}$-H), 129.1 (**C**$_{arom}$-H), 122.4 (**C**$_{arom}$-H), 81.8 (**C**HCO$_2$CH$_2$CH$_3$), 61.3 (O**C**H$_2$CH$_3$), 45.3 (**C**H$_2$), 35.9*, 35.6 (**C**H), 31.4, 31.1* (**C**$_{chain}$H$_2$), 29.1*, 28.7 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.2, 13.9 (**C**H$_3$).

IR (neat) cm^{-1}: 1726 (CO), 1509 (N=N).

Determination of absolute configuration:

(1*S*,5*S*)-8-Benzyl 4-ethyl 2-(4-methoxyphenyl)-2,3,8- triazabicyclo[3.3.1]non-3-ene-4,8-dicarboxylate (50n)



To a solution of the hemiaminal **43n** (310 mg, 0.68 mmol) in CH_2Cl_2 (5.0 mL) were added PCC (438 mg, 2.04 mmol) and molecular sieves (4Å). The reaction was stirred at room temperature until completion (~30 min) and the reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (*n*-hexane/EtOAc 7:3) yielding the bicyclic product **50n** (300 mg, 0.68 mmol) as a colourless oil.

Yield: 99%.

dr: >95:5.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 16.88 min, τ_{minor} = 13.54 min.

$[\alpha]_D^{20}$: +324.0 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm; rotameric ratio 6:4; *denotes minor rotamer): 7.53-7.17 (m, 9H, C_{arom}-**H**), 6.88* (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 6.69* (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.29 (s, 1H, NC**H**N), 6.12* (s, 1H, NC**H**N), 5.30* (d, *J* = 12.0 Hz, 1H, OC**H**$_a$CH$_b$Ph), 5.20-5.11 (m, 2H, OC**H**$_a$C**H**$_b$Ph), 5.05* (d, *J* = 12.0 Hz, 1H, OCH$_a$C**H**$_b$Ph), 4.39-4.21 (m, 2H, OC**H**$_2$CH$_3$), 4.18-3.96 (m, 1H, CHC**H**$_a$CH$_b$CH), 3.78 (s, 3H, OC**H**$_3$), 3.75* (s, 3H, OC**H**$_3$), 3.31 (s, 1H, C**H**C=N), 2.83-2.58 (m, 1H, CHCH$_a$C**H**$_b$CH), 2.10-2.02 (m, 1H, NC**H**$_a$CH$_b$), 1.89-1.72 (m, 3H, NCH$_a$C**H**$_b$ + C**H**$_2$), 1.44-1.29 (m, 3H, OCH$_2$C**H**$_3$).

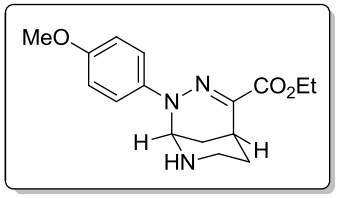
^{13}C-NMR (δ, ppm; rotameric ratio 6:4; *denotes minor rotamer): 164.3, 164.2* (**C**O), 155.9*, 155.7 (**C**$_{arom}$-OCH$_3$), 154.2, 153.5* (N**C**O), 138.6*, 138.5 (**C**=N), 136.3, 136.1* (**C**$_{arom}$-CH$_2$), 134.7*, 134.3 (**C**$_{arom}$-NH), 128.7 (**C**$_{arom}$-H), 128.6, 128.5* (**C**$_{arom}$-H), 128.2*, 127.8 (**C**$_{arom}$-H), 118.2, 117.2* (**C**$_{arom}$-H), 114.4, 114.3* (**C**$_{arom}$-H), 67.8*, 67.4 (O**C**H$_2$Ph), 61.2 (O**C**H$_2$CH$_3$), 61.0, 60.8* (N**C**HN), 55.5 (O**C**H$_3$), 38.5, 38.3* (CH**C**H$_2$CH), 29.2, 28.7* (**C**H$_2$), 26.7*, 26.3 (N**C**H$_2$), 24.9, 24.8* (**C**HC=N), 14.4 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 1694 (**C**O), 1510 (C=N).

MS (EI) m/z (relative abundance): 432 (100), 430 (98), 387 (4), 303 (3), 208 (6), 182 (7), 149 (49), 122 (54), 121 (84), 105 (30), 77 (18).

HRMS: Calculated for $[C_{24}H_{28}N_3O_5]^+$: 438.2029 $[M+H]^+$; found: 438.2048.

(1*S*,5*S*)-Ethyl 2-(4-methoxyphenyl)-2,3,8-triazabicyclo[3.3.1]non-3-ene-4-carboxylate (51n)



To a solution of bicyclic compound **50n** (50 mg, 0.11 mmol) in dry methanol (3.0 mL), under an inert atmosphere, was added palladium hydroxide (5 mg, 10% w) and the reaction mixture was stirred at room temperature under an atmosphere of H_2 (1 atm) until completion (~2 h). The reaction was filtered through Celite® to remove the palladium salts. The collected filtrate was evaporated under reduced pressure and purified by flash chromatography (*n*-hexane/EtOAc gradient from 1:1 to EtOAc) yielding the corresponding debenzoylated product **51n** (28 mg, 0.09 mmol) as a white solid.

Yield: 84%.

dr: >95:5.

ee: 97%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min. τ_{major} = 13.88 min, τ_{minor} = 10.54 min.

$[\alpha]_D^{20}$: +328.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.29 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 6.89 (d, *J* = 9.1 Hz, 2H, C_{arom}-**H**), 5.00 (s, 1H, NC**H**N), 4.40-4.20 (m, 2H, OC**H**$_2$CH$_3$), 3.79 (s, 3H, OC**H**$_3$), 3.27 (s, 1H, C**H**C=N), 2.81 (dd, *J* = 11.9, 3.8 Hz, 1H, NC**H**$_a$CH$_b$), 2.55 (td, *J* = 12.2, 3.3 Hz, 1H, CHC**H**$_a$CH$_b$CH), 2.33 (bs, 1H, N**H**), 2.22 (d, *J* = 11.9

Hz, 1H, NC**H**$_a$CH$_b$), 1.93 (tt, *J* = 12.2, 4.3 Hz, 1H, CHCH$_a$C**H**$_b$CH), 1.74 (t, *J* = 13.7 Hz, 2H, C**H**$_2$), 1.37 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 164.6 (**C**O), 155.6 (**C**$_{arom}$-OCH$_3$), 138.9 (**C**=N), 134.9 (**C**$_{arom}$-NH), 117.4 (**C**$_{arom}$-H), 114.6 (**C**$_{arom}$-H), 63.8 (O**C**H$_2$CH$_3$), 60.8 (N**C**HN), 55.6 (O**C**H$_3$), 39.2 (CH**C**H$_2$CH), 29.7 (**C**H$_2$), 26.3 (N**C**H$_2$), 25.6 (**C**HC=N), 14.4 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3343.0 (NH), 1687.4 (CO), 1507.1 (C=N).

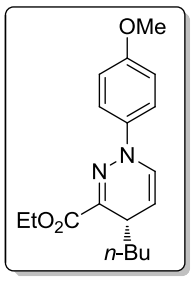
M.p. (*n*-hexane/EtOAc) (ºC): 88-90.

MS (EI) m/z (relative abundance): 303 (35), 230 (8), 181 (7), 123 (51), 107 (100), 82 (24), 56 (11).

HRMS: Calculated for [C$_{16}$H$_{22}$N$_2$O$_3$]$^+$: 304.1661 [M+H]$^+$; found: 304.1663.

5.3 Induction of the [1,3]-hydride shift.

(*S*)-Ethyl 4-butyl-1-(4-methoxyphenyl)-1,4-dihydropyridazine-3-carboxylate (44a)



To a solution of the aldehyde **43a** (184 mg, 0.54 mmol) in a mixture of diethyl ether (4.0 mL) and water (2.0 mL) was added hydrochloric acid (0.2 mL of a 6M solution, 1.11 mmol) and the reaction was stirred at room temperature for 2 hours. The organic layer was separated and aqueous phase extracted with CH_2Cl_2 (3 x 10.0 mL). The collected organic fractions were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced

pressure. The residual material was purified by flash chromatography (*n*-hexane/EtOAc gradient from 19:1 to 9:1), yielding the corresponding dehydrated product **44a** (126 mg, 0.40 mmol) as a yellow oil.

Yield: 70%.

ee: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 13.01 min, τ_{minor} = 11.33 min.

$[\alpha]_D^{20}$: +472.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 7.35-7.27 (m, 2H, C_{arom}-**H**), 6.93-6.83 (m, 2H, C_{arom}-**H**), 6.66 (d, *J* = 7.5 Hz, 1H, NC**H**=CH), 5.10 (dd, *J* = 7.5, 6.0 Hz, 1H, NCH=C**H**), 4.39-4.26 (m, 2H, OC**H**$_2$CH$_3$), 3.79 (s, 3H, OC**H**$_3$), 3.54 (q, *J* = 5.9 Hz, 1H, C**H**), 1.49- 1.21 (m, 9H, OCH$_2$C**H**$_3$ + 3 x C_{chain}**H**$_2$), 0.87 (t, *J* = 6.8 Hz, 3H, C**H**$_3$).

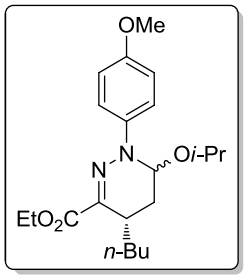
^{13}C-NMR (δ, ppm): 165.1 (**C**O), 156.4 (**C**$_{arom}$-OCH$_3$), 138.4 (**C**=N), 134.5 (**C**$_{arom}$-NH), 126.4 (N**C**H=CH), 118.4 (**C**$_{arom}$-H), 114.4 (**C**$_{arom}$-H), 105.0 (NCH=**C**H), 61.2 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 35.3 (**C**H), 30.4 (**C**$_{chain}$H$_2$), 27.0 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$).

IR (neat) cm^{-1}: 1700 (**C**O), 1546 (C=N).

MS (EI) m/z (relative abundance): 316 (9), 285 (5), 259 (100), 231 (19), 171 (8), 77 (4).

HRMS: Calculated for $[C_{18}H_{25}N_2O_3]^+$: 317.1865 $[M+H]^+$; found: 317.1866.

(4*S*)-Ethyl 4-butyl-6-isopropoxy-1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (47a)



To a solution of aldehyde **43a** (83 mg, 0.25 mmol) in *i*-PrOH (2.0 mL) was added ammonium chloride (13 mg, 0.25 mmol) at 0 ºC and the reaction mixture was stirred at this temperature for 5 hours. The mixture was diluted with H_2O (6.0 mL), the organic layer was separated and aqueous phase extracted with CH_2Cl_2 (3 x 10.0 mL). The collected organic fractions were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residual material was purified by flash chromatography (*n*-hexane/EtOAc gradient from 19:1 to 9:1) yielding the corresponding product **47a** (89 mg, 0.23 mmol) as a yellow oil.

Yield: 95%.

dr: 50:50.

ee: d_1: 92%; d_2: 92%.

HPLC: d_1: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 12.74 min, τ_{minor} = 11.87 min; d_2: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 93:7, flow rate 1.0 mL/min. τ_{major} = 5.41 min, τ_{minor} = 5.99 min.

$[\alpha]_D^{20}$: d_1: +146.3 (c = 1.0, CH_2Cl_2); d_2: + 24.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): d_1: 7.29-7.19 (m, 2H, C_{arom}-**H**), 6.94-6.77 (m, 2H, C_{arom}-**H**), 5.26 (s, 1H, C**H**OCH$(CH_3)_2$), 4.29 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.70-3.58 (m, 1H, OC**H**$(CH_3)_2$), 2.96-2.79 (m, 1H, C**H**), 2.31-2.18 (m,

1H, C**H**$_a$H$_b$), 2.00-1.83 (m, 1H, C$_{chain}$**H**$_a$H$_b$), 1.73 (td, *J* = 13.1, 2.6 Hz, 1H, CH$_a$**H**$_b$), 1.61-1.46 (m, 1H, C$_{chain}$H$_a$**H**$_b$), 1.41-1.21 (m, 7H, OCH$_2$C**H**$_3$ + 2 x C$_{chain}$**H**$_2$), 1.10 (d, *J* = 6.1 Hz, 3H, OCH(C**H**$_3$)$_2$), 1.01 (d, *J* = 6.1 Hz, 3H, OCH(C**H**$_3$)$_2$), 0.90 (t, *J* = 6.5 Hz, 3H, C**H**$_3$); d$_2$: 7.41-7.16 (m, 2H, C$_{arom}$-**H**), 6.96-6.75 (m, 2H, C$_{arom}$-**H**), 5.28 (s, 1H, C**H**OCH(CH$_3$)$_2$), 4.29 (q, *J* = 7.4 Hz, 2H, OC**H**$_2$CH$_3$), 3.79 (s, 3H, OC**H**$_3$), 3.79-3.71 (m, 1H, OC**H**(CH$_3$)$_2$), 2.89-2.64 (m, 1H, C**H**), 2.40-2.31 (m, 1H, C**H**$_a$H$_b$), 1.93-1.80 (m, 1H, C$_{chain}$**H**$_a$H$_b$), 1.77-1.66 (m, 2H, CH$_a$**H**$_b$ + C$_{chain}$H$_a$**H**$_b$), 1.53-1.27 (m, 7H, OCH$_2$C**H**$_3$ + 2 x C$_{chain}$**H**$_2$), 1.14 (d, *J* = 6.1 Hz, 3H, OCH(C**H**$_3$)$_2$), 1.08 (d, *J* = 6.8 Hz, 3H, OCH(C**H**$_3$)$_2$), 0.92 (t, *J* = 7.0 Hz, 3H, C**H**$_3$).

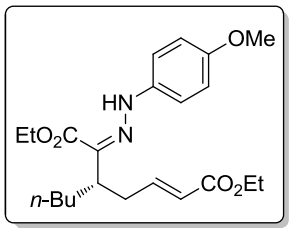
^{13}C-NMR (δ, ppm): d$_1$:164.6 (**C**O), 155.6 (**C**$_{arom}$-OCH$_3$), 140.4 (**C**=N), 139.4 (**C**$_{arom}$-NH), 119.2 (**C**$_{arom}$-H), 114.2 (**C**$_{arom}$-H), 79.7 (**C**HOCH(CH$_3$)$_2$), 69.1 (O**C**H(CH$_3$)$_2$), 60.6 (O**C**H$_2$CH$_3$), 55.5 (O**C**H$_3$), 31.0 (**C**H$_2$), 30.9 (**C**$_{chain}$H$_2$), 28.6 (**C**H$_2$), 27.8 (**C**$_{chain}$H$_2$), 22.8 (OCH(**C**H$_3$)$_2$), 22.8 (OCH(**C**H$_3$)$_2$), 22.7 (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$); d$_2$: 165.2 (**C**O), 155.7 (**C**$_{arom}$-OCH$_3$), 140.5 (**C**=N), 137.3 (**C**$_{arom}$-NH), 119.2 (**C**$_{arom}$-H), 114.2 (**C**$_{arom}$-H), 79.3 (**C**HOCH(CH$_3$)$_2$), 69.0 (O**C**H(CH$_3$)$_2$), 60.7 (O**C**H$_2$CH$_3$), 55.5 (O**C**H$_3$), 30.5 (**C**H$_2$), 29.2 (**C**$_{chain}$H$_2$), 28.1 (**C**H$_2$), 24.9 (**C**$_{chain}$H$_2$), 22.6 (OCH(**C**H$_3$)$_2$), 22.5 (**C**$_{chain}$H$_2$), 22.3 (OCH(**C**H$_3$)$_2$), 14.4 (OCH$_2$**C**H$_3$), 14.1 (**C**H$_3$).

IR (neat) cm^{-1}: d$_1$:1700 (**C**O), 1547 (C=N); d$_2$:1701 (**C**O), 1546 (C=N).

MS (EI) m/z (relative abundance): d$_1$: 377 (4), 376 (7), 317 (79), 316 (62), 272 (19), 271 (100), 259 (85); d$_2$: 377 (5), 376 (8), 317 (73), 316 (61), 272 (19), 271 (100), 259 (88).

HRMS: Calculated for [C$_{21}$H$_{33}$N$_2$O$_4$]$^+$: 377.2440 [M+H]$^+$; d$_1$ found: 377.2422; d$_2$ found: 377.2413.

(*S*,2*E*,6*Z*)-Diethyl 5-butyl-6-(2-(4-methoxyphenyl)hydrazono)hept-2-enedioate (48a)



To a solution of the aldehyde **43a** (148 mg, 0.44 mmol) in CH_2Cl_2 (3.0 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (200 mg, 0.58 mmol) and the reaction was stirred at room temperature for 4 hours. Once the reaction was complete, TFA (0.2 mL, 2.22 mmol) was added and the reaction was allowed to stir at this temperature until completion (~10 minutes). The mixture was diluted with H_2O (6.0 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10.0 mL) and the collected organic fractions were combined, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The residual material was purified by flash chromatography (*n*-hexane/EtOAc gradient from 19:1 to 9:1), yielding the corresponding product **48a** (130 mg, 0.32 mmol) as a yellow oil.

Yield: 73%.

ee: 90%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 7.54 min, τ_{minor} = 6.62 min.

$[\alpha]_D^{20}$: +142.9 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.13 (s, 1H, N**H**), 7.16-7.05 (m, 2H, C_{arom}-**H**), 6.97 (dt, *J* = 15.3, 7.3 Hz, 1H, C**H**=CHCO$_2$CH$_2$CH$_3$), 6.90-6.82 (m, 2H, C_{arom}-**H**), 5.81 (d, *J* = 15.3 Hz, 1H, CH=C**H**CO$_2$CH$_2$CH$_3$), 4.26 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 4.15

(q, J = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.11-2.88 (m, 1H, C**H**), 2.67-2.50 (m, 1H, C**H**$_a$H$_b$), 2.47-2.33 (m, 1H, CH$_a$**H**$_b$), 1.77-1.62 (m, 1H, C$_{chain}$**H**$_a$H$_b$), 1.60-1.41 (m, 1H, C$_{chain}$H$_a$**H**$_b$), 1.35 (t, J = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.31-1.18 (m, 7H, OCH$_2$C**H**$_3$ + 2 x C$_{chain}$H$_2$), 0.87 (t, J = 6.8 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 166.6 (**C**O), 163.8 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 148.1 (**C**H=CHCO$_2$CH$_2$CH$_3$), 137.6 (**C**=N), 128.3 (**C**$_{arom}$-NH), 122.3 (CH=**C**HCO$_2$CH$_2$CH$_3$), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 60.1 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 39.9 (**C**H), 37.0 (**C**H$_2$), 34.0 (**C**$_{chain}$H$_2$), 29.3 (**C**$_{chain}$H$_2$), 22.8 (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$), 14.0 (**C**H$_3$).

IR (neat) cm^{-1}: 1700 (**C**O), 1538 (C=N).

MS (EI) m/z (relative abundance): 405 (100), 404 (80), 359 (13), 291 (28), 123 (25), 122 (30).

HRMS: Calculated for [C$_{22}$H$_{33}$N$_2$O$_3$]$^+$: 405.2389 [M+H]$^+$; found: 405.2374.

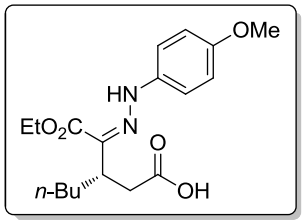
5.4 Oxidation of the aldehydes: synthesis of γ-hydrazono carboxylic acids 49a-t and 52p-r.

General procedure:

A solution of aldehyde **43** (1.00 mmol) in 2-methyl-2-butene (1.0 mL), *tert*-butanol (4.0 mL) and H$_2$O (2.0 mL) was cooled down to 4ºC prior to the addition of KH$_2$PO$_4$, (136 mg, 1.00 mmol) and NaClO$_2$ (113 mg, 1.00 mmol). The reaction was allowed to stir at this temperature until completion (~2 hours). The mixture was diluted with H$_2$O (10.0 mL) and the organic layer separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20.0 mL) and the combined organic layers were washed

with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography (FC).

(*S*,*Z*)-3-[2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]heptanoic acid (49a)



Following the general procedure, **49a** (192 mg, 0.55 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43a** (200 mg, 0.60 mmol), 2-methyl-2-butene (0.6 mL), *tert*-butanol (2.4 mL), H_2O (1.2 mL), KH_2PO_4 (83 mg, 0.60 mmol) and $NaClO_2$ (68 mg, 0.60 mmol).

Yield: 91%.

ee: 92%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 3.99 min, τ_{minor} = 7.19 min.

$[\alpha]_D^{20}$: +22.8 (c = 2.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.07 (s, 1H, N**H**), 7.10 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.86 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.35-4.18 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.78 (s, 3H, $OC\mathbf{H}_3$), 3.36-3.27 (m, 1H, C**H**), 2.79 (dd, *J* = 16.0, 8.9 Hz, 1H, $C\mathbf{H}_aH_b$), 2.53 (dd, *J* = 16.0, 6.0 Hz, 1H, $CH_a\mathbf{H}_b$), 1.75-1.59 (m, 1H, $C_{chain}\mathbf{H}_aH_b$), 1.56-1.40 (m, 1H, $C_{chain}H_a\mathbf{H}_b$), 1.40-1.23 (m, 7H, $OCH_2C\mathbf{H}_3$ + 2 x $C_{chain}\mathbf{H}_2$), 0.87 (t, *J* = 6.7 Hz, 3H, $C\mathbf{H}_3$).

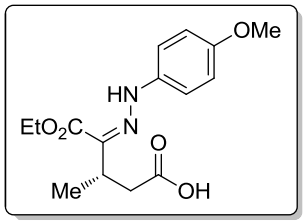
^{13}C-NMR (δ, ppm): 179.0 (**C**OOH), 163.7 (**C**O), 155.0 ($\mathbf{C}_{arom}$-OCH_3), 137.6 (**C**=N), 128.3 ($\mathbf{C}_{arom}$-NH), 114.8 ($\mathbf{C}_{arom}$-H), 114.7 ($\mathbf{C}_{arom}$-H), 60.5 ($O\mathbf{C}H_2CH_3$), 55.6 ($O\mathbf{C}H_3$), 37.8 ($\mathbf{C}H_2$), 36.9 (**C**H), 34.1 ($\mathbf{C}_{chain}H_2$), 29.0 ($\mathbf{C}_{chain}H_2$), 22.7 ($\mathbf{C}_{chain}H_2$), 14.1 ($OCH_2\mathbf{C}H_3$), 14.0 ($\mathbf{C}H_3$).

IR (neat) cm^{-1}: 3255 (OH), 1705 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 332 (100), 229 (11), 201 (12), 121 (78).

HRMS: Calculated for $[C_{18}H_{27}N_2O_5]^+$: 351.1920 $[M+H]^+$; found: 351.1916.

(*S*,*Z*)-3-[2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]heptanoic acid (49b)



Following the general procedure, **49b** (180 mg, 0.58 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43b** (200 mg, 0.68 mmol), 2-methyl-2-butene (0.7 mL), *tert*-butanol (2.8 mL), H_2O (1.4 mL), KH_2PO_4 (92 mg, 0.68 mmol) and $NaClO_2$ (77 mg, 0.68 mmol).

Yield: 86%.

ee: 92%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.75 min, τ_{minor} = 9.15 min.

$[\alpha]_D^{20}$: +72.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.02 (s, 1H, N**H**), 7.09 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.41-4.19 (m, 2H, OC**H**$_2$CH$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.42-3.33 (m, 1H, C**H**), 2.83 (dd, *J* = 16.0, 7.8 Hz, 1H, C**H**$_a$H$_b$), 2.48 (dd, *J* = 16.0, 7.0 Hz, 1H, CH$_a$**H**$_b$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.20 (d, *J* = 6.8 Hz, 3H, C**H**$_3$).

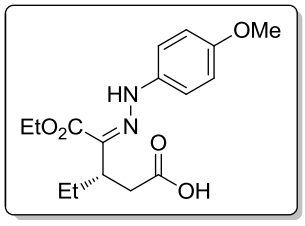
^{13}C-NMR (δ, ppm): 178.7 (**C**OOH), 163.4 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.5 (**C**=N), 129.0 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.6 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 39.3 (**C**H$_2$), 32.4 (**C**H), 19.8 (**C**H$_3$), 14.2 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3259 (OH), 1706 (CO), 1674 (CO), 1545 (C=N).

MS (EI) m/z (relative abundance): 290 (100), 163 (14), 149 (15), 134 (12), 122 (50), 121 (92), 107 (24).

HRMS: Calculated for $[C_{15}H_{21}N_2O_5]^+$: 309.1450 $[M+H]^+$; found: 309.1436.

(*S*,*Z*)-5-Ethoxy-3-ethyl-4-[2-(4-methoxyphenyl)hydrazono]-5-oxopentanoic acid (49c)



Following the general procedure, **49c** (208 mg, 0.64 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43c** (245 mg, 0.80 mmol), 2-methyl-2-butene (0.8 mL), *tert*-butanol (3.2 mL), H_2O (1.6 mL), KH_2PO_4 (109 mg, 0.80 mmol) and $NaClO_2$ (90 mg, 0.80 mmol).

Yield: 81%.

ee: 96%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.15 min, τ_{minor} = 7.29 min.

$[\alpha]_D^{20}$: +10.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.08 (s, 1H, N**H**), 7.09 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.36-4.17 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.32-3.23 (m, 1H, C**H**), 2.80 (dd, *J* = 16.0, 8.8 Hz, 1H, C**H**$_a$H$_b$), 2.54 (dd, *J* = 16.0, 6.1 Hz, 1H, CH$_a$**H**$_b$), 1.80-1.46 (m, 2H, C_{chain}**H**$_2$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 0.89 (t, *J* = 7.4 Hz, 3H, C**H**$_3$).

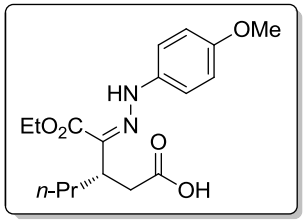
^{13}C-NMR (δ, ppm): 179.1 (**C**OOH), 163.7 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.6 (**C**=N), 128.0 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 38.3 (**C**H$_2$), 37.4 (**C**H), 27.1 (**C**$_{chain}$H$_2$), 14.2 (OCH$_2$**C**H$_3$), 11.2 (**C**H$_3$).

IR (neat) cm^{-1}: 3253 (OH), 1705 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 305 (16), 304 (100), 201 (11), 149 (12), 122 (46), 121 (79), 107 (16).

HRMS: Calculated for $[C_{16}H_{23}N_2O_5]^+$: 323.1607 $[M+H]^+$; found: 323.1608.

(*S*,*Z*)-3-[2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]hexanoic acid (49d)



Following the general procedure, **49d** (146 mg, 0.43 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43d** (165 mg, 0.51 mmol), 2-methyl-2-butene (0.5 mL), *tert*-butanol (2.0 mL), H_2O (1.0 mL), KH_2PO_4 (69 mg, 0.51 mmol) and $NaClO_2$ (57 mg, 0.51 mmol).

Yield: 85%.

ee: 91%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.23 min, τ_{minor} = 7.88 min.

$[\alpha]_D^{20}$: +6.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.07 (s, 1H, N**H**), 7.09 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.36-4.16 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.38-3.29 (m, 1H, C**H**), 2.79 (dd, *J* = 15.9, 8.9 Hz, 1H, C**H**$_a$H$_b$), 2.54 (dd, *J* = 15.9, 6.0 Hz, 1H, CH$_a$**H**$_b$), 1.70-1.59 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.56-1.39 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.39-1.23 (m, 5H, OCH$_2$C**H**$_3$ + C_{chain}**H**$_2$), 0.90 (t, *J* = 7.2 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm): 179.1 (**C**OOH), 163.7 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.6 (**C**=N), 128.3 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6

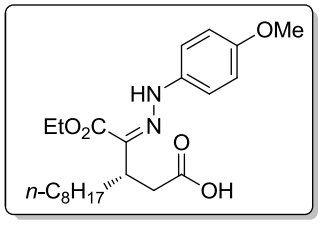
(O**C**H_3), 37.9 (**C**H_2), 36.7 (**C**H), 36.7 (**C**$_{chain}H_2$), 20.0 (**C**$_{chain}H_2$), 14.1 (OCH_2**C**H_3), 14.1 (**C**H_3).

IR (neat) cm^{-1}: 3250 (OH), 1705 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 318 (100), 229 (11), 201 (14), 149 (13), 122 (58), 121 (95), 107 (21).

HRMS: Calculated for $[C_{17}H_{25}N_2O_5]^+$: 337.1763 $[M+H]^+$; found: 337.1768.

(*S*,*Z*)-3-[2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]undecanoic acid (49e)



Following the general procedure, **49e** (224 mg, 0.55 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43e** (230 mg, 0.59 mmol), 2-methyl-2-butene (0.6 mL), *tert*-butanol (2.4 mL), H_2O (1.2 mL), KH_2PO_4 (80 mg, 0.59 mmol) and $NaClO_2$ (66 mg, 0.59 mmol).

Yield: 93%.

ee: 94%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.01 min, τ_{minor} = 6.83 min.

$[\alpha]_D^{20}$: +12.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.07 (s, 1H, N**H**), 7.09 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.38-4.15 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.36-3.27 (m, 1H, C**H**), 2.79 (dd, *J* = 16.0, 8.9 Hz, 1H, C**H**$_a$H$_b$), 2.54 (dd, *J* = 16.0, 6.0 Hz, 1H, CH$_a$**H**$_b$), 1.75-1.56 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.56-1.40 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.39-1.18 (m, 15H, OCH$_2$C**H**$_3$ + 6 x C_{chain}**H**$_2$), 0.87 (t, *J* = 6.6 Hz, 3H, C**H**$_3$).

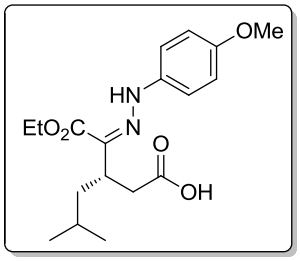
^{13}C-NMR (δ, ppm): 179.0 (**C**OOH), 163.7 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.6 (**C**=N), 128.3 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 37.9 (**C**H$_2$), 37.0 (**C**H), 34.4 (**C**$_{chain}$H$_2$), 31.9 (**C**$_{chain}$H$_2$), 29.6 (**C**$_{chain}$H$_2$), 29.5 (**C**$_{chain}$H$_2$), 29.3 (**C**$_{chain}$H$_2$), 26.9 (**C**$_{chain}$H$_2$), 22.6 (**C**$_{chain}$H$_2$), 14.2 (OCH$_2$**C**H$_3$), 14.1 (**C**H$_3$).

IR (neat) cm^{-1}: 3253 (OH), 1706 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 400 (2), 295 (73), 294 (71), 280 (21), 264 (100), 220 (12), 180 (6), 152 (13).

HRMS: Calculated for $[C_{22}H_{35}N_2O_5]^+$: 407.2546 $[M+H]^+$; found: 407.2538.

(*S*,*Z*)-3-[2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]-5-methylhexanoic acid (49f)



Following the general procedure, **49f** (165 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43f** (160 mg, 0.48 mmol), 2-methyl-2-butene (0.5 mL), *tert*-butanol (2.0 mL), H_2O (1.0 mL), KH_2PO_4 (65 mg, 0.48 mmol) and $NaClO_2$ (54 mg, 0.48 mmol).

Yield: 98%.

ee: 92%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 5.47 min, τ_{minor} = 10.86 min.

$[\alpha]_D^{20}$: +42.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.07 (s, 1H, N**H**), 7.09 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 4.38-4.15 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.46-3.31 (m, 1H, C**H**), 2.77 (dd, *J* = 15.9, 9.0 Hz, 1H, C**H**$_a$H$_b$), 2.52 (dd, *J* = 15.9, 5.7 Hz, 1H, CH$_a$**H**$_b$), 1.61-1.54 (m, 2H, C**H**$_2$CH(CH$_3$)$_2$), 1.40-1.11 (m, 4H, OCH$_2$C**H**$_3$ + CH$_2$C**H**(CH$_3$)$_2$), 0.91 (d, *J* = 5.9 Hz, 6H, CH$_2$CH(C**H**$_3$)$_2$).

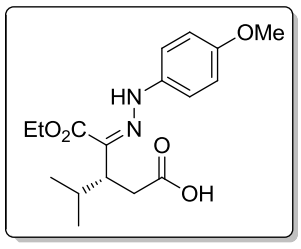
^{13}C-NMR (δ, ppm): 178.1 (**C**OOH), 163.7 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.5 (**C**=N), 128.5 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 44.1 (**C**H$_2$), 38.1 (**C**H$_2$CH(CH$_3$)$_2$), 35.2 (**C**H), 25.7 (CH$_2$**C**H(CH$_3$)$_2$), 22.8 (CH$_2$CH(**C**H$_3$)$_2$), 22.7 (CH$_2$CH(**C**H$_3$)$_2$), 14.1 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3260 (OH), 1707 (CO), 1677 (CO), 1545 (C=N).

MS (EI) m/z (relative abundance): 332 (100), 259 (4), 229 (10), 201 (12), 162 (8), 149 (10), 122 (43), 121 (64), 107 (13), 77 (7).

HRMS: Calculated for $[C_{18}H_{27}N_2O_5]^+$: 351.1920 $[M+H]^+$; found: 351.1926.

(*R*,*Z*)-5-Ethoxy-3-isopropyl-4-[2-(4-methoxyphenyl)hydrazono]-5-oxopentanoic acid (49g)



Following the general procedure, **49g** (108 mg, 0.32 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43g** (110 mg, 0.34 mmol), 2-methyl-2-butene (0.4 mL), *tert*-butanol (1.4 mL), H_2O (0.7 mL), KH_2PO_4 (46 mg, 0.34 mmol) and $NaClO_2$ (38 mg, 0.34 mmol).

Yield: 94%.

ee: 99%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 3.97 min, τ_{minor} = 6.24 min.

$[\alpha]_D^{20}$: +111.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.09 (s, 1H, N**H**), 7.08 (d, *J* = 9.4 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 9.4 Hz, 2H, C_{arom}-**H**), 4.35-4.17 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.32-3.19 (m, 1H, C**H**), 2.85 (dd, *J* = 16.2, 10.7 Hz, 1H, C**H**$_a$H$_b$), 2.52 (dd, *J* = 16.2, 4.4 Hz, 1H, CH$_a$**H**$_b$), 1.99-1.89 (m, 1H, C**H**(CH$_3$)$_2$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 0.94 (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.85 (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$).

^{13}C-NMR (δ, ppm): 179.3 (**C**OOH), 163.9 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.6 (**C**=N), 127.9 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6

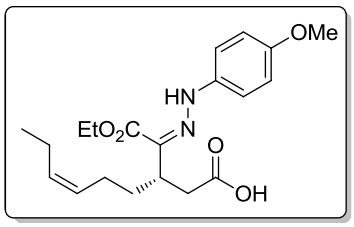
(O**C**H_3), 42.2 (**C**H), 33.9 (**C**H_2), 31.4 (**C**H(CH_3)$_2$), 20.4 (CH(**C**H_3)$_2$), 18.7 (CH(**C**H_3)$_2$), 14.1 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 3253 (OH), 1706 (CO), 1672 (CO), 1541 (C=N).

MS (EI) m/z (relative abundance): 318 (100), 229 (26), 201 (6), 149 (10), 121 (67), 107 (13).

HRMS: Calculated for $[C_{17}H_{25}N_2O_5]^+$: 337.1763 $[M+H]^+$; found: 337.1763.

(*S*,*Z*)-3-[(Z)-2-Ethoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]non-6-enoic acid (49h)



Following the general procedure, **49h** (198 mg, 0.53 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43h** (230 mg, 0.62 mmol), 2-methyl-2-butene (0.2 mL), *tert*-butanol (2.5 mL), H_2O (1.2 mL), KH_2PO_4 (84 mg, 0.62 mmol) and $NaClO_2$ (70 mg, 0.62 mmol).

Yield: 85%.

ee: 96%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.5 min, τ_{minor} = 7.20 min.

$[\alpha]_D^{20}$: +20.6 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.09 (s, 1H, N**H**), 7.09 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 5.45-5.23 (m, 2H, C**H**=C**H**), 4.38-4.18 (m, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.44-3.26 (m, 1H, C**H**), 2.79 (dd, *J* = 15.9, 8.8 Hz, 1H, C**H**$_a$H$_b$), 2.54 (dd, *J* = 15.9, 6.0 Hz, 1H, CH$_a$**H**$_b$), 2.08-1.93 (m, 4H, 2 x C_{chain}**H**$_2$), 1.80-1.69 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.60-1.48 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 0.91 (t, *J* = 7.5 Hz, 3H, C**H**$_3$).

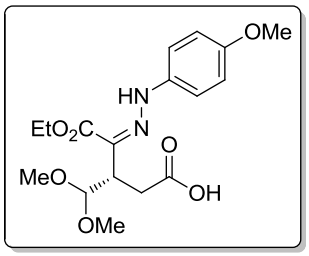
^{13}C-NMR (δ, ppm): 178.8 (**C**OOH), 163.6 (**C**O), 155.0 (**C**$_{arom}$-OCH$_3$), 137.5 (**C**=N), 132.1 (**C**H=CH), 128.4 (CH=**C**H), 127.9 (**C**$_{arom}$-NH), 114.8 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 37.8 (**C**H$_2$), 36.8 (**C**H), 34.2 (**C**$_{chain}$H$_2$), 24.5 (**C**$_{chain}$H$_2$), 20.5 (**C**$_{chain}$H$_2$), 14.3 (OCH$_2$**C**H$_3$), 14.1 (**C**H$_3$).

IR (neat) cm^{-1}: 3250 (OH), 1706 (CO), 1674 (CO), 1543 (C=N).

MS (EI) m/z (relative abundance): 358 (100), 329 (11), 275 (20), 247 (11), 203 (13), 149 (16), 122 (69), 107 (22).

HRMS: Calculated for $[C_{20}H_{28}N_2O_5]^+$: 377.2076 $[M+H]^+$; found: 377.2076.

(*S*,*Z*)-3-(Dimethoxymethyl)-5-ethoxy-4-[2-(4-methoxyphenyl)hydrazono]-5-oxopentanoic acid (49i)



Following the general procedure, **49i** (174 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43i** (220 mg, 0.62 mmol), 2-methyl-2-butene (0.2 mL), *tert*-butanol (2.5 mL), H_2O (1.2 mL), KH_2PO_4 (84 mg, 0.62 mmol) and $NaClO_2$ (70 mg, 0.62 mmol).

Yield: 76%.

ee: 94%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 12.67 min, τ_{minor} = 25.05 min.

$[\alpha]_D^{20}$: +42.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.11 (s, 1H, N**H**), 7.09 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.84 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.46 (d, *J* = 6.8 Hz, 1H, C**H**$(OCH_3)_2$), 4.33-4.22 (m, 2H, OC**H**$_2$CH$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.76-3.66 (m, 1H, C**H**), 3.35 (s, 3H, CH(OC**H**$_3$)(OCH$_3$)), 3.32 (s, 3H, CH(OCH$_3$)(OC**H**$_3$)), 2.83 (dd, *J* = 16.2, 9.1 Hz, 1H, C**H**$_a$H$_b$), 2.72 (dd, *J* = 16.2, 5.4 Hz, 1H, CH$_a$**H**$_b$), 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

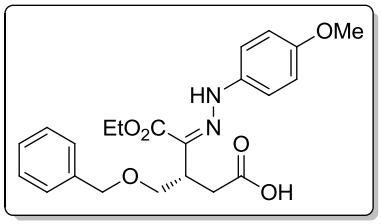
^{13}C-NMR (δ, ppm): 178.0 (**C**OOH), 163.6 (**C**O), 155.2 (**C**$_{arom}$-OCH$_3$), 137.3 (**C**=N), 125.0 (**C**$_{arom}$-NH), 114.9 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 106.7 (**C**H$(OCH_3)_2$), 60.7 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 54.5, 54.4 (CH(O**C**H$_3$)$_2$), 40.4 (**C**H$_2$), 33.9 (**C**H), 14.1 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3251 (OH), 1708 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 247 (31), 201 (30), 174 (8), 122 (100), 121(30).

HRMS: Calculated for $[C_{17}H_{25}N_2O_7]^+$: 309.1450 $[M+H]^+$; found: 309.1436.

(*S*,*Z*)-3-(Benzyloxymethyl)-5-ethoxy-4-[2-(4-methoxyphenyl)hydrazono]-5-oxopentanoic acid (49j)



Following the general procedure, **49j** (215 mg, 0.52 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43j** (250 mg, 0.63 mmol), 2-methyl-2-butene (0.7 mL), *tert*-butanol (2.5 mL), H_2O (1.3 mL), KH_2PO_4 (86 mg, 0.63 mmol) and $NaClO_2$ (71 mg, 0.63 mmol).

Yield: 82%.

ee: 96%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 5.89 min, τ_{minor} = 13.50 min.

$[\alpha]_D^{20}$: +17.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.14 (s, 1H, N**H**), 7.36-7.21 (m, 5H, C_{arom}-**H**), 7.08 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 4.52 (s, 2H, OC**H**$_2$Ph), 4.23 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.75-3.61 (m, 2H, C**H**$_2$OCH$_2$Ph), 3.49-3.42 (m, 1H, C**H**), 2.91-2.75 (m, 2H, C**H**$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 177.8 (**C**OOH), 163.4 (**C**O), 155.2 (**C**$_{arom}$-OCH$_3$), 138.2 (**C**=N), 137.3 (**C**$_{arom}$-CH$_2$), 128.3 (**C**$_{arom}$-H), 127.6 (**C**$_{arom}$-H), 127.5 (**C**$_{arom}$-NH), 125.1 (**C**$_{arom}$-H), 114.9 (**C**$_{arom}$-H), 114.7 (**C**$_{arom}$-H), 72.9 (O**C**H$_2$Ph), 72.3

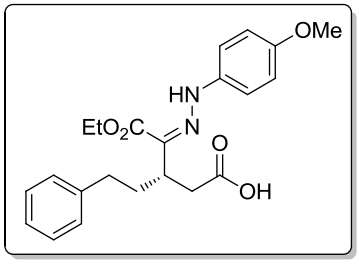
(**C**H_2OCH_2Ph), 60.6 (O**C**H_2CH_3), 55.6 (O**C**H_3), 37.8 (**C**H_2), 35.3 (**C**H), 14.1 (OCH_2**C**H_3).

IR (neat) cm^{-1}: 3253 (OH), 1706 (CO), 1674 (CO), 1543 (C=N).

MS (EI) m/z (relative abundance): 342 (100), 327 (22), 310 (6), 239 (15), 155 (10), 28 (37).

HRMS: Calculated for $[C_{22}H_{27}N_2O_6]^+$: 415.1869 $[M+H]^+$; found: 415.1881.

(*S*,*Z*)-5-Ethoxy-4-[2-(4-methoxyphenyl)hydrazono]-5-oxo-3-phenethylpentanoic acid (49k)



Following the general procedure, **49k** (155 mg, 0.39 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43k** (192 mg, 0.50 mmol), 2-methyl-2-butene (0.5 mL), *tert*-butanol (2.0 mL), H_2O (1.0 mL), KH_2PO_4 (68 mg, 0.50 mmol) and $NaClO_2$ (57 mg, 0.50 mmol).

Yield: 78%.

ee: 99%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 5.73 min, τ_{minor} = 10.27 min.

$[\alpha]_D^{20}$: -14.4 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.11 (s, 1H, N**H**), 7.26 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 7.19-7.10 (m, 5H, C_{arom}-**H**), 6.87 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.36-4.14 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.79 (s, 3H, $OC\mathbf{H}_3$), 3.48-3.29 (m, 1H, C**H**), 2.84 (dd, *J* = 15.9, 8.6 Hz, 1H, $C\mathbf{H}_aH_b$), 2.72-2.52 (m, 3H, $CH_a\mathbf{H}_b$ + $CH_2C\mathbf{H}_2Ph$), 2.11-1.99 (m, 1H, $C\mathbf{H}_aH_bCH_2Ph$), 1.92-1.80 (m, 1H, $CH_a\mathbf{H}_bCH_2Ph$), 1.32 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$).

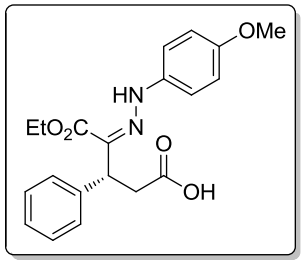
^{13}C-NMR (δ, ppm): 178.7 (**C**OOH), 163.6 (**C**O), 155.1 ($\mathbf{C}_{arom}$-OCH_3), 142.0 (**C**=N), 137.5 ($\mathbf{C}_{arom}$-CH_2), 128.4 ($\mathbf{C}_{arom}$-H), 128.3 ($\mathbf{C}_{arom}$-H), 127.7 ($\mathbf{C}_{arom}$-NH), 125.8 ($\mathbf{C}_{arom}$-H), 114.9 ($\mathbf{C}_{arom}$-H), 114.7 ($\mathbf{C}_{arom}$-H), 60.6 ($O\mathbf{C}H_2CH_3$), 55.6 ($O\mathbf{C}H_3$), 38.0 ($\mathbf{C}H_2$), 36.9 (**C**H), 35.9 ($CH_2\mathbf{C}H_2Ph$), 33.3 ($\mathbf{C}H_2CH_2Ph$), 14.2 ($OCH_2\mathbf{C}H_3$).

IR (neat) cm^{-1}: 3250 (OH), 1705 (CO), 1673 (CO), 1541 (C=N).

MS (EI) m/z (relative abundance): 241 (14), 149 (59), 123 (71), 108 (100), 80 (40).

HRMS: Calculated for $[C_{22}H_{25}N_2O_4]^+$: 381.1814 $[M+H]^+$; found: 381.1815.

(*R*,*Z*)-5-Ethoxy-4-[2-(4-methoxyphenyl)hydrazono]-5-oxo-3-phenylpentanoic acid (49l)



Following the general procedure, **49l** (60 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43l** (80 mg, 0.23 mmol), 2-methyl-2-butene (0.3 mL), *tert*-butanol (1.0 mL), H_2O (0.5 mL), KH_2PO_4 (31 mg, 0.23 mmol) and $NaClO_2$ (26 mg, 0.23 mmol).

Yield: 70%.

ee: 74%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 7.07 min, τ_{minor} = 18.46 min.

^{1}H-NMR (δ, ppm): 12.07 (s, 1H, N**H**), 7.35-7.11 (m, 7H, C_{arom}-**H**), 6.88 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 4.52 (dd, *J* = 9.9, 5.9 Hz, 1H, C**H**), 4.10 (q, *J* = 7.0 Hz, 2H, OC**H**$_2$CH$_3$), 3.80 (s, 3H, OC**H**$_3$), 3.23 (dd, *J* = 16.1, 9.9 Hz, 1H, C**H**$_a$H$_b$), 2.74 (dd, *J* = 16.1, 5.9 Hz, 1H, CH$_a$**H**$_b$), 1.14 (t, *J* = 7.0 Hz, 3H, OCH$_2$C**H**$_3$).

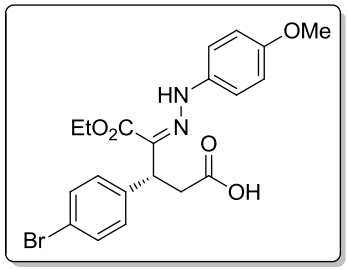
^{13}C-NMR (δ, ppm): 177.1 (**C**OOH), 163.2 (**C**O), 155.1 (**C**$_{arom}$-OCH$_3$), 142.1 (**C**=N), 137.5 (**C**$_{arom}$-CH$_2$), 128.4 (**C**$_{arom}$-H), 127.9 (**C**$_{arom}$-H), 127.1 (**C**$_{arom}$-NH), 126.7 (**C**$_{arom}$-H), 114.8 (**C**$_{arom}$-H), 114.8 (**C**$_{arom}$-H), 60.5 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 43.5 (**C**H), 39.1 (**C**H$_2$), 13.8 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3251 (OH), 1714 (CO), 1673 (CO), 1542 (C=N).

MS (EI) m/z (relative abundance): 314 (100), 155 (61), 139 (7), 105 (32), 91 (56), 77 (20), 28 (16).

HRMS: Calculated for $[C_{20}H_{23}N_2O_5]^+$: 371.1607 $[M+H]^+$; found: 371.1606.

(*R*,*Z*)-3-(4-Bromophenyl)-5-ethoxy-4-[2-(4-methoxyphenyl)hydrazono]-5-oxopentanoic acid (49m)



Following the general procedure, **49m** (213 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43m** (255 mg, 0.57 mmol), 2-methyl-2-butene (0.6 mL), *tert*-butanol (2.3 mL), H_2O (1.1 mL), KH_2PO_4 (78 mg, 0.57 mmol) and $NaClO_2$ (64 mg, 0.57 mmol).

Yield: 83%.

ee: 86%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 4.78 min, τ_{minor} = 16.63 min.

$[\alpha]_D^{20}$: -224.7 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.10 (s, 1H, N**H**), 7.38 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.16-7.11 (m, 4H, C_{arom}-**H**), 6.88 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 4.48 (dd, *J* = 9.3, 6.3 Hz, 1H, C**H**), 4.11 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.80 (s, 3H, OC**H**$_3$), 3.19 (dd, *J* = 16.5, 9.3 Hz, 1H, C**H**$_a$H$_b$), 2.72 (dd, *J* = 16.5, 6.3 Hz, 1H, CH$_a$**H**$_b$), 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm): 177.4 (**C**OOH), 163.1 (**C**O), 155.3 (**C**$_{arom}$-OCH$_3$), 141.2 (**C**=N), 137.3 (**C**$_{arom}$-CH$_2$), 131.5 (**C**$_{arom}$-Br), 129.7 (**C**$_{arom}$-H), 126.5 (**C**$_{arom}$-NH),

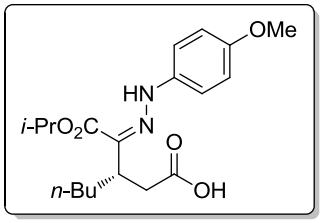
120.6 (**C**$_{arom}$-H), 114.9 (**C**$_{arom}$-H), 114.8 (**C**$_{arom}$-H), 60.7 (O**C**H$_2$CH$_3$), 55.6 (O**C**H$_3$), 42.9 (**C**H), 38.9 (**C**H$_2$), 13.9 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 3253 (OH), 1708 (CO), 1677 (CO), 1547 (C=N).

MS (EI) m/z (relative abundance): 352 (100), 309 (8), 225 (6), 149 (23), 121 (51), 107 (18), 103 (9), 77 (14).

HRMS: Calculated for $[C_{20}H_{22}N_2O_5Br]^+$: 449.0712 $[M+H]^+$; found: 449.0694.

(*S*,*Z*)-3-[2-*iso*-Propoxy-1-[2-(4-methoxyphenyl)hydrazono]-2-oxoethyl]heptanoic acid (49o)



Following the general procedure, **49o** (258 mg, 0.71 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43o** (270 mg, 0.78 mmol), 2-methyl-2-butene (0.8 mL), *tert*-butanol (3.2 mL), H_2O (1.6 mL), KH_2PO_4 (106 mg, 0.78 mmol) and $NaClO_2$ (88 mg, 0.78 mmol).

Yield: 91%.

ee: 94%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min. τ_{major} = 4.03 min, τ_{minor} = 5.46 min.

$[\alpha]_D^{20}$: +17.9 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.09 (s, 1H, N**H**), 7.09 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 6.85 (d, *J* = 8.9 Hz, 2H, C_{arom}-**H**), 5.16-5.08 (m, 1H, OC**H**$(CH_3)_2$), 3.78 (s, 3H, OC**H**$_3$), 3.39-3.22 (m, 1H, C**H**), 2.78 (dd, *J* = 15.9, 8.9 Hz, 1H, C**H**$_a$H$_b$), 2.53 (dd, *J* = 15.9, 5.9 Hz, 1H, CH$_a$**H**$_b$), 1.76-1.58 (m, 1H, C_{chain}**H**$_a$H$_b$), 1.57-1.40 (m, 1H, C_{chain}H$_a$**H**$_b$), 1.38-1.18 (m, 10H, OC**H**$(CH_3)_2$ + 2 x C_{chain}**H**$_2$), 0.87 (t, *J* = 6.5 Hz, 3H, C**H**$_3$).

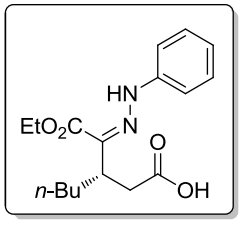
^{13}C-NMR (δ, ppm): 178.7 (**C**OOH), 163.3 (**C**O), 154.9 ($\mathbf{C}_{arom}$-OCH_3), 137.6 (**C**=N), 128.8 ($\mathbf{C}_{arom}$-NH), 114.7 ($\mathbf{C}_{arom}$-H), 114.7 ($\mathbf{C}_{arom}$-H), 68.3 (O**C**H$(CH_3)_2$), 55.6 (O**C**H$_3$), 37.9 (**C**H$_2$), 36.9 (**C**H), 34.1 ($\mathbf{C}_{chain}H_2$), 29.1 ($\mathbf{C}_{chain}H_2$), 22.7 ($\mathbf{C}_{chain}H_2$), 21.8 (OCH(**C**H$_3$)$_2$), 21.8 (OCH(**C**H$_3$)$_2$), 14.0 (**C**H$_3$).

IR (neat) cm^{-1}: 3246 (OH), 1708 (CO), 1670 (CO), 1543 (C=N).

MS (EI) m/z (relative abundance): 346 (100), 304 (8), 229 (12), 149 (13), 122 (48), 107 (12).

HRMS: Calculated for $[C_{19}H_{29}N_2O_5]^+$: 365.2076 $[M+H]^+$; found: 365.2093.

(*S*,*Z*)-3-[2-Ethoxy-2-oxo-1-(2-phenylhydrazono)ethyl]heptanoic acid (49t)



Following the general procedure, **49t** (58 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43t** (65 mg, 0.21 mmol), 2-methyl-2-butene (0.2 mL), *tert*-butanol (0.8 mL), H_2O (0.4 mL), KH_2PO_4 (29 mg, 0.21 mmol) and $NaClO_2$ (24 mg, 0.21 mmol).

Yield: 86%.

ee: 98%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min. τ_{major} = 3.54 min, τ_{minor} = 3.83 min.

$[\alpha]_D^{20}$: +48.3 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 12.08 (s, 1H, N**H**), 7.31-7.25 (m, 2H, C_{arom}-**H**), 7.15 (d, *J* = 7.6 Hz, 2H, C_{arom}-**H**), 6.94 (t, *J* = 7.3 Hz, 1H, C_{arom}-**H**), 4.40-4.17 (m, 2H, O**C**$\mathbf{H}_2$$CH_3$), 3.38-3.29 (m, 1H, C**H**), 2.81 (dd, *J* = 16.1, 9.0 Hz, 1H, C$\mathbf{H}_a$$H_b$), 2.55 (dd, *J* = 16.1, 5.9 Hz, 1H, $CH_a$$\mathbf{H}_b$), 1.79-1.58 (m, 1H, $C_{chain}$$\mathbf{H}_a$$H_b$), 1.56-1.41 (m, 1H, $C_{chain}$$H_a$$\mathbf{H}_b$), 1.39-1.21 (m, 7H, $OCH_2C\mathbf{H}_3$ + 2 x $C_{chain}$$\mathbf{H}_2$), 0.87 (t, *J* = 6.7 Hz, 3H, C$\mathbf{H}_3$).

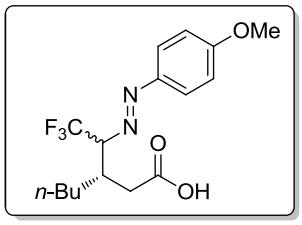
^{13}C-NMR (δ, ppm): 178.8 (**C**OOH), 163.5 (**C**O), 143.6 ($\mathbf{C}_{arom}$-CH), 129.7 ($\mathbf{C}_{arom}$-H), 129.3 ($\mathbf{C}_{arom}$-H), 121.8 ($\mathbf{C}_{arom}$-H), 113.7 ($\mathbf{C}_{arom}$-H), 60.7 (O**C**H_2CH_3), 37.7 (**C**H_2), 37.0 (**C**H), 34.0 ($\mathbf{C}_{chain}H_2$), 29.0 ($\mathbf{C}_{chain}H_2$), 22.7 ($\mathbf{C}_{chain}H_2$), 14.1 ($OCH_2\mathbf{C}H_3$), 14.0 (**C**H_3).

IR (neat) cm^{-1}: 3257 (OH), 1706 (CO), 1677 (CO), 1544 (C=N).

MS (EI) m/z (relative abundance): 302 (100), 274 (5), 245 (11), 229 (15), 199 (58), 171 (27), 132 (22), 91 (37), 77 (46).

HRMS: Calculated for $[C_{17}H_{25}N_2O_4]^+$: 321.1814 $[M+H]^+$; found: 321.1825.

(3*S*)-3-[2,2,2-Trifluoro-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl]heptanoic acid (52p)



Following the general procedure, **52p** (162 mg, 0.47 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43p** (190 mg, 0.58 mmol), 2-methyl-2-butene (0.6 mL), *tert*-butanol (2.3 mL), H_2O (1.2 mL), KH_2PO_4 (78 mg, 0.58 mmol) and $NaClO_2$ (65 mg, 0.58 mmol).

Yield: 81%.

dr: 90:10.

ee: 80% (calculated after esterification to **52p-ester**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 10.35 (bs, 1H, O**H**), 7.76 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 6.97 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 6.79* (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 4.26-4.04 (m, 1H, C**H**CF_3), 3.87 (s, 3H, OC**H**$_3$), 3.01 (dd, *J* = 16.8, 4.2 Hz, 1H, C**H**$_a$H$_b$), 2.91-2.78 (m, 1H, C**H**), 2.34 (dd, *J* = 16.8, 8.6 Hz, 1H, CH$_a$**H**$_b$), 1.41-1.28 (m, 6H, 3 x C_{chain}**H**$_2$), 0.90 (t, *J* = 6.2 Hz, 3H, C**H**$_3$), 0.76* (t, *J* = 6.2 Hz, 3H, C**H**$_3$).

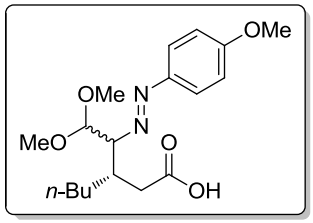
^{13}C-NMR (δ, ppm): 178.7 (**C**OOH), 162.7 (**C**$_{arom}$-N_2), 145.9 (**C**$_{arom}$-OCH_3), 125.0 (**C**$_{arom}$-H), 114.2 (**C**$_{arom}$-H), 78.0 (q, *J* = 24.8 Hz, **C**HCF_3), 55.6 (O**C**H$_3$), 35.0 (**C**H), 34.8 (**C**H$_2$), 31.2 (**C**$_{chain}$H$_2$), 28.6 (**C**$_{chain}$H$_2$), 22.4 (**C**$_{chain}$H$_2$), 13.8 (**C**H$_3$).

IR (neat) cm^{-1}: 2933 (OH), 1710 (CO), 1510 (N=N).

MS (EI) m/z (relative abundance): 328 (100), 243 (6), 162 (7), 149 (8), 122 (62), 107 (19), 92 (8), 77 (11).

HRMS: Calculated for $[C_{16}H_{20}N_2O_2F_3]^+$: 329.1477 $[M+H-H_2O]^+$; found: 329.1479.

(3*S*)-3-[2,2-Dimethoxy-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl]heptanoic acid (52q)



Following the general procedure, **52q** (27 mg, 0.08 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43q** (75 mg, 0.22 mmol), 2-methyl-2-butene (0.2 mL), *tert*-butanol (1.0 mL), H_2O (0.5 mL), KH_2PO_4 (30 mg, 0.22 mmol) and $NaClO_2$ (25 mg, 0.22 mmol).

Yield: 35%.

dr: 70:30.

ee: 70/92% (calculated after esterification to **52q-ester**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.70 (d, J = 8.8 Hz, 2H, C_{arom}-**H**), 6.94 (d, J = 8.8 Hz, 2H, C_{arom}-**H**), 5.13 (d, J = 7.4 Hz, 1H, C**H**$(OCH_3)_2$), 5.02* (d, J = 7.4 Hz, 1H, C**H**$(OCH_3)_2$), 3.92-3.80 (m, 4H, C**H**CH$(OCH_3)_2$ + O**C**H_3), 3.43* (s, 3H, CH(O**C**H_3)(OCH_3)), 3.42 (s, 3H, CH(O**C**H_3)(OCH_3)), 3.27 (s, 3H, CH(OCH_3)(O**C**H_3)), 2.98* (dd, J = 15.9, 4.5 Hz, 1H, CH_aH_b), 2.69-2.56 (m, 1H, C**H**), 2.50-2.26 (m, 2H, CH_aH_b), 1.86-1.72* (m, 6H, 3 x $C_{chain}H_2$), 1.46-1.17 (m, 6H, 3 x $C_{chain}H_2$), 0.91-0.81 (m, 3H, CH_3).

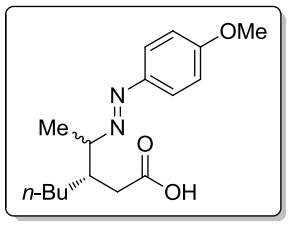
^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 179.3*, 178.7 (**C**OOH), 161.8*, 161.7 ($\mathbf{C}_{arom}$-N_2), 146.2 ($\mathbf{C}_{arom}$-OCH_3), 124.4*, 124.4 ($\mathbf{C}_{arom}$-H), 114.0 ($\mathbf{C}_{arom}$-H), 102.7*, 102.5 (**C**H$(OCH_3)_2$), 79.9, 79.1* (**C**HCH$(OCH_3)_2$), 55.5 (O**C**H_3), 53.9*, 53.4, 53.3*, 53.0 (CH(O**C**$H_3)_2$), 36.1, 35.9* (**C**H), 35.7, 35.6* (**C**H_2), 31.7, 29.6* ($\mathbf{C}_{chain}H_2$), 29.4, 28.7* ($\mathbf{C}_{chain}H_2$), 22.8, 22.6* ($\mathbf{C}_{chain}H_2$), 14.0 (**C**H_3).

IR (neat) cm^{-1}: 2931 (OH), 1705 (CO), 1514 (N=N).

MS (EI) m/z (relative abundance): 165 (100), 150 (61), 134 (32), 122 (12), 107 (8), 94 (14), 77 (12).

HRMS: Calculated for $[C_{18}H_{29}N_2O_5]^+$: 353.2076 $[M+H]^+$; found: 353.2060.

(3*S*)-3-[1-(*E*)-(4-Methoxyphenyldiazenyl]ethyl)heptanoic acid (52r)



Following the general procedure, **52r** (97 mg, 0.33 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 3:7) as a yellow oil, starting from aldehyde **43r** (125 mg, 0.45 mmol), 2-methyl-2-butene (0.5 mL), *tert*-butanol (1.8 mL), H_2O (0.9 mL), KH_2PO_4 (61 mg, 0.45 mmol) and $NaClO_2$ (51 mg, 0.45 mmol).

Yield: 73%.

dr: 60:40.

ee: 40/95% (calculated after esterification to **52r-ester**).

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.66 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 6.94 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 6.70* (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**),

3.91-3.66 (m, 4H, C**H**CH_3 + O$C\mathbf{H}_3$), 2.74-2.59 (m, 1H, $C\mathbf{H}_aH_b$), 2.50-2.32 (m, 2H, C**H** + $CH_a\mathbf{H}_b$), 1.61-1.19 (m, 9H, $CHC\mathbf{H}_3$ + 3 x $C_{chain}\mathbf{H}_2$), 0.88 (t, J = 6.7 Hz, 3H, $C\mathbf{H}_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 179.4 (**C**OOH), 161.6, 161.5* ($\mathbf{C}_{arom}$-N_2), 146.2*, 146.1 ($\mathbf{C}_{arom}$-OCH_3), 124.1 ($\mathbf{C}_{arom}$-H), 114.0 ($\mathbf{C}_{arom}$-H), 74.0, 73.9* (**C**HCH_3), 55.5 (O$\mathbf{C}H_3$), 39.9, 39.3* (**C**H), 35.7, 35.4* ($\mathbf{C}H_2$), 31.1, 30.8* ($\mathbf{C}_{chain}H_2$), 29.2*, 28.6 ($\mathbf{C}_{chain}H_2$), 22.8 ($\mathbf{C}_{chain}H_2$), 16.7 (CH**C**H_3), 14.6*, 14.0 (**C**H_3).

IR (neat) cm^{-1}: 2933 (OH), 1707 (CO), 1510 (N=N).

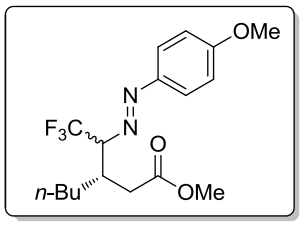
MS (EI) m/z (relative abundance): 274 (3), 247 (5), 155 (100), 109 (9), 43 (40).

HRMS: Calculated for $[C_{16}H_{25}N_2O_3]^+$: 293.3813 $[M+H]^+$; found: 293.3816.

General procedure for the esterification of acids **52p-r***:*

To a solution of acid **52** (0.50 mmol) in anhydrous THF (4.0 mL) were added trimethylsilyldiazomethane (1.0 mL, 2.00 mmol) and MeOH (1.0 mL) at 0 ºC. The reaction was allowed to stir at this temperature until completion (~15 min). The mixture was quenched with H_2O and diluted with CH_2Cl_2 for extraction. The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography (FC).

(3*S*)-Methyl 3-[2,2,2-trifluoro-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl] heptanoate (52p-ester)



Following the general procedure, **52p-ester** (122 mg, 0.34 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil, starting from acid **52p** (155 mg, 0.45 mmol), trimethylsilyldiazomethane (0.9 mL, 1.8 mmol), THF (3.6 mL) and MeOH (0.9 mL).

Yield: 75%.

dr: 90:10.

ee: 80%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min. τ_{major} = 5.76 min, τ_{minor} = 5.27 min.

^{1}H-NMR (δ, ppm): 7.76-7.72 (m, 2H, C_{arom}-**H**), 6.99-6.94 (m, 2H, C_{arom}-**H**), 4.17-4.02 (m, 1H, C**H**CF_3), 3.88 (s, 3H, OC**H**$_3$), 3.65 (s, 3H, CO_2C**H**$_3$), 2.99-2.76 (m, 2H, C**H**$_a$H$_b$ + C**H**), 2.29 (dd, *J* = 16.1, 8.4 Hz, 1H, CH$_a$**H**$_b$), 1.46-1.20 (m, 6H, 3 x C_{chain}**H**$_2$), 0.88 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

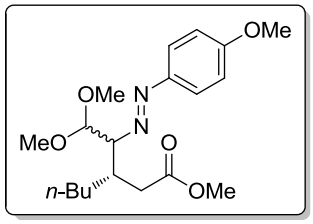
^{13}C-NMR (δ, ppm): 172.8 (**C**O), 162.6 (**C**$_{arom}$-N_2), 146.0 (**C**$_{arom}$-OCH_3), 124.9 (**C**$_{arom}$-H), 114.1 (**C**$_{arom}$-H), 78.1 (q, *J* = 24.7 Hz, **C**HCF_3), 55.6 (O**C**H$_3$), 51.6 (CO_2**C**H$_3$), 35.1 (**C**H), 35.0 (**C**H$_2$), 31.1 (**C**$_{chain}$H$_2$), 28.6 (**C**$_{chain}$H$_2$), 22.4 (**C**$_{chain}$H$_2$), 13.9 (**C**H$_3$).

IR (neat) cm^{-1}: 1740 (CO), 1510 (N=N).

MS (EI) m/z (relative abundance): 360 (4), 329 (10), 135 (81), 122 (9), 107 (100), 92 (20), 77 (31).

HRMS: Calculated for $[C_{17}H_{24}N_2O_3F_3]^+$: 361.1739 $[M+H]^+$; found: 361.1728.

(3*S*)-Methyl 3-[2,2-dimethoxy-1-(*E*)-(4-methoxyphenyldiazenyl)ethyl] heptanoate (52q-ester)



Following the general procedure, **52q-ester** (22 mg, 0.06 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil, starting from acid **52q** (27 mg, 0.08 mmol), trimethylsilyldiazomethane (160 μL, 0.32 mmol), THF (0.8 mL) and MeOH (0.2 mL).

Yield: 77%.

dr: 70:30.

ee: d_{major}: 70%; d_{minor}: 92%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 99:1, flow rate 0.6 mL/min. d_{major}: τ_{major} = 30.83 min, τ_{minor} = 27.21 min; d_{minor}: τ_{major} = 25.93 min, τ_{minor} = 28.70 min.

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.68 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 6.94 (d, *J* = 9.0 Hz, 2H, C_{arom}-**H**), 5.13 (d, *J* = 7.5 Hz, 1H, C**H**$(OCH_3)_2$), 5.02* (d, *J* = 7.5 Hz, 1H, C**H**$(OCH_3)_2$), 3.93-3.75 (m, 4H, C**H**CH$(OCH_3)_2$ + O**CH$_3$**), 3.66* (s, 3H, CO_2C**H$_3$**), 3.64 (s, 3H, CO_2C**H$_3$**), 3.41 (s, 3H,

CH(OC**H**$_3$)(OCH$_3$)), 3.26 (s, 3H, CH(OCH$_3$)(OC**H**$_3$)), 2.91* (dd, *J* = 15.6, 4.6 Hz, 1H, C**H**$_a$H$_b$), 2.69-2.55 (m, 1H, C**H**), 2.45-2.24 (m, 2H, C**H**$_a$**H**$_b$), 1.92-1.75* (m, 6H, 3 x C$_{chain}$**H**$_2$), 1.47-1.18 (m, 6H, 3 x C$_{chain}$**H**$_2$), 0.97-0.82 (m, 3H, C**H**$_3$).

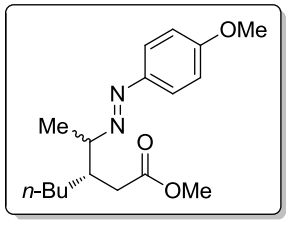
^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 173.9*, 173.4 (**C**OOH), 161.7*, 161.6 (**C**$_{arom}$-N$_2$), 146.3 (**C**$_{arom}$-OCH$_3$), 124.3 (**C**$_{arom}$-H), 113.9 (**C**$_{arom}$-H), 102.6*, 102.3 (**C**H(OCH$_3$)$_2$), 80.1, 79.2* (**C**HCH(OCH$_3$)$_2$), 55.5 (O**C**H$_3$), 53.8*, 53.4, 53.3*, 52.8 (CH(O**C**H$_3$)$_2$), 51.5*, 51.4 (C$_2$O**C**H$_3$), 36.4, 36.1* (**C**H), 35.8, 35.6* (**C**H$_2$), 31.6*, 29.6 (**C**$_{chain}$H$_2$), 29.5, 28.7* (**C**$_{chain}$H$_2$), 22.8, 22.6* (**C**$_{chain}$H$_2$), 14.0, 13.9* (**C**H$_3$).

IR (neat) cm^{-1}: 1735 (CO), 1513 (N=N).

MS (EI) m/z (relative abundance): 366 (2), 306 (11), 135 (96), 122 (11), 107 (100), 92 (10), 75 (58).

HRMS: Calculated for [C$_{19}$H$_{31}$N$_2$O$_5$]$^+$: 367.2233 [M+H]$^+$; found: 367.2249.

(3*S*)-Methyl 3-[1-(*E*)-(4-methoxyphenyldiazenyl)ethyl]heptanoate (52r-ester)



Following the general procedure, **52r-ester** (47 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a yellow oil, starting from acid **52r** (55 mg, 0.19 mmol), trimethylsilyldiazomethane (0.4 mL, 0.76 mmol), THF (1.9 mL) and MeOH (0.5 mL).

Yield: 80%.

dr: 60:40.

ee: 40/95%.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 99:1, flow rate 0.6 mL/min. d_{major}: τ_{major} = 15.50 min, τ_{minor} = 14.66 min; d_{minor}: τ_{major} = 13.92 min, τ_{minor} = 13.49 min.

^{1}H-NMR (δ, ppm; *denotes minor diastereoisomer): 7.65 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 6.93 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 3.91-3.68 (m, 4H, C**H**CH_3 + O**C**H_3), 3.65* (s, 3H, CO_2C**H**$_3$), 3.64 (s, 3H, CO_2C**H**$_3$), 2.76-2.58 (m, 1H, C**H**$_a$H$_b$), 2.51-2.34 (m, 2H, C**H** + CH_a**H**$_b$), 1.60-1.18 (m, 9H, CHC**H**$_3$ + 3 x C_{chain}**H**$_2$), 0.88 (t, *J* = 6.7 Hz, 3H, C**H**$_3$).

^{13}C-NMR (δ, ppm; *denotes minor diastereoisomer): 173.2 (**C**O), 161.5, 161.5* (C_{arom}-N_2), 146.1*, 146.0 (C_{arom}-OCH_3), 124.2 (C_{arom}-H), 114.1 (C_{arom}-H), 74.1, 73.9* (**C**HCH_3), 55.5 (O**C**H_3), 51.4*, 51.3 (C_2O**C**H_3), 39.9, 39.4* (**C**H), 35.7, 35.5* (**C**H_2), 31.0, 30.8* ($C_{chain}H_2$), 29.2*, 28.7 ($C_{chain}H_2$), 22.9 ($C_{chain}H_2$), 16.8 (CH**C**H_3), 14.4*, 14.1 (**C**H_3).

IR (neat) cm^{-1}: 1738 (CO), 1509 (N=N).

MS (EI) m/z (relative abundance): 306 (6), 275 (5), 171 (10), 135 (87), 107 (100).

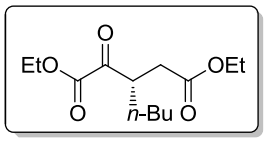
HRMS: Calculated for $[C_{17}H_{27}N_2O_3]^+$: 307.4079 $[M+H]^+$; found: 307.4080.

5.5 Transformation of γ-hydrazono carboxylic acids: access to α-keto-1,5-diesters 55a-h.

General procedure:

To a solution of hydrazone **49** (0.50 mmol) in an acetonitrile:H_2O mixture (6:1, 2.0 mL), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (0.60 mmol) was added at 0 ºC. The reaction was allowed to stir at room temperature until reaction completion (~30 min). The mixture was diluted with CH_2Cl_2 (5.0 mL), washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography to afford the cyclic azo-compounds **53**. Next, to a cooled solution (0 ºC) of the obtained azo-compound **53** in ethanol (4.0 mL) was added K_2CO_3 (0.50 mmol). The reaction mixture was allowed to stir at this temperature until completion (~30 min). After this time, a solution of saturated aqueous NH_4Cl (2.0 mL) was added to the reaction mixture. This solution was extracted with CH_2Cl_2 (5.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. This residual material (containing α-hydroxy azo-compound **54**) was then dissolved in chloroform (4.0 mL) and allowed to stir with a few drops of concentrated HCl overnight at 0 ºC. The reaction mixture was diluted with water (2.0 mL), the organic phase separated and aqueous phase extracted with CH_2Cl_2 (3 x 5.0 mL). Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residual material was charged onto silica gel and subjected to flash chromatography (FC) to afford **55**.

(*S*)-Diethyl 3-butyl-2-oxopentanedioate (55a)



Following the general procedure, **55a** (125 mg, 0.48 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a colourless oil, starting from acid **49a** (211 mg, 0.60 mmol), PIFA (310 mg, 0.72 mmol), MeCN (1.8 mL), H_2O (0.3 mL), K_2CO_3 (72 mg, 0.52 mmol) and EtOH (4.0 mL).

Yield: 81%.

ee: 92%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min. τ_{major} = 9.28 min, τ_{minor} = 7.83 min.

$[\alpha]_D^{20}$: -42.2 (c = 1.0, CH_2Cl_2).

^{1}H-NMR (δ, ppm): 4.32 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 4.07 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.71-3.57 (m, 1H, C**H**), 2.79 (dd, *J* = 17.0, 10.1 Hz, 1H, C**H**$_a$H$_b$), 2.51 (dd, *J* = 17.0, 4.6 Hz, 1H, CH$_a$**H**$_b$), 1.73-1.61 (m, 1H, C$_{chain}$**H**$_a$H$_b$), 1.49-1.15 (m, 11H, C$_{chain}$H$_a$**H**$_b$ + 2 x OCH$_2$C**H**$_3$+ 2 x C$_{chain}$**H**$_2$), 0.86 (t, *J* = 6.7 Hz, 3H, C**H**$_3$).

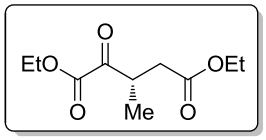
^{13}C-NMR (δ, ppm): 196.5 (**C**O), 171.9 (CO**C**O$_2$CH$_2$CH$_3$), 161.0 (**C**O$_2$CH$_2$CH$_3$), 62.4 (O**C**H$_2$CH$_3$), 60.9 (O**C**H$_2$CH$_3$), 42.9 (**C**H), 35.6 (**C**H$_2$), 30.6 (**C**$_{chain}$H$_2$), 28.9 (**C**$_{chain}$H$_2$), 22.5 (**C**$_{chain}$H$_2$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (OCH$_2$**C**H$_3$), 13.7 (**C**H$_3$).

IR (neat) cm^{-1}: 1725 (CO).

MS (EI) m/z (relative abundance): 213 (3), 185 (100), 157 (33), 129 (4), 111 (56), 83 (53), 69 (24), 55 (26), 41 (11), 29 (18).

HRMS: Calculated for $[C_{13}H_{23}O_5]^+$: 259.1545 $[M+H]^+$; found: 259.1558.

(*S*)-Diethyl 3-butyl-2-oxopentanedioate (55b)



Following the general procedure, **55b** (32 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a colourless oil, starting from acid **49b** (55 mg, 0.18 mmol), PIFA (94 mg, 0.22 mmol), MeCN (0.6 mL), H_2O (0.1 mL), K_2CO_3 (37 mg, 0.15 mmol) and EtOH (2.0 mL).

Yield: 83%.

ee: 86%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min. τ_{major} = 10.57 min, τ_{minor} = 9.02 min.

^{1}H-NMR (δ, ppm): 4.34 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 4.10 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.77-3.55 (m, 1H, C**H**), 2.81 (dd, *J* = 16.9, 8.8 Hz, 1H, C**H**$_a$H$_b$), 2.48 (dd, *J* = 16.9, 5.5 Hz, 1H, CH$_a$**H**$_b$), 1.37 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.26-1.16 (m, 6H, OCH$_2$C**H**$_3$ + C**H**$_3$).

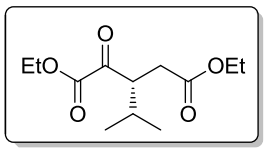
^{13}C-NMR (δ, ppm): 196.3 (**C**O), 171.6 (CO**C**O$_2$CH$_2$CH$_3$), 160.9 (**C**O$_2$CH$_2$CH$_3$), 62.4 (O**C**H$_2$CH$_3$), 60.9 (O**C**H$_2$CH$_3$), 38.3 (**C**H), 37.0 (**C**H$_2$), 15.9 (**C**H$_3$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 1725 (CO).

MS (EI) m/z (relative abundance): 171 (5), 143 (95), 115 (100), 87 (39), 73 (15), 43 (24), 29 (28).

HRMS: Calculated for $[C_{10}H_{17}O_5]^+$: 217.1076 $[M+H]^+$; found: 217.1077.

(*R*)-Diethyl 3-isopropyl-2-oxopentanedioate (55g)



Following the general procedure, **55g** (51 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a colourless oil, starting from acid **49g** (121 mg, 0.39 mmol), PIFA (201 mg, 0.39 mmol), MeCN (1.2 mL), H_2O (0.2 mL), K_2CO_3 (49 mg, 0.35 mmol) and EtOH (4.0 mL).

Yield: 74%.

ee: 99%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min. τ_{major} = 8.39 min, τ_{minor} = 7.27 min.

^{1}H-NMR (δ, ppm): 4.34 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 4.08 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.64 (ddd, *J* = 11.3, 5.7, 3.7 Hz, 1H, C**H**), 2.83 (dd, *J* = 17.2, 11.3 Hz, 1H, C**H**$_a$H$_b$), 2.51 (dd, *J* = 17.2, 3.7 Hz, 1H, CH$_a$**H**$_b$), 2.10-1.99 (m, 1H, C**H**(CH$_3$)$_2$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$), 0.99 (d, *J* = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.88 (d, *J* = 6.9 Hz, 3H, CH(C**H**$_3$)$_2$).

^{13}C-NMR (δ, ppm): 196.6 (**C**O), 172.4 (CO**C**O$_2$CH$_2$CH$_3$), 161.1 (**C**O$_2$CH$_2$CH$_3$), 62.4 (O**C**H$_2$CH$_3$), 60.9 (O**C**H$_2$CH$_3$), 48.3 (**C**H), 32.7 (**C**H$_2$), 29.4

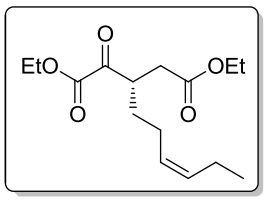
(**C**H(CH$_3$)$_2$), 20.6 (CH(**C**H$_3$)$_2$), 18.9 (CH(**C**H$_3$)$_2$), 14.1 (OCH$_2$**C**H$_3$), 14.0 (OCH$_2$**C**H$_3$).

IR (neat) cm^{-1}: 1728 (CO).

MS (EI) m/z (relative abundance): 199 (4), 171 (100), 143 (38), 115 (22), 97 (63), 69 (61), 55 (28), 41 (15), 29 (22).

HRMS: Calculated for $[C_{12}H_{21}O_5]^+$: 245.1389 $[M+H]^+$; found: 245.1400.

(*S,Z*)-Diethyl 3-(hex-3-en-1-yl)-2-oxopentanedioate (55h)



Following the general procedure, **55h** (88 mg, 0.31 mmol) was isolated by FC (*n*-hexane/EtOAc 9:1) as a colourless oil, starting from acid **49h** (165 mg, 0.44 mmol), PIFA (227 mg, 0.53 mmol), MeCN (1.4 mL), H_2O (0.2 mL), K_2CO_3 (46 mg, 0.33 mmol) and EtOH (4.0 mL).

Yield: 71%.

ee: 94%.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min. τ_{major} = 9.15 min, τ_{minor} = 7.93 min.

^{1}H-NMR (δ, ppm): 5.50-5.34 (m, 1H, C**H**=CH), 5.33-5.16 (m, 1H, CH=C**H**), 4.34 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 4.10 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.72-3.63 (m, 1H, C**H**), 2.82 (dd, *J* = 17.0, 10.0 Hz, 1H, C**H**$_a$H$_b$), 2.55 (dd, *J* = 17.0, 4.6 Hz, 1H, CH$_a$**H**$_b$), 2.10-1.93 (m, 4H, 2 x C$_{chain}$**H**$_2$), 1.87-1.66 (m,

1H, $C_{chain}\mathbf{H}_aH_b$), 1.56-1.44 (m, 1H, $C_{chain}H_a\mathbf{H}_b$), 1.38 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.22 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$), 0.94 (t, *J* = 7.5 Hz, 3H, $C\mathbf{H}_3$).

^{13}C-NMR (δ, ppm): 196.2 (**C**O), 171.8 (CO**C**$O_2CH_2CH_3$), 160.9 (**C**$O_2CH_2CH_3$), 133.3 (**C**H=CH), 127.2 (CH=**C**H), 62.4 (O**C**H_2CH_3), 60.9 (O**C**H_2CH_3), 42.7(**C**H), 35.6 (**C**H_2), 30.9 ($\mathbf{C}_{chain}H_2$), 24.5 ($\mathbf{C}_{chain}H_2$), 20.5 ($\mathbf{C}_{chain}H_2$), 14.2 ($OCH_2\mathbf{C}H_3$), 14.1 ($OCH_2\mathbf{C}H_3$), 14.0 (**C**H_3).

IR (neat) cm^{-1}: 1728 (CO).

MS (EI) m/z (relative abundance): 238 (2), 220 (14), 211 (16), 192 (29), 165 (100), 142 (23), 129 (21), 119 (22), 105 (25), 95 (28), 82 (29), 67 (43), 55 (31), 41 (31), 29 (28).

HRMS: Calculated for $[C_{15}H_{25}O_5]^+$: 285.1702 $[M+H]^+$; found: 285.1719.

Appendix

Abbreviations, acronyms and symbols

Å	Angstrom
Ac	Acetyl
ACDC	Asymmetric Counterion Directed Catalysis
AcOH	Acetic acid
anh.	Anhydrous
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
AU	Absorbance units
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	Broad signal
BSA	Benzeneseleninic anhydride
***i*-Bu**	*iso*-Butyl
***n*-Bu**	*n*-Butyl
***t*-Bu**	*tert*-Butyl
Bz	Benzoyl
c	Concentration (measured in g/100mL)
ºC	Degree Celsius
C.D.	Compact Disc
C_{arom}	Aromatic carbon
Cat.	Catalyst
Cbz	Benzoxycarbonyl
C_{chain}	Carbon from the side chain
cf.	*Confer* (compare)
CI	Chemical ionization
cm	Centimetres

Conc.	Concentration or concentrated
COSY	Correlation spectroscopy
CPMP	European Committee for Proprietary Medicinal Products
δ	Chemical shift
d	Doublet
D,L-Pro	D,L-Proline
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabycyclo[5.4.0]undec-5-ene
dd	Double of doublets
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
ΔG	Change in Gibbs free energy
DLD	Dihydrolipoamide dehydrogenase
dm	Decimetres
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPP	Diphenylphosphoric acid
dr	Diastereomeric ratio
E	Electrophile
e.g.	*Exempli gratia* (for example)
ed.	Edition
Ed.	Editor
EDG	Electron-donating group
ee	Enantiomeric excess
EI	Electron ionization
ent.	Enantiomer
equiv.	Equivalent
Et	Ethyl
et al.	*Et alii* (and others)

EtCN	Propionitrile
EtOAc	Ethyl acetate
EtOH	Ethanol
eV	Electron volt
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
g	Gram
GC	Gas chromatography
GSK	Glycogen synthase kinase
h	Hours
H_{arom}	Aromatic proton
H_{chain}	Proton from the side chain
hHK2	Hexokinase 2 inhibitor
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)
IBX	2-Iodoxybenzoic
IR	Infrared
J	Coupling constant
kcal	kilocalorie
Kras	Kirsten rat sarcoma viral oncogene homolog
LAH	Lithium aluminium hydride
L-Pro	L-Proline
LUMO	Lowest unoccupied molecular orbital
m	Multiplet or metres
M	Molar concentration
M.p.	Melting point
m/z	Mass-to-charge ratio

M^+	Molecular ion
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligrams
mGlu2R	Metabotropic glutamate 2 receptor
MHz	Megahertz
min	Minutes
mL	Millilitres
mm	Millimetres
mmol	Millimole
MMPP	Magnesium monoperoxyphthalate hexahydrate
MS	Mass spectrometry or Molecular sieves
MTBE	Methyl *tert*-butyl ether
MW	Microwave
N	Normal
n.d.	Not determined
n.O.e.	Nuclear Overhauser effect
NHC	*N*-Heterocyclic carbene
nm	Nanometres
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
Np	2-Naphthyl
Ns	*p*-Nitrobenzenesulfonyl
Nu	Nucleophile
OAc	Acetate
Obs.	Observed
PCC	Pyridinium chlorochromate
Ph	Phenyl
PIFA	bis-Trifluoroacetoxy iodobenzene
PMP	*p*-Methoxyphenyl

ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
***i*-Pr**	*iso*-Propyl
***n*-Pr**	*n*-Propyl
Prod.	Product
***i*-PrOH**	*iso*-Propanol
PTC	Phase-Transfer Catalysis
q	Quartet
QTOF	Quadrupole-time of flight
R	Alkyl group
r.t.	Room temperature
rac	Racemic
s	Singlet
SAMP	(*S*)-1-Amino-2-methoxymethylpyrrolidine
sat.	Aqueous saturated solution
SOMO	Single Occupied Molecular Orbital
t	Triplet or time
T	Temperature
TBA	Tetrabutylammonium
TBAF	Tetrabutylammoniun fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TDS	Dimethylthexylsilyl
TEA	Triethylamine
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
TS	Transition state
***p*-TsOH**	*p*-Toluenesulfonic acid
UPLC	Ultra performance liquid chromatography
vs.	Versus
X	Halogen
&	And
λ	Wavelength
μL	Microlitres
μM	Micromolar

Resumen extendido

En el trabajo de investigación recogido en la presente memoria se han estudiado una serie de estrategias que tienen como finalidad la síntesis asimétrica de compuestos de interés con elevado rendimiento y control estereoquímico. Éstas están enmarcadas en el uso de aminas secundarias quirales a modo de elementos estereocontroladores, donde el tipo de activación del sustrato de partida se basa en la formación de iones iminio como intermedios clave del ciclo catalítico. En este sentido, se ha demostrado que las hidrazidas e hidrazonas son dadores de Michael versátiles y eficientes, que pueden ser aplicados a reacciones de adición conjugada bajo este tipo de activación.

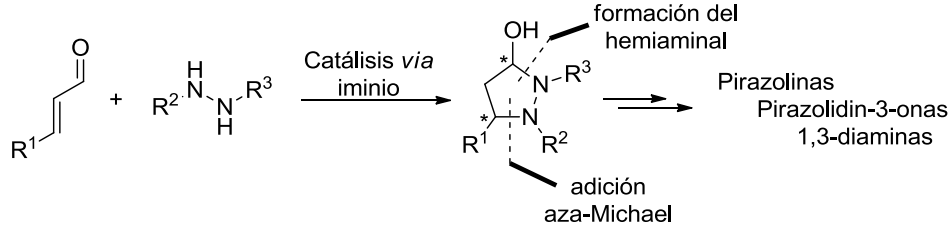
Las reacción de adición conjugada de nucleófilos a compuestos α,β-insaturados se encuentra entre una de las más empleadas para la formación de enlaces carbono-carbono o carbono-heteroátomo. En este contexto, las metodologías más empleadas para inducir estereocontrol han sido las basadas en auxiliares quirales o catalizadores quirales derivados de metales de transición. Sin embargo, la organocatálisis ha surgido recientemente como una alternativa a las reacciones catalizadas por metales. Estas reacciones de adición conjugada pueden ser catalizadas tanto por complejos metálicos como por una gran variedad de moléculas orgánicas de pequeño tamaño (organocatalizadores). Hay que destacar que las versiones catalíticas asimétricas de esta reacción empleando organocatalizadores quirales son de reciente desarrollo, aunque han evolucionado mucho en los últimos años. El desarrollo del concepto de activación *via* iminio, en el cual una amina secundaria quiral activa a un aldehído o cetona α,β-insaturado hacia la adición conjugada a través de la formación de un ion iminio intermedio, ha supuesto un

logro importante al permitir el empleo de aldehídos α,β-insaturados como aceptores Michael, ya que éstos no dan buenos resultados bajo condiciones de catálisis metálica.

En este contexto, y en conexión con los trabajos de nuestro grupo de investigación en el campo de la organocatálisis asimétrica, nos propusimos como objetivo del presente trabajo el empleo compuestos nitrogenados, en concreto hidrazidas e hidrazonas, como dadores de Michael para reacciones de adición conjugada sobre aldehídos α,β-insaturados, empleando la activación *via* iminio como estrategia catalítica. Así, para el presente trabajo se propusieron dos objetivos concretos: el primero de ellos pretendía desarrollar nuevas metodologías para llevar a cabo procesos en cascada iniciados por reacciones aza-Michael aminocatalizadas empleando hidrazidas e hidrazonas como pro-nucleófilos nitrogenados, mientras que en el segundo caso se diseñaría una metodología para la adición conjugada de equivalentes de aniones acilo a enales, explorando ahora la reactividad *umpolung* de las hidrazonas.

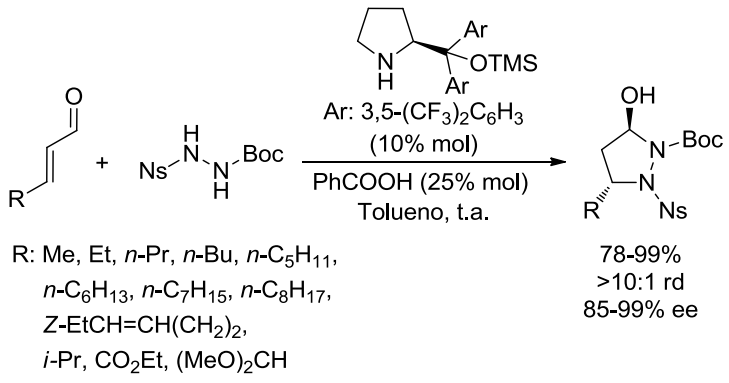
Así, tras un primer capítulo inicial en el que se presenta una introducción al campo de la organocatálisis, y más concretamente al de la aminocatálisis, el segundo capítulo de esta memoria recoge la evaluación de la aplicabilidad de hidrazidas e hidrazonas como nucleófilos nitrogenados. En este contexto, se han estudiado dos reacciones en cascada iniciadas por reacciones aza-Michael.

La primera de ellas, empleando hidrazidas y aldehídos α,β-insaturados para llevar a cabo un proceso aminocatalítico en cascada de reacción aza-Michael/hemiaminalización, nos proporciona una nueva metodología para la síntesis directa de pirazolidinas y derivados (Esquema 1).



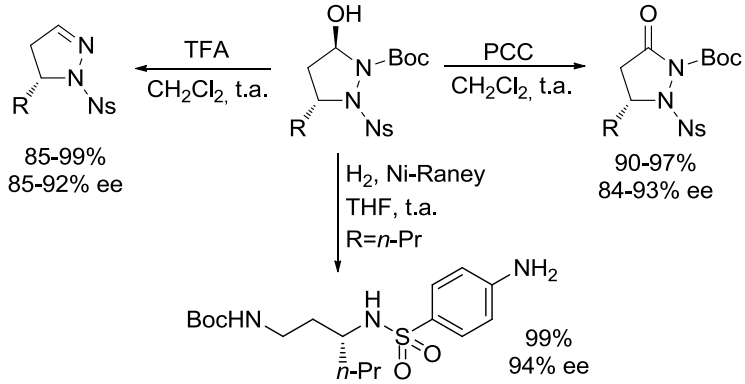
Esquema 1

Tras un proceso de optimización para identificar las mejores condiciones de reacción, del que se concluyó que la hidrazida *N*-Boc-*N'*-(*p*-nitrobenzenosulfonyl) disustituida era capaz de proporcionar la reactividad esperada de una manera eficiente, se extendió la metodología al empleo de enales con diferentes sustituciones en la posición β. Así, se obtuvo una serie de pirazolidin-3-oles con excelentes rendimientos, regio- y estereoselectividades (Esquema 2).



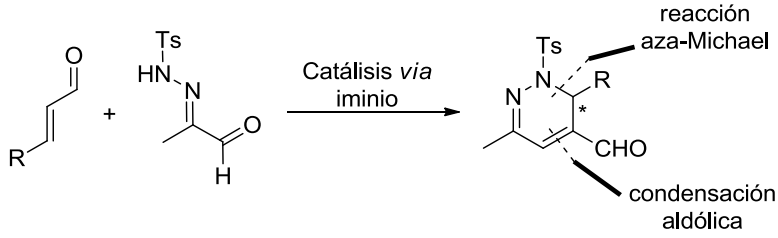
Esquema 2

Además, la versatilidad sintética de los aductos obtenidos ha permitido llevar a cabo una serie de derivatizaciones posteriores, pudiéndose destacar la síntesis de compuestos de interés, tales como las pirazolinas, pirazolidinonas y 1,3-diaminas, mediante procesos simples y eficientes (Esquema 3).



Esquema 3

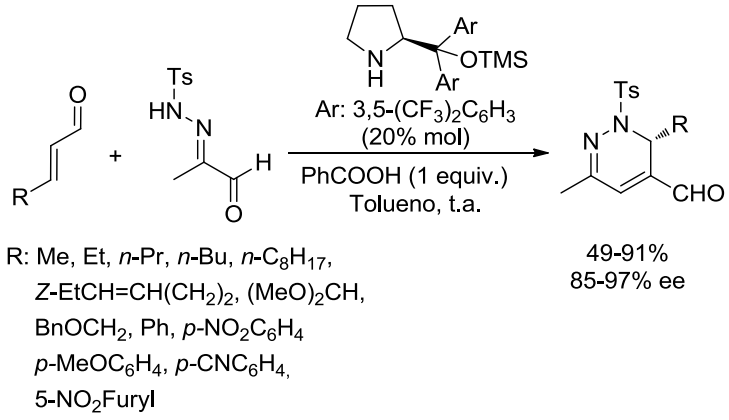
La segunda reacción desarrollada durante el segundo capítulo demuestra que hidrazonas adecuadamente funcionalizadas pueden ser empleadas en reacciones en cascada iniciadas por reacción aza-Michael. En concreto, se describe una reacción en cascada aza-Michael/condensación aldólica entre aldehídos α,β-insaturados y una hidrazona derivada del piruvaldehído, para dar lugar a la síntesis de dihidropiridazinas (Esquema 4).



Esquema 4

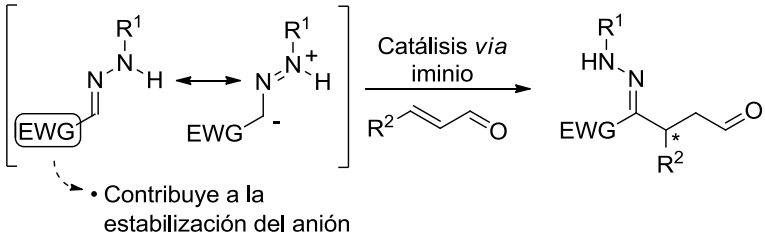
Del mismo modo que en el ejemplo anterior, tras el correspondiente proceso de optimización, pudo extenderse la metodología al empleo de una serie de aldehídos α,β-insaturados con diferentes sustituciones, en este caso, tanto alifáticas como aromáticas o funcionalizadas. Así, pudo sintetizarse una amplia serie de

dihidropiridazinas con muy buenos rendimientos, y excelentes enatioselectividades (ver Esquema 5).



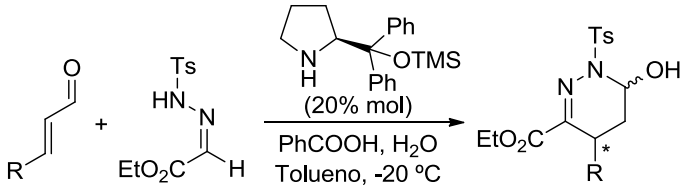
Esquema 5

En lo que al tercer capítulo de la memoria se refiere, en él se demuestra la capacidad de las hidrazonas para actuar como nucleófilos carbonados. En este sentido, se ha estudiado la reacción de adición conjugada de hidrazonas *N*-monosustituidas a diferentes enales bajo activación *via* iminio, observando que las hidrazonas que contienen un grupo electrón atractor en la posición azometínica son las más adecuadas para llevar a cabo este proceso (ver Esquema 6).



Esquema 6

En un primer lugar, se evaluó el empleo de hidrazonas *N*-tosyl sustituidas derivadas del glioxilato de etilo con enales, empleando aminas secundarias como catalizadores. Como podemos observar en el Esquema 7, ésta proporcionaba la reactividad esperada, dando lugar a la correspondiente adición conjugada inicial de la hidrazona por el carbono azometínico. Sin embargo, un posterior paso de hemiacetalización favorecido por la alta acidez del grupo N-H daba lugar a la formación de productos configuracionalmente inestables.

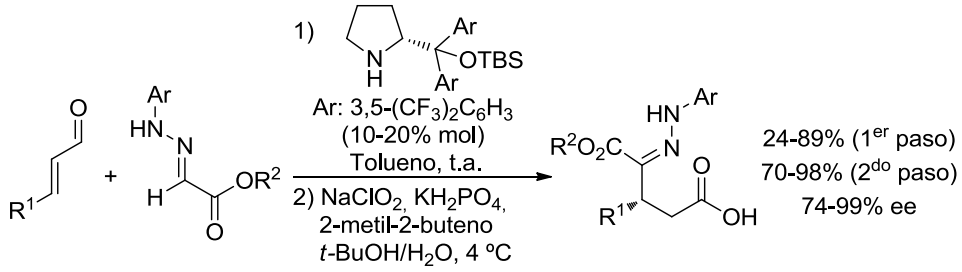


R: Me, Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *Z*-EtCH=CH$(CH_2)_2$, $(MeO)_2CH$, *p*-$NO_2C_6H_4$, *o*-$NO_2C_6H_4$

29-94%

Esquema 7

En un intento de solventar el problema surgido, se decidió emplear una hidrazona con un sustituyente electrón-donante, que proporcionase menos acidez y ayudase en la formación de la especie aza-enamínica reactiva. Así, cuando se utilizó una hidrazona *N*-(*p*-metoxifenil) sustituida pudimos obtener los correspondientes compuestos carbonílicos β-hidrazono sustituidos en muy buenos rendimientos y con excelentes enantioselectividades (Esquema 8).



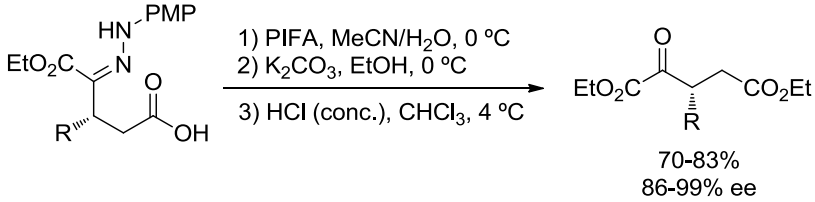
R^1: Me, Et, *n*-Pr, *n*-Bu, *n*-C_8H_{17}, *i*-Pr, *i*-Bu, *Z*-EtCH=CH$(CH_2)_2$, $(MeO)_2CH$, $BnOCH_2$, $PhCH_2CH_2$, Ph, *p*-BrC_6H_4

R^2: Et, *i*-Pr

Ar: *p*-MeOPh, Ph

Esquema 8

Finalmente, la actuación de estas hidrazonas como equivalentes sintéticos de aniones acilo se ha resaltado mediante la síntesis de compuestos 1,4-dicarbonílicos. Así, tras una ruptura oxidativa de las hidrazonas obtenidas, pudo obtenerse una serie de compuestos β-acil sustituidos en muy buenos rendimientos y manteniendo la enantioselectividad de los compuestos (Esquema 9).



Esquema 9

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

1. *"Organocatalytic Enantioselective Synthesis of Pyrazolidines, Pyrazolines and Pyrazolidinones"*.
Maitane Fernández, Efraím Reyes, Jose L. Vicario, Dolores Badía, Luisa Carrillo.
Adv. Synth. Catal. **2012***, 354,* 371.

2. *"Organocatalytic Enantioselective Synthesis of 2,3-Dihydropyridazines"*.
Maitane Fernández, Jose L. Vicario, Efraím Reyes, Luisa Carrillo, Dolores Badía.
Chem. Commun. **2012***, 48,* 2092.

3. *"Organocatalytic Enantioselective aza-Michael Reactions"*.
Efraím Reyes, Maitane Fernández, Uxue Uria, Jose L. Vicario, Dolores Badía, Luisa Carrillo.
Curr. Org. Chem. **2012**, *16*, 521.

4. *"Enantioselective Conjugate Addition of Donor-Acceptor Hydrazones to α,β-Unsaturated Aldehydes through formal Diaza-Ene Reaction. Access to 1,4-Dicarbonyl Compounds"*.
Maitane Fernández, Uxue Uria, Jose L. Vicario, Efraím Reyes, Luisa Carrillo.
J. Am. Chem. Soc. **2012**, *134*, 11872.

Papers

COMMUNICATIONS

DOI: 10.1002/adsc.201100722

Organocatalytic Enantioselective Synthesis of Pyrazolidines, Pyrazolines and Pyrazolidinones

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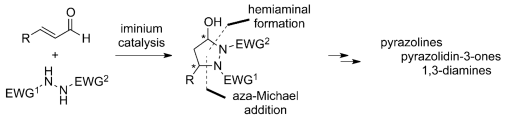
Abstract: Enantiopure pyrazolidines, pyrazolines and pyrazolidinones have been accessed in a direct and efficient manner through an organocatalytic, enantioselective aza-Michael/hemiaminal formation cascade process from enals and *N*,*N*′-disubstituted hydrazides. The process takes place with high regio- and stereoselectivities and furnishes the target compounds in high overall yields by means of an operationally very simple methodology.

Keywords: asymmetric catalysis; domino reaction; heterocycles; hydrazines; organocatalysis

Pyrazolidines are privileged heterocyclic structures in medicinal chemistry, principally due to their presence, as important subunits, in many natural and synthetic bioactive compounds.[1,2] Pyrazolidines can be easily oxidized to afford pyrazolines, which are also motifs of high relevance because of their presence in a wide range of biologically active molecules.[3] However, despite their interest and potential as promising candidates in drug discovery programs, the number of available synthetic procedures for the stereoselective preparation of pyrazolidines and/or pyrazolines is still very limited. Most of the methodologies reported rely on the use of chiral Lewis acids, involving typically [3+2]cycloaddition chemistry using dipoles such as diazoalkanes,[4] nitrile imines[5] or hydrazones,[6] or by means of metal-catalyzed amination of allenes.[7] Alternatively, one report addressed the access to these heterocycles in a stereocontrolled manner by cyclocondensation of chalcones with a primary hydrazine, also in the presence of chiral transition metal complexes as catalysts, although only moderate levels of enantioselectivity were obtained.[8]

In this context, organocatalysis has emerged as a useful alternative tool for the development of enantioselective versions of certain transformations which do not proceed efficiently with metal catalysis. The enantioselective synthesis of pyrazolines is a representative example of the complementary natures of these two different methodological approaches, with a couple of reports describing the access to these heterocycles under metal-free conditions. On the one hand, List and co-workers developed an enantioselective version of the Fischer reaction that proceeds through a 6π-electrocyclization mechanism in the presence of a chiral Brønsted acid catalyst, generating 5-substituted 3-methylpyrazolines by reacting methyl alkenyl ketones with primary hydrazines.[9] Excellent results were obtained for β-aryl-substituted enones, but the use of β-alkyl-substituted substrates led to an important reduction of both yield and enantioselectivity. Alternatively, cyclocondensation of enones with primary monosubstituted hydrazides has been reported by Brière and co-workers using chiral phase-transfer catalysis.[10] Although very efficient and straightforward, this later methodology was limited to the use of chalcones. It should also be highlighted that these two approaches rely on the use of enones as starting materials, thus generating pyrazolines containing an aryl or a methyl substituent at the 3-position. However, the use of α,β-unsaturated aldehydes in this transformation which would lead to enantioenriched pyrazolines without any substitution at this 3-position still remains elusive.

With these precedents in mind, we envisaged that pyrazolidin-3-ols could be accessible by the reaction between α,β-unsaturated aldehydes and *N*,*N*′-disubstituted hydrazines, by means of a cascade process consisting of an aza-Michael/hemiaminal formation sequence (Scheme 1). Moreover, this proposal presents a possibility for the development of an enantioselec-



Scheme 1. Direct organocatalytic enantioselective pyrazolidine synthesis through iminium activation.

tive version of the transformation, using organocatalysis as the methodological approach, *via* iminium activation.

These pyrazolidin-3-ols have the potential to be further elaborated in order to obtain an array of chemically related heterocyclic structures of interest, such as 3-unsubstituted pyrazolines. What is more, simple transformations of these adducts can also provide a direct access to chiral pyrazolidin-3-ones and 1,3-diamines, which are also important chiral building blocks in synthesis.

We thought that the design of the proposed reaction could show some selectivity issues due to the similar nucleophilic characters of both the catalyst and the hydrazine. The idea of using monosubstituted hydrazines was discarded from the beginning, since these would probably undergo either a condensation with the enal furnishing a highly stable hydrazone side product or, alternatively, they could undergo uncatalyzed cyclocondensation reactions, affording racemic pyrazoline adducts. In order to avoid these perceived condensation issues, *N,N′*-disubstituted hydrazines were selected for the transformation, although issues regarding selectivity towards 1,4-addition *vs.* undesired 1,2-addition to the enal have still to be considered. Moreover, for the cases in which the two substituents of the hydrazine are different, an additional regioselectivity issue appears. In addition, it is known that aza-Michael transformations are reversible in nature, which in turn results in the conjugate addition products very often being configurationally unstable. However, this reversibility problem was thought to be irrelevant to our case, since the subsequent intramolecular hemiaminal formation step would presumably make the overall process irreversible.

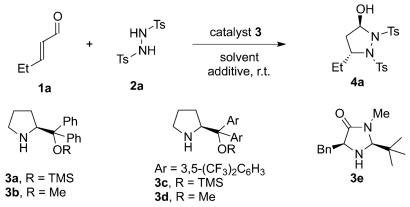
In an initial approach and in order to avoid the aforementioned regioselectivity problem related to the use of hydrazines with two different substituents, *N,N′*-bis(*p*-toluenesulfonyl)hydrazide (**2a**) was selected as model substrate, also considering that the high acidity of the N–H protons would favourably assist the first conjugate addition step (Table 1). The viability of the reaction was initially tested for different catalysts using toluene as solvent and working at room temperature. In this context, diphenylprolinol derivatives **3a** and **3b** delivered the desired product **4a** in high isolated yield and diastereoselectivity, although with low enantiocontrol (entries 1 and 2). In contrast, enantioselectivity was improved when the bulkier catalysts **3c** and **3d** were employed, although the yield was diminished (entries 3 and 4). Imidazolidinone **3e** developed by MacMillan was also tested, providing **4a** in good yield but low enantioselectivity (entry 5). Next, the effect of the solvent was studied in conjunction with optimal catalyst **3c** (entries 6–9), but it was observed that the use of more polar solvents resulted in a less efficient reaction. In an attempt to improve the yield of the transformation, we also surveyed the incorporation of a base as a co-catalyst, which was thought to activate the hydrazide by forming the corresponding anion. However, no reaction was observed when employing DABCO (entry 9) and, although DBU gave an improved yield of the pyrazolidin-3-ol, enantiocontrol was lost (entry 10).

Using the conditions shown in entry 3 of Table 1, we decided to investigate the influence that the substitution pattern of the hydrazide reagent would have on the reaction. In this context, a family of different *N,N′*-disubstituted hydrazides was tested in the reaction (Table 2). Initially, no reaction was observed when the less acidic hydrazide **2b** was used (entry 2), and low yields of the pyrazolidinol adduct were observed when phthalohydrazide **2c** was employed (entry 3). The need for two strongly electron-withdrawing substituents like the tosyl group was confirmed when hydrazides **2d** and **2e** were tested, for which no reaction was observed (entries 4 and 5). In contrast, the reaction between the enal **1a** and the unsymmetrically substituted *N*-Boc-*N′*-(*p*-nitrobenzenesulfonyl) hydrazide **2f** proceeded smoothly, providing the desired pyrazolidin-3-ol **4f** in excellent yield, enantioselectivity and remarkably as a single regioisomer (entry 6). The high reactivity and complete regioselectivity observed may be understood in terms of the higher acidity of the N–H group attached to the nosyl (Ns) substituent, which presumably makes this nitrogen group more nucleophilic for the initial aza-Michael process.

We next proceeded to extend the reaction to the use of α,β-unsaturated aldehydes with different substitution patterns in order to survey the scope of the reaction and its performance for the preparation of differently substituted pyrazolidin-3-ols (Table 3).

From the results summarized in Table 3 we observed that hydrazide **2f** reacted efficiently with α,β-unsaturated aldehydes containing linear alkyl chains

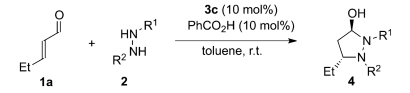
Table 1. Screening for the best reaction conditions.[a]



Entry	Solvent	**3**	Additive[b]	Yield of **4a** [%][c]	*dr*[d]	*ee* [%][e]
1	toluene	**3a**	$PhCO_2H$	83	>10:1	20
2	toluene	**3b**	$PhCO_2H$	80	>10:1	11
3	toluene	**3c**	$PhCO_2H$	54	>10:1	97
4	toluene	**3d**	$PhCO_2H$	30	>10:1	92
5	toluene	**3e**	TFA	67	10:1	45
6	CH_2Cl_2	**3c**	$PhCO_2H$	24	>10:1	38
7	CH_3CN	**3c**	$PhCO_2H$	38	>10:1	36
8	EtOH	**3c**	$PhCO_2H$	32	>10:1	39
9	toluene	**3c**	DABCO	<10	n.d.[f]	n.d.[f]
10	toluene	**3c**	DBU	61	>10:1	0

[a] Reactions performed on a 0.2-mmol scale of **1a** and **2a** using 10 mol% of catalyst **3** in 2.0 mL of the corresponding solvent.
[b] 10 mol% used.
[c] Isolated yield.
[d] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] Determined by HPLC on a chiral stationary phase.
[f] n.d.: not determined.

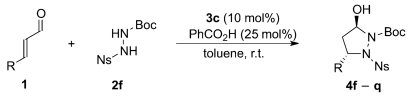
Table 2. Effect of hydrazide substitution.[a]



Entry	**2**	R^1	R^2	**4**	Yield [%][b]	*dr*[c]	*ee* [%][e]
1	**2a**	Ts	Ts	**4a**	54	>10:1	97
2	**2b**	Boc	Boc	**4b**	<5%	–	–
3	**2c**			**4c**	23	n.d.[f]	n.d.[f]
4	**2d**	*p*-MeO-C_6H_4	Ts	**4d**	<5%	–	–
5	**2e**	*p*-NO_2-C_6H_4	Ts	**4e**	<5%	–	–
6	**2f**	Boc	Ns	**4f**	87	>10:1	93

[a] Reactions performed on a 0.2-mmol scale of **1a** and **2**.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] Determined by HPLC on a chiral stationary phase.
[f] n.d.: not determined.

Table 3. Scope of the reaction.[a]



Entry	**1** (R)	**4**	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1a** (Et)	**4f**	87	>10:1	93
2[e]	**1b** (Me)	**4g**	93	>10:1	85
3	**1c** (*n*-Pr)	**4h**	99	>20:1	92
4	**1d** (*n*-Bu)	**4i**	91	>20:1	94
5	**1e** (n-C_5H_{11})	**4j**	95	>20:1	93
6	**1f** (n-C_6H_{13})	**4k**	78	>20:1	93
7	**1g** (n-C_7H_{15})	**4l**	78	>20:1	92
8	**1h** (n-C_8H_{17})	**4m**	99	>20:1	94
9	**1i** (*Z*-EtCH=CHCH$_2$CH$_2$-)	**4n**	68	>20:1	90
10	**1j** (*i*-Pr)	**4o**	50	>20:1	97
11	**1k** (CO_2Et)	**4p**	65	20:1	89
12	**1l** ($CH(OMe)_2$)	**4q**	95	>20:1	>99
13[f]	**1a** (Et)	**4a**	54	>10:1	97
14[f]	**1d** (*n*-Bu)	**4r**	21	>20:1	96

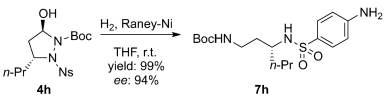
[a] Reactions performed on a 0.2-mmol scale of **1** and **2f** using 10 mol% of catalyst **3c** in 2.0 mL of toluene.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[d] Determined by HPLC on a chiral stationary phase.
[e] Reaction carried out at 4 °C.
[f] Hydrazide **2a** was used.

of different length and size, whilst maintaining both high yield and high levels of stereoselectivity (entries 1–8).[11] Furthermore, branched and unsaturated β-alkyl substituents were tested with success in the reaction (entries 9 and 10). Functionalized α,β-unsaturated aldehydes, such as **1k** or **1l** also performed well, furnishing the final adducts in high yield and stereocontrol (entries 11 and 12). Again, all these cases showed the formation of a single regioisomer, regardless the substitution pattern at the enal reagent. It is interesting to note that when hydrazide **2a** was employed, a very significant dependence of the yield on the length of the β-alkyl substituent was observed, obtaining very poor yields when longer substituents were incorporated, although enantioselectivity remained high (entries 13 and 14). The absolute configuration of products **4** was assigned by analogy after a single-crystal X-ray analysis of a pyrazolidine product obtained from the reduction of the pyrazolidin-3-ol **4a** (see the Supporting Information).[12]

Having established a robust route to the pyrazolidine motif, we proceeded to run a series of simple transformations in order to synthesize other pyrazolidine-related heterocyclic structures of interest (Table 4). Treating compounds **4** with TFA led to sequential deprotection/dehydration, obtaining a series of pyrazolines **5** in excellent yields whilst maintaining the stereochemical integrity of the stereocenter, although these types of heterocycles have been found to be rather configurationally unstable.[13] Additionally, pyrazolidin-3-ones **6** were also obtained in excellent yields and as highly enantiopure materials by oxidation of pyrazolidin-3-ols.

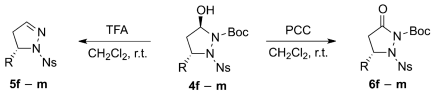
Another potential synthetic application of this type of heterocycle relies on the possibility to cleave the N–N bond, giving access to highly important enantioenriched 1,3-diamines.[6,14] In particular, enantiopure 1,3-diamine **7h** could be obtained after treating pyrazolidin-3-ol **4h** with H_2 in the presence of Raney-Ni, which occurred concomitant with the reduction of the nitro group present at the nosyl substituent (Scheme 2).

In conclusion, we have developed the first asymmetric aminocatalytic direct synthesis of pyrazolidines based on the aza-Michael/hemiaminalization reaction of α,β-unsaturated aldehydes and hydrazides under iminium activation. The reaction was catalyzed by the



Scheme 2. Synthesis of 1,3-diamine **7h** from pyrazolin-3-ol **4h**.

Table 4. Synthesis of pyrazolines **5** and pyrazolidinones **6**.



5f – m **4f – m** **6f – m**

Entry	**4** (R)	Yield of **5** [%][a]	*ee* of **5** [%][b]	Yield of **6** [%][a]	*ee* of **6** [%][b]
1	**4f** (Et)	97	92	95	93
2[c]	**4g** (Me)	85	85	94	84
3	**4h** (*n*-Pr)	99	92	97	92
4	**4i** (*n*-Bu)	99	91	90	90
5	**4j** (n-C_5H_{11})	87	91	97	91
6	**4k** (n-C_6H_{13})	86	90	93	91
7	**4l** (n-C_7H_{15})	99	92	96	91
8	**4m** (n-C_8H_{17})	99	90	94	90

[a] Isolated yield.
[b] Determined by HPLC on a chiral stationary phase (see Supporting Information).
[c] Reaction carried out at 4 °C.

commercially available diarylprolinol silyl ether **3c** and took place in very high yields and excellent stereoselectivities, allowing the synthesis of a wide array of nitrogen-containing heterocycles of relevance in medicinal chemistry. Furthermore, a series of simple transformations of adducts has been presented, which easily allows the formation of some pyrazolidine derivatives, increasing the utility of the presented methodology.

Experimental Section

General Methods and Materials

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, $\delta = 7.26$ ppm for ^1H NMR, $CDCl_3$, $\delta = 77.0$ ppm for ^{13}C NMR). IR spectra were measured in a Perkin–Elmer 1600 and a Perkin–Elmer Spectrum BX apparatus. Mass spectra (MS) were recorded on an Agilent 7890 A gas chromatograph coupled to an Agilent 5975 mass spectrometer. High-resolution mass spectra (HR-MS) were recorded on a micromass GCT spectrometer using chemical ionization (CI) or Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using the electrospray (ESI) technique. Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or *p*-anisaldehyde dip. Melting points were measured in a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on Perkin–Elmer 241 and Jasco P-2000 polarimeters. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC in a Waters 2695 with a Waters 2998 photodiode array detector (Daicel Chiralpak IA, IC, AS-H and AD-H columns).

Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230–400 mesh, Merck) was employed.

General Procedure for the Preparation of Pyrazolidinols 4

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3c** (0.02 mmol, 10 mol%), PhCOOH (0.05 mmol, 25 mol%) and toluene (2 mL). Then, hydrazine **2** (0.20 mmol) and the α,β-unsatured aldehyde **1** (0.20 mmol) were added. The stirring was maintained at room temperature until the reaction was complete (24–72 h) and the crude reaction mixture was concentrated and directly charged onto silica gel and subjected to FC. The racemic standards for HPLC separation conditions were prepared using D,L-proline (0.02 mmol, 10 mol%) instead of catalyst **3c**, without PhCOOH and in CH_2Cl_2 (2 mL) at room temperature.

General Procedure for the Deprotection of Pyrazolidinols 4: Synthesis of Pyrazolines 5

A vial equipped with a magnetic stirring bar was charged with the pyrazolidinol **4** (0.2 mmol) in 2 mL of CH_2Cl_2. Then TFA (2 mmol) was added. The reaction mixture was stirred at rrom temperature until completion of the reaction (5 h). The reaction mixture was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude was charged onto silica gel and subjected to FC.

General Procedure for the Oxidation of Pyrazolidinols 4: Synthesis of Pyrazolidin-3-ones 6

A vial equipped with a magnetic stirring bar was charged with the pyrazolidinol **4** (0.18 mmol) in CH_2Cl_2 (5 mL). Then PCC (0.91 mmol) and molecular sieves (4 Å) were added. The reaction mixture was stirred at room temperature until completion (16 h) and the crude mixture was con-

centrated and directly charged onto silica gel and subjected to FC.

Supporting Information

General methods and materials, experimental procedures, characterization data, and determination of the absolute configuration as well as copies of the NMR spectra and HPLC traces are available in the Supporting Information.

Acknowledgements

This work was supported by the University of the Basque Country UPV/EHU (fellowship to E.R.), the Spanish MICINN (CTQ2008-00136/BQU), and the Basque Government (fellowship to M.F.) and subvención a Grupos IT-328-10.

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COMMUNICATION

Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines†

Maitane Fernández, Jose L. Vicario,* Efraím Reyes, Luisa Carrillo and Dolores Badía

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We have developed an efficient procedure for the easy and straightforward preparation of functionalized dihydropyridazines as highly enantiopure materials by reaction of pyruvaldehyde 2-tosyl hydrazone with a variety of α,β-unsaturated aldehydes using a chiral secondary amine as catalyst. The overall process consists of a cascade reaction involving an initial aza-Michael reaction, in which the stereocentre is installed, followed by an intramolecular aldol reaction/dehydration step.

Pyridazines belong to a family of heterocyclic compounds that possess remarkable pharmaceutical activities and have also shown important applications in materials science. For example, several members of this class of compounds have been utilised in the development of therapeutic agents that have been employed as analgesic and anti-inflammatory,[1] antibacterial,[2] antihypertensive,[3] antidiabetic[4] or antihistaminic[5] agents and have also been incorporated into semi-conductor materials as well as in substances with non-linear optical properties.[6] Among this wide range of different applications and activities displayed, chirality also plays a crucial role, which is exemplified with the case of levosimendan (Fig. 1), an inotropic commercial drug with vasodilatory activity in which only the (*R*) enantiomer is pharmacologically active.[7]

In this context, and as part of the continuing efforts of our group directed towards the development of new synthetic methodologies for the preparation of chiral heterocycles, we have found that the pyridazine framework can be easily accessed from α,β-unsaturated aldehydes and a functionalized hydrazone of type **2** by means of a cascade reaction consisting

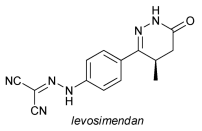

Fig. 1 The structure of the pharmacologically active enantiomer of pyridazine-containing drug Simendan.

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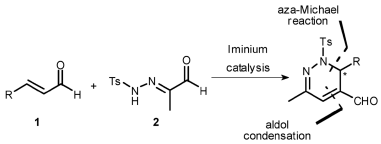
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, copies of ^{1}H and ^{13}C-NMR spectra and chiral HPLC traces. CCDC 855796. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17370k

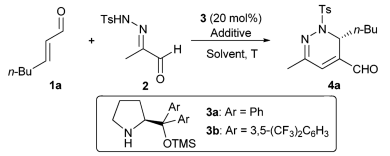


Scheme 1 Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines by aza-Michael reaction/aldol condensation cascade through iminium/enamine activation.

of an initial aza-Michael reaction followed by intramolecular aldol condensation (Scheme 1). Moreover, we have also investigated generation of the target compounds in an enantioselective manner by using the iminium/enamine activation manifold,[8] thus employing a chiral secondary amine as catalyst for this transformation. In this context, the chiral catalyst would play a crucial role in the initial aza-Michael reaction step proceeding under iminium activation by providing the desired stereocontrol. The subsequent enamine-mediated intramolecular aldol reaction/dehydration step would provide the required driving force for the reaction to proceed to completion, pushing forward all of the equilibriums participating in the catalytic cycle and avoiding the problems associated with the inherent reversible character of the aza-Michael reaction, which would eventually lead to low conversions and/or lack of enantiocontrol.[9]

According to this reaction design, we decided to use the tosyl hydrazone **2** assuming that this compound would have an enhanced profile (compared to alternative protecting groups) to undergo the initial aza-Michael reaction step, since the high acidity of the NH moiety would presumably favour its deprotonation under the neutral or slightly basic conditions associated with iminium catalysis.[10] It should be pointed out that even though the use of aza-Michael/aldol condensation cascades exploiting the iminium/enamine manifold for the construction of different classes of nitrogen heterocycles is well documented in the literature,[11] there are no examples that explore the use of functionalized hydrazones in cascade reactions. Moreover, there is only one example in which hydrazones were used as nitrogen-centered pro-nucleophiles for the aza-Michael reaction with enones, using a chiral Brønsted base catalyst.[12] Therefore, this is the first example demonstrating that hydrazones can be successfully employed as nitrogen-centered nucleophiles for the enantioselective conjugate addition reaction under iminium catalysis.

Table 1 Screening for the best experimental conditions using the reaction between **1a** and **2** as a model system[a]



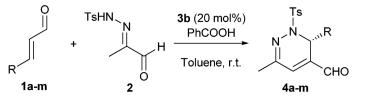
Entry	Catalyst	Additive	Solvent	T/°C	Yield[b] (%)	ee[c] (%)
1	**3a**	PhCOOH	Toluene	rt	54	82
2	**3b**	PhCOOH	Toluene	rt	60	98
3	**3b**	4-$(NO_2)C_6H_4COOH$	Toluene	rt	31	n.d.[d]
4	**3b**	AcOH	Toluene	rt	42	98
5	**3b**	$(Ph)_2CHCOOH$	Toluene	rt	48	98
6	**3b**	DABCO	Toluene	rt	—	—
7	**3b**	PhCOOH	$CHCl_3$	rt	24	94
8	**3b**	PhCOOH	CH_2Cl_2	rt	30	94
9	**3b**	PhCOOH	THF	rt	13	n.d.[d]
10	**3b**	PhCOOH	EtOH	rt	18	n.d.[d]
11[e]	**3b**	PhCOOH	Toluene	rt	84	96

[a] Reactions performed on a 0.3 mmol scale of **1a** and **2** using 20 mol% of catalyst in 3.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC (see ESI). [d] Not determined. [e] Reaction carried out using **2** equiv. of **2** in 6.0 mL of toluene.

With these precedents in mind, we started our work by surveying the viability of the projected cascade process using the reaction between 2-heptenal (**1a**) and tosylhydrazone **2**, the later being synthesized by direct condensation of commercially available pyruvic aldehyde and tosylhydrazine,[13] as a representative model system (Table 1). We first tested diarylprolinol derivatives **3a** and **3b** as chiral secondary amine catalysts, which have already demonstrated their performance in many other examples of conjugate addition reactions under iminium activation,[14] working in toluene at room temperature. We incorporated benzoic acid as Brønsted acid co-catalyst since its ability to accelerate the formation of the activated iminium ion intermediate is also well known. In this context, *O*-trimethylsilyl protected diphenylprolinol **3a** delivered the desired product **4a** in moderate isolated yield albeit with high enantiocontrol. When the bulkier catalyst **3b** was employed, enantioselectivity improved significantly and also a slight increase in the yield of the process was observed (entries 1 and 2). Once a catalyst that provided high enantiocontrol had been identified (**3b**), we directed our efforts to the improvement of the yield of the reaction, first studying the role of the Brønsted acid co-catalyst by testing carboxylic acids of different acidity. However, the incorporation of additives with higher or lower pK_a compared to $PhCO_2H$ led to a considerable loss in the yield of the desired compound **4a** (entries 3–5), although enantioselectivities remained intact. The incorporation of a base as a co-catalyst was also surveyed but in this case formation of the desired product was not observed (entry 6).

We next studied the influence of the solvent (entries 7–10) and, as shown in Table 1, toluene appeared to be the most efficient one in terms of both conversion and enantioselectivity.

Table 2 Scope of the reaction[a]



Entry	Aldehyde	R	Product	Yield[b] (%)	ee[c] (%)
1	**1a**	*n*-Bu	**4a**	84	96
2	**1b**	Me	**4b**	91	89
3	**1c**	Et	**4c**	74	96
4	**1d**	*n*-Pr	**4d**	72	96
5	**1e**	$n\text{-}C_8H_{17}$	**4e**	63	97
6	**1f**	*Z*-EtCH=$CH(CH_2)_2$	**4f**	68	97
7	**1g**	$CH(OMe)_2$	**4g**	61	97
8	**1h**	$BnOCH_2$	**4h**	69	96
9	**1i**	Ph	**4i**	19	86
10[d]	**1i**	Ph	**4i**	49	89
11[d]	**1j**	*p*-$(NO_2)C_6H_4$	**4j**	52	95
12[d]	**1k**	*p*-$(MeO)C_6H_4$	**4k**	60	85
13[d]	**1l**	*p*-$(CN)C_6H_4$	**4l**	72	94
14[d]	**1m**	5-(NO_2)-Furyl	**4m**	55	90

[a] Reactions performed on a 0.6 mmol scale of **2** and 0.3 mmol scale of **1** using 20 mol% of catalyst **3b** in 6.0 mL of toluene. [b] Isolated yield. [c] Determined by HPLC on a chiral stationary phase (see ESI). [d] Reactions performed on a 0.6 mmol scale of **1** and 0.3 mmol scale of **2**.

Slightly more polar solvents like chloroform or dichloromethane yielded the desired adduct still in high enantioselectivities but with an accentuated drop in isolated yield (entries 7 and 8), while the incorporation of strongly polar solvents like THF or EtOH resulted in very poor conversion after the same reaction time (entries 9 and 10). Finally, we succeeded in improving the yield of the reaction by increasing the amount of hydrazone reagent, reaching an 84% yield of dihydropyridazine **4a** and a 96% ee (entry 11).

Once the best protocol for the reaction had been established, we next proceeded to extend the reaction to the use of α,β-unsaturated aldehydes with different substitution patterns in order to determine the scope of the reaction and its performance for the preparation of differently substituted 2,3-dihydropyridazines. From the results summarized in Table 2 we observed that the hydrazone **2** reacted in a satisfactory way in most of the cases studied, furnishing the adducts **4a–m** in moderate to very good yields and excellent enantioselectivities. The reaction tolerates well the use of different β-substituted α,β-unsaturated aldehydes containing linear alkyl chains of different length and size (entries 1–5), also observing that the yield of the process became only moderately affected when the size of the chain was considerably increased (entry 5). Furthermore, functionalized α,β-unsaturated aldehydes such as **1f**, **1g** or **1h** also performed well, furnishing the final adducts in good yield and very high stereocontrol (entries 6–8).

On the other hand, cinnamaldehyde **1i** showed a remarkably lower reactivity and slightly decreased enantiocontrol under the same reaction conditions (entry 9). This led us to survey modified reaction conditions in order to improve this result and, after several attempts, it was found that the reaction proceeded more efficiently by simply changing the proportion of reagents from using excess of hydrazone reagent to employing

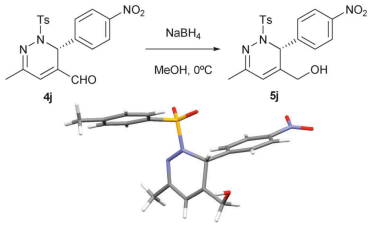


Fig. 2 Synthesis of compound **5j** and its crystal structure.

an excess of enal (entry 10). These conditions were further extended to other β-aryl substituted α,β-unsaturated aldehydes leading to the formation of the corresponding adducts in moderate to good yields and high enantioselectivities (entries 11–14).

The absolute configuration of the cycloadducts obtained in this cascade process was assigned by X-ray analysis of primary alcohol **5j** obtained after sodium borohydride reduction of **4j** (Fig. 2). This compound provided monocrystal structures suitable for single-crystal X-ray analysis (see ESI†) showing an (3*R*) absolute configuration. The absolute stereochemical outcome for the rest of the adducts **4a–m** synthesized was established by analogy, assuming an identical configuration based on mechanistic analogy for the reaction in all the cases. This configuration is also in good agreement with the sense of the chirality induction provided by catalyst **3b** in other conjugate addition reactions in which this catalyst has been employed.[14]

In conclusion, we have demonstrated that hydrazone **2** can efficiently be employed as a bifunctional reagent in the reaction with α,β-unsaturated aldehydes in the presence of a chiral secondary amine as catalyst in a cascade reaction operating through the iminium/enamine manifold. This compound is able to first behave as a N-nucleophile, initiating the process with an aza-Michael-type reaction, in which the stereochemical information is installed with very high stereocontrol. Secondly, the enamine intermediate reacts intramolecularly with the remaining formyl moiety through an aldol condensation. According to the recent classification of organocatalytic cascade/one-pot reactions made by Jørgensen,[15] this reaction can be classified as a TypeA-1-1C1X process with a Y_{PBF} (yield per bond formed) of 70–95%, a Y_{PMO} (yield per manual operation) of 49–91% and a P_f (purification factor) of 0. As far as we know this is the first example of the use of a hydrazone as a nitrogen-based pro-nucleophile in conjugate addition reactions under iminium activation and also the first case of a hydrazone reagent that is able to react bifunctionally in an enantioselective manner in a cascade process under iminium/enamine activation. This procedure also represents an efficient way for building up the pyridazine scaffold, a heterocyclic architecture of remarkable interest for medicinal chemists. Moreover, this simple protocol allows the preparation of chiral derivatives as highly enantiopure materials which incorporate different functionalities with potential for further manipulations, therefore anticipating the synthetic utility of the methodology.

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Enantioselective Conjugate Addition of Donor−Acceptor Hydrazones to α,β-Unsaturated Aldehydes through Formal Diaza−Ene Reaction: Access to 1,4-Dicarbonyl Compounds

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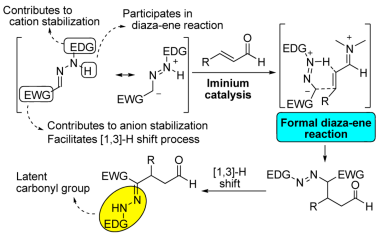
Supporting Information

ABSTRACT: Donor−acceptor monosubstituted hydrazones participate as suitable reagents able to undergo an enantioselective formal diaza−ene reaction with α,β-unsaturated aldehydes under chiral secondary amine catalysis. This constitutes a new approach for the enantioselective conjugate addition of hydrazones to enals under metal-free conditions and leads to the formation of γ-hydrazono carboxylic acids after oxidation/[1,3]-H shift. The methodology is also useful for the synthesis of enantioenriched β-substituted α-keto-1,5-diesters by using the hydrazone moiety as a masked carbonyl group.

The discovery of new umpolung transformations in which inversion of the natural reactivity pattern of a given chemical reagent takes place during the overall process has been an important field of research since Corey and Seebach introduced the concept.[1] In particular, conjugate addition of acyl anion equivalents, the archetypical example of umpolung reactivity, enables the preparation of 1,4-dicarbonyl compounds, a molecular architecture that is difficult to access by conventional methods. In this context, several approaches have been devised using conveniently designed nucleophilic reagents that, after the conjugate addition process takes place, are able to deliver the final 1,4-dicarbonyl compound by unmasking the γ-carbonyl group through a simple and high-yielding transformation.[2] In addition, if an enantiomerically enriched product is desired, several catalytic enantioselective approaches have been reported in the past few years, focused on the use of either metal catalysis[3] or organocatalysis.[4] Alternatively, the enantioselective Stetter reaction using N-heterocyclic carbenes as catalysts can be extremely efficient for the direct conjugate addition of acyl anions,[5] directly affording the final 1,4-dicarbonyl adduct without the need for additional synthetic steps to reveal the latent carbonyl functionality. However, this reaction normally demands a highly electrophilic Michael acceptor, such as a nitroalkene or an alkylidene malonate, in order to proceed with high yield for the intermolecular version.[6]

With these precedents in mind and in connection with our ongoing efforts to develop new organocatalytic reactions, we decided to survey the possibility of carrying out the conjugate addition of a suitable acyl anion equivalent to α,β-unsaturated aldehydes by applying the iminium activation concept,[7] therefore opening the way to achieve enantiocontrol by using a chiral secondary amine as the catalyst. In particular, we thought of donor−acceptor hydrazones such as those shown in Scheme 1 as potential acyl anion equivalents. The principles behind the reaction design rely on the ability of an N-monosubstituted hydrazone to undergo a diaza−ene reaction with a chiral α,β-unsaturated iminium ion intermediate that operates as an activated Michael acceptor. This initial step would deliver a γ-azoaldehyde adduct that, after a [1,3]-hydride shift, would render a γ-hydrazono aldehyde product where the hydrazone moiety could be considered as a latent carbonyl functionality. Under this design, we anticipated that a donor−acceptor hydrazone reagent would presumably fulfill the requisites for becoming an active Michael donor in the projected reaction under the typical neutral or slightly basic conditions associated with iminium catalysis. In particular, it was envisaged that the concurrent incorporation of an electron-donating group (EDG) as the nitrogen substituent and an electron-withdrawing group (EWG) as the substituent at the azomethine carbon would enhance the reactivity of the azomethine carbon atom toward its interaction with the electrophilic β-carbon of the iminium ion, therefore resulting in a highly productive situation.

Scheme 1. Donor−acceptor Monosubstituted Hydrazones as Acyl Anion Equivalents in Enantioselective Conjugate Addition under Iminium Activation



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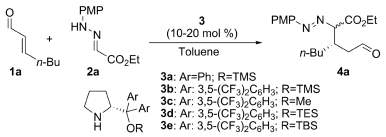
It should be mentioned that there is one precedent in the literature describing the use of disubstituted *N*,*N*-dialkylhydrazones derived from formaldehyde as Michael donors in the conjugate addition to β,γ-unsaturated α-keto esters under chiral Brønsted acid catalysis, furnishing moderate levels of enantioselectivity.[8] Monosubstituted hydrazones have also been used by Scheidt under cooperative Mg(II)/NHC catalysis,[9] but in that case, they act as *electrophiles*, which is the natural reactivity pattern expected for these azomethine compounds. Thus, even though formaldehyde pyrrolidinyl hydrazones have been employed as nucleophiles in several transformations,[10] there are no precedents showing their behavior toward α,β-unsaturated aldehydes or ketones under iminium activation. This is probably due to their predictable tendency to undergo intramolecular condensation after conjugate addition, rendering the corresponding aromatic *N*-aminopyrrole derivatives.[11] In addition, and to the best of our knowledge, the application of this type of donor–acceptor hydrazone in catalytic enantioselective diaza–ene-type reactions is still unprecedented in the chemical literature,[12] and even the possibility of carrying out this reaction in an asymmetric fashion under metal-free conditions is still undocumented.

On the basis of these postulates, we started our work by surveying the viability of the projected transformation using the reaction between enal **1a** and hydrazone **2a** as a representative model system (Table 1). We first tested the performance of *O*-trimethylsilyl (*O*-TMS)-substituted diphenylprolinol derivative **3a** as a chiral secondary amine catalyst in toluene at 4 °C, which are standard reaction conditions employed in other examples of conjugate addition reactions under iminium activation.[7,13] This demonstrated the ability of the hydrazone reagent **2a** to behave as we anticipated in Scheme 1, leading to the formation of the desired γ-azoaldehyde **4a** in moderate yield as a 70:30 mixture of diastereoisomers (entry 1) in a rather fast reaction (3 h reaction time). However, even though the enantioselectivity offered by this catalyst for the main diastereoisomer was remarkably high (98% ee), the minor diastereoisomer was isolated in only 10% ee. In this sense, and taking into consideration that both diastereoisomers of **4a** would converge into a single product after the projected [1,3]-hydride shift process, we next focused on searching for the best conditions to obtain a highly enantioenriched material regardless the diastereomeric proportion. We therefore tested the use of catalyst **3b** containing larger aryl groups, which delivered **4a** in a similar yield but with a significant improvement in the enantioselectivity of the minor diastereoisomer (entry 2). We next evaluated a family of related diarylprolinol catalysts incorporating substituents of different sizes at the oxygen atom (entries 3–5), observing that the use of *O*-methyl-containing catalyst **3c** provided poorer results in terms of both yield and stereoselectivity (entry 3), whereas results similar to those for the **3b**-catalyzed reaction were obtained when the steric bulk was slightly increased to triethylsilyl in **3d** (entry 4 vs 2). Interestingly, the introduction of an even larger *O*-trialkylsilyl group (catalyst **3e**; entry 5) increased the enantioselectivity for the minor diastereoisomer up to a satisfactory 86% ee while maintaining a 98% ee for the major diastereoisomer.

Once the optimal catalyst had been identified, we directed our efforts to improving the yield of the reaction, which was achieved by working at a higher temperature, without this affecting the enantioselectivity significantly (entry 6). Finally, we also demonstrated that the reaction performed well with a lower catalyst loading (10 mol %; entry 7), which resulted in just a slight decrease in the yield while keeping identical levels of stereoselection. These last conditions were therefore chosen as the optimal ones for our reaction.[14]

Having established a robust experimental protocol for the conjugate addition reaction, and in line with the overall reaction design shown in Scheme 1, we next proceeded to study the most appropriate conditions for inducing a [1,3]-hydride shift process on the conjugate addition adduct **4a** (Scheme 2). Treatment of the aldehyde with different Brønsted acids under a variety of conditions led to the projected [1,3]-hydride shift process smoothly, forming the desired γ-hydrazono aldehyde. However, the isolated compound had a pronounced tendency to undergo intramolecular hemiaminal formation and subsequent dehydration, forming cyclic dihydropyridazine derivative **5a**, albeit with retention of enantiopurity.

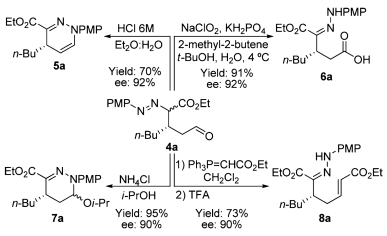
Table 1. Screening for the Best Experimental Conditions Using the Reaction of Enal 1a with Hydrazone 2a as a Model System[a]



entry	catalyst	T (°C)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	4	51	70:30	98/10
2	**3b**	4	63	70:30	95/78
3	**3c**	4	20	70:30	74/12
4	**3d**	4	66	70:30	96/75
5	**3e**	4	64	70:30	98/86
6	**3e**	r.t.	83	70:30	96/84
7[e]	**3e**	r.t.	79	70:30	96/84

[a]Reaction conditions: 2.0 mmol of **1a**, 1.0 mmol of **2a**, and catalyst **3** (20 mol %) were stirred in toluene at the specified temperature for 2–3 h. [b]Yields of pure product as mixtures of diastereoisomers after flash column chromatography. [c]Diastereomeric ratios determined by NMR analysis of the crude reaction mixtures. [d]ee values for the major and minor diastereoisomers respectively, as determined by chiral-stationary-phase HPLC analysis (see the Supporting Information). [e]10 mol % catalyst **3e** was used.

Scheme 2. Transformations Carried out on Aldehyde 4a

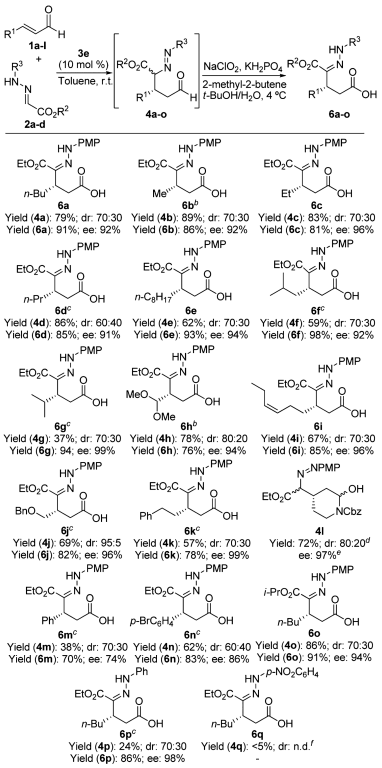


To avoid this cyclization process, we decided to carry out the oxidation of the aldehyde moiety. This proceeded simultaneously with the [1,3]-hydride shift process, affording the desired γ-hydrazono carboxylic acid **6a** in excellent yield without erosion of enantiopurity (see Scheme 2). Alternatively, dehydration after the acid-mediated [1,3]-hydride shift could be avoided by using isopropyl alcohol as the solvent, leading to the formation of **7a** in good yield as a mixture of α- and β-anomers, both of which were isolated with high enantiopurity. We also surveyed the possibility of elaborating these adducts by exploiting their aldehyde reactivity. In this sense, Wittig reaction under standard conditions followed by addition of trifluoroacetic acid (TFA) led to the formation of α,β-unsaturated ε-hydrazono ester **8a** in excellent yield and retaining the ee of the starting material.

We next proceeded to extend the reaction, exploring other α,β-unsaturated aldehydes with different substitution patterns in order to determine the scope of the reaction and its performance for the preparation of differently substituted γ-hydrazono carboxylic acids. The results summarized in Scheme 3 show that the reaction proceeded satisfactorily in almost all cases, furnishing adducts **4a**−**o** in good yields, which were further subjected to oxidation leading to γ-hydrazono carboxylic acids **6a**−**o** in excellent overall yields and enantioselectivities. The reaction tolerates well the use of different β-substituted enals containing alkyl chains of different length and size, and we also observed that the yield of the process was only moderately affected when the length of the chain was considerably increased (compounds **6a**−**e**). Aldehydes containing nonlinear alkyl chains also performed well, providing excellent enantioselectivities (compounds **6f** and **6g**), although with an appreciable drop in isolated yield when the size of the substituent was notably increased (i.e., compound **6g**). Furthermore, functionalized α,β-unsaturated aldehydes **1h**−**l** also performed well, furnishing the final adducts in good yields with high enantiopurities. A particular situation appeared with the case of δ-amino aldehyde **1l**, which led to the formation of the final adduct **4l** as the corresponding hemiaminal, resulting from intramolecular reaction between the aldehyde and the pendant protected amine. This adduct showed a different behavior during oxidation (see the Supporting Information for details), leading to the formation of a bicyclic aminal structure after the [1,3]-H shift process, from which suitable crystals for X-ray analysis were obtained, allowing the determination of its absolute stereostructure. This configuration was extended to all the adducts **4a**−**p** and is also in good agreement with the expected stereochemical outcome described for other conjugate addition reactions catalyzed by this type of O-silylated α,α-diarylprolinol derivative.[15] The reactivity of β-aryl-substituted α,β-unsaturated aldehydes proved to be highly dependent on the electronic nature of the aryl group. Aromatic enal **1n** incorporating an electron-withdrawing substituent performed very well in the reaction, leading to **6n** in good yield and enantioselectivity, while cinnamaldehyde (**1m**) reacted very slowly. On the other hand, isopropyl glyoxylate-based hydrazone **2b** could also be utilized, delivering the expected adduct **6o** in high yield and enantioselectivity. An important validation of our strategy was to see the effect of changing the electronic properties of the *N*-aryl group. In this sense, we found out that *N*-phenyl-substituted hydrazone **2c** furnished the conjugate addition product **6p** in 24% yield, although still with excellent stereocontrol, while the related *p*-nitrophenyl-substituted hydrazone **2d** was unable to react with **1a** under the optimized reaction conditions. This is an indication of the appropriateness of the aforementioned strategic design for the hydrazone reagent.

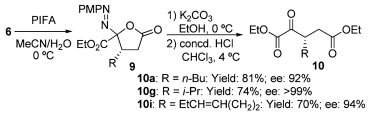
Finally, having succeeded in the development of a general method for the conjugate addition of hydrazones to enals, we proceeded to find the appropriate conditions for transforming the hydrazone into a carbonyl group (Scheme 4). After several

Scheme 3. Scope of the Reaction[a]



[a]All of the reactions were carried out on a 1.00 mmol scale. Shown are yields of pure products after flash column chromatography, dr values determined by NMR analysis of the crude reaction mixtures, and ee values determined by HPLC analysis (see the Supporting Information). [b]Reaction performed at 4 °C. [c]20 mol % catalyst loading. [d]An 80:20 mixture of diastereoisomers, each one as a 1:1 mixture of anomers, was obtained. [e]Calculated for the bicyclic aminal obtained after the [1,3]-H shift process (see the Supporting Information). [f]n.d. = not determined.

Scheme 4. Oxidative Cleavage of the Hydrazone Moiety



10a: R = *n*-Bu: Yield: 81%; ee: 92%
10g: R = *i*-Pr: Yield: 74%; ee: >99%
10i: R = EtCH=CH(CH$_2$)$_2$: Yield: 70%; ee: 94%

unsuccessful attempts under different conditions for hydrolysis or oxidative cleavage through ozonolysis, we found that the hydrazone moiety could be cleanly and easily converted into the corresponding ketone by phenyliodonium bis-(trifluoroacetate) (PIFA)-mediated oxidative hydrolysis.[16] Under the employed conditions, azolactone intermediates **9** were formed first by oxidation of the hydrazone followed by intramolecular reaction with the carboxylic acid moiety. Next, an ethanolysis/acid hydrolysis sequence provided the desired α-keto-1,5-diesters **10**. These conditions were employed for a set of representative compounds **6**, and we observed that in all cases the reaction proceeded cleanly in excellent overall yields without erosion of the enantiopurity of the starting materials.

In summary, we have shown that donor−acceptor hydrazones such as **2** can participate in enantioselective diaza−ene reactions with α,β-unsaturated aldehydes via iminium activation in the presence of a chiral secondary amine as the catalyst. The reaction leads to the formation of γ-azoaldehydes, which are converted into enantiopure γ-hydrazono carboxylic acids through an oxidation/[1,3]-hydride shift sequence,. Moreover, we have also developed a procedure for the conversion of these adducts into 1,4-dicarbonyl compounds, resulting in a very efficient enantioselective methodology for the indirect β-glyoxylation of enals using monosubstituted hydrazones as masked acyl anion equivalents.[17]

■ ASSOCIATED CONTENT

Supporting Information

Characterization of all new compounds, copies of ^{1}H and ^{13}C NMR spectra and HPLC traces, and crystal structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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