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New Methods in Organocatalysis

Presentata da: **Elisa Montroni**

Coordinatore Dottorato **Relatore**

Prof. Aldo Roda **Prof. Claudio Trombini**

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Abstract

In the following chapters new methods in organocatalysis are described. The design of new catalysts is explored starting from the synthesis and the study of ion tagged prolines to their applications and recycle, then moving to the synthesis of new bicyclic diarylprolinol silyl ethers and their use in organocatalytic transformations.

The study of new organocatalytic reaction is also investigated, in particular bifunctional thioureas are employed to catalyse the conjugate addition of nitro compounds to 3-yilidene oxindoles in sequential and domino reactions.

Finally, preliminary results on photochemical organocatalytic atom transfer radical addition to alkenes are discussed in the last chapter.

Chapter 1

Asymmetric Organocatalysis

1. Introduction

In organic chemistry the ‘‘value’’ of a product is directly related to purity; in most instances, when the molecule is chiral, this implies that it must be present only one enantiomer. In recent years the number of methods available for high-yielding and enantioselective transformations of organic compounds has increased tremendously and new concepts and methods are emerging continuously.

Amongst the different ways of creating enantiomerically enriched products, catalytic methods are considered as the most appealing ones as they provide better atom economy. Enantioselective catalysis needs to be efficient, facile, reliable and economic if it has to be used widely in particular for pharmaceutical synthesis.

Between the extremes of transition metal catalysis and enzymatic transformations, a third general approach to the catalytic production of enantiomerically pure organic compounds has emerged, that is asymmetric organocatalysis.[1,2] The principle of organocatalysis is that small organic molecules (without metal elements) could function as efficient and selective catalysts for a large variety of enantioselective transformations. It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis, complementary to the organometallic and bio-catalysis.

[1] Books on organocatalysis: (a) Berkessel A., Gröger H., *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis* (**2005**), Wiley-VCH; (b) Dalko P. I., *Enantioselective Organocatalysis – Reactions and Experimental Procedures* (**2007**), Wiley-VCH.

[2] Reviews on organocatalysis: (a) MacMillan D. W. C., *Nature* **2008**, 455, 304-308; (b) Gaunt M. J., Johansson C. C. C., McNally A., Vo N. T., *Drug Discovery Today* **2007**, 12, 8-27; (c) Seayad J., List B., *Org. Biomol. Chem.* **2005**, 3, 719-724; (d) Dalko P. I., Moisan L., *Angew. Chem. Int. Ed.* **2004**, 43, 5138-5175.

The use of small organic molecules as catalysts has been known for more than a century. But only in the past decade organocatalysis has become a thriving area of general concepts and widely applicable asymmetric reactions.

In fact, the historic roots of organocatalysis date back to the first half of the 20th century when the attempts to use low-molecular weight organic compounds were focused to both understand and mimic the catalytic activity and selectivity of enzymes.

Isolated examples of enantioselective organocatalytic processes were reported from the 1960s to the 1980s, for example the alkaloid-catalysed addition of alcohols to prochiral ketenes by Pracejus et al.,[3] the Hajos–Parrish–Eder–Sauer–Wiechert reaction,[4] the hydrocyanantion of aldehydes using the Inoue catalyst,[5] or the Juliá–Colonna epoxidation,[6] but these chemical studies were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field.

It was not until 2000, however, that the field of organocatalysis was effectively launched, by two publications that appeared almost simultaneously: one from Carlos Barbas III, Richard Lerner and Benjamin List,[7] on enamine catalysis, and the other from MacMillan group,[8] on iminium catalysis.

The work of Barbas, Lerner and List was significant because it showed that the underlying mechanism of the Hajos–Parrish reaction could be extended and applied to transformations that have a broader applicability (specifically, the intermolecular aldol reaction). Moreover, this work showed that small organic molecules (such as proline) could catalyse the same chemical reactions as much larger organic molecules (enzymes) by using similar mechanisms. Meanwhile, the report of iminium catalysis conceptualized "organocatalysis" in three important ways: by delineating how organocatalysts could provide economic, environmental and scientific benefits; by describing a general activation strategy for organocatalysis that could be applied to a

[3] (a) Pracejus H., *Justus Liebigs Ann. Chem.* **1960**, 634, 9-22; (b) Pracejus H., Mäthe H., *J. Prakt. Chem.* **1964**, 24, 195-205.

[4] (a) Eder U., Sauer G., Wiechert R., *Angew. Chem. Int. Ed.* **1971**, 10, 496-497; (b) Hajos Z. G., Parrish D. R., *J. Org. Chem.* **1974**, 39, 1615-1621.

[5] (a) Oku J., Inoue S., *J. Chem. Soc., Chem. Commun.* **1981**, 229-230; (b) Oku J., Ito N., Inoue S., *Macromol. Chem.* **1982**, 183, 579-589.

[6] (a) Juliá S., Guixer J., Masana J., Rocas J., Colonna S., Annuziata R., Molinari H., *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317-1324; (b) Juliá S., Masana J., Vega J. C., *Angew. Chem. Int. Ed.* **1980**, 19, 929-931.

[7] List B., Lerner R. A., Barbas III C. F., *J. Am. Chem. Soc.* **2000**, 122, 2395-2396.

[8] Ahrendt K. A., Borths C. J., MacMillan D. W. C., *J. Am. Chem. Soc.* **2000**, 122, 4243-4244.

broad range of reaction classes and by introducing the term organocatalysis to the chemical literature.

Organocatalysis has several significant advantages over conventional metal catalysis: organocatalysts are usually robust, inexpensive and generally readily available in both enantiomeric forms. Because of their stability toward moisture and oxygen, demanding reaction conditions like inert atmosphere, low temperatures, absolute solvents, etc., are usually not required. Organocatalysts are mostly inexpensive indeed they are chiral-pool compounds themselves, or they are derived from these readily available sources of chirality by means of few synthetic steps. They are bench-stable compounds which are incomparably more robust than enzymes or other bioorganic catalysts. Some "privileged" organocatalysts are shown in Figure 1.

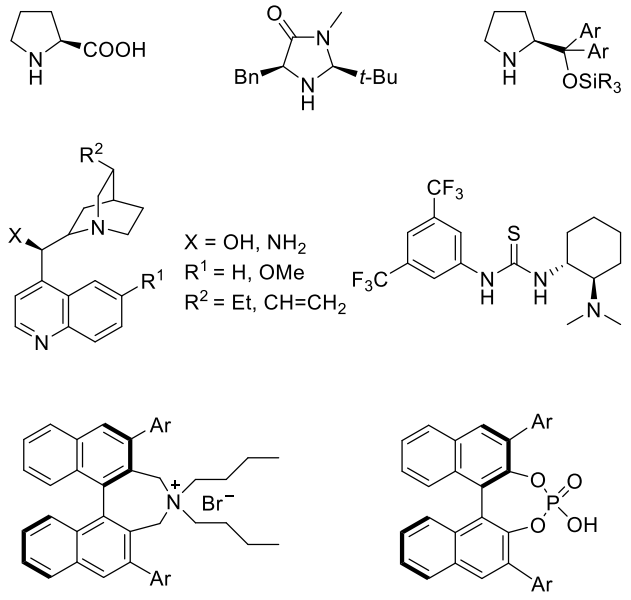


Figure 1

Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical products. Organocatalysts are typically less toxic than metal-based catalysts (although little is known about the toxicity of many organic catalysts), can be tolerated to a large extent in waste streams and are more easily removed from waste streams, again mitigating the cost of high catalyst loadings.

The operational simplicity, ready availability of catalysts and low toxicity associated with organocatalysis make it an attractive method to synthesise complex structures and give it a great potential in discovery chemistry.

Together with the ease and low cost of carrying out organocatalytic reactions in the laboratory, most crucial to the success of organocatalysis has been the invention or identification of generic modes of catalyst activation, induction and reactivity. A generic activation mode describes a reactive species, whose formation allow the reaction to proceed. This reactive species can participate in many reaction types providing, in many istances, high enantioselectivity. Such reactive species arise from the interaction of the substrate with a single chiral catalyst, owning a determined functional group, in a highly organized and predictable manner. The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions.

2. Covalent organocatalysis

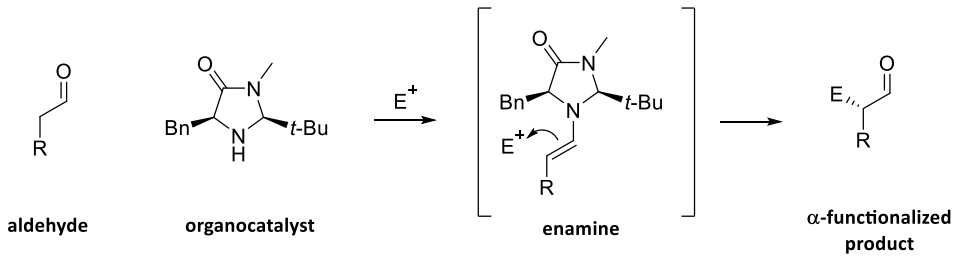
Covalent catalysis involves the formation of a covalent adduct between catalyst and substrate within the catalytic cycle.

Between the various types of organocatalysis belonging to this category, the most widespread and best known is without any doubt the aminocatalysis.[9]

In aminocatalysis is possible to distinguish different activation modes: enamine, iminium ion, SOMO (Singly Occupied Molecular Orbital) and photoredox catalysis.

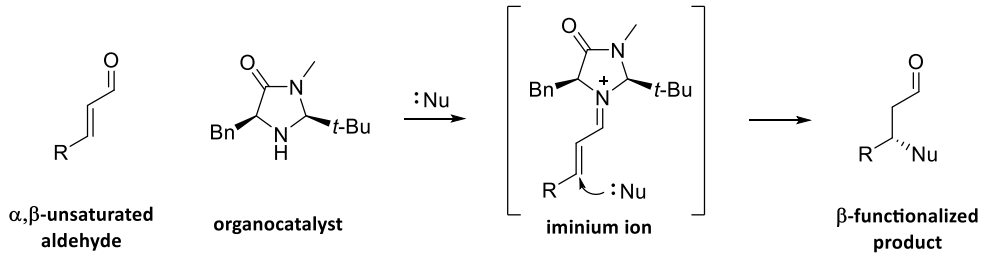
Enamine catalysis[10] (Scheme 1) was first introduced in 2000 by List, Barbas and Lerner;[7] it is based on the HOMO (Highest Occupied Molecular Orbital) activation of carbonyl compounds with the corresponding increase of electron density at the reaction centre allowing their α-functionalization. The reaction can take place with a diverse array of electrophiles making possible reactions like aldol, Mannich and conjugate additions, α-oxygenation, amination, chlorination, fluorination, etc..

[9] Melchiorre P., Marigo M., Carlone A., Bartoli G., *Angew. Chem. Int. Ed.* **2008**, 47, 6138-6171.
[10] Mukherjee S., Yang J. W., Hoffmann S., List B., *Chem. Rev.* **2007**, 107, 5471-5569.



Scheme 1

Meanwhile MacMillan's group presented the concept of asymmetric iminium catalysis[8,11] (Scheme 2). It is based on the capacity of chiral amines to work as enantioselective catalysts for several transformations that traditionally use Lewis acid catalysts. The reversible formation of iminium ions from α,β-unsaturated aldehydes or ketones and chiral amines might emulate the equilibrium dynamics and π-orbital electronics involved in Lewis acid catalysis. This LUMO (Lowest Unoccupied Molecular Orbital) lowering activates the intermediate toward the attack from a wide variety of nucleophiles to afford β-substituted carbonyl compounds or toward pericyclic reactions.



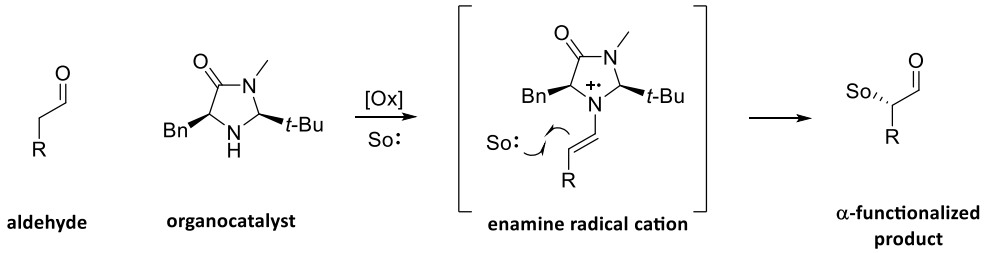
Scheme 2

MacMillan's group extended the versatility of traditional enamine chemistry through the establishment of two novel, radical-based activation modes.

The first one is SOMO catalysis[12] (Scheme 3), based on one-electron oxidation of the enamine that generates a reactive radical cation with 3π-electrons. This intermediate can react readily with a variety of π-nucleophiles (SOMOphiles) at the α-carbon of the parent enamine, resulting in formal alkylation products. The alkylation in α-position of carbonyl compounds is not possible with simple enamine catalysis thus making SOMO catalysis a complementary way of α-functionalization.

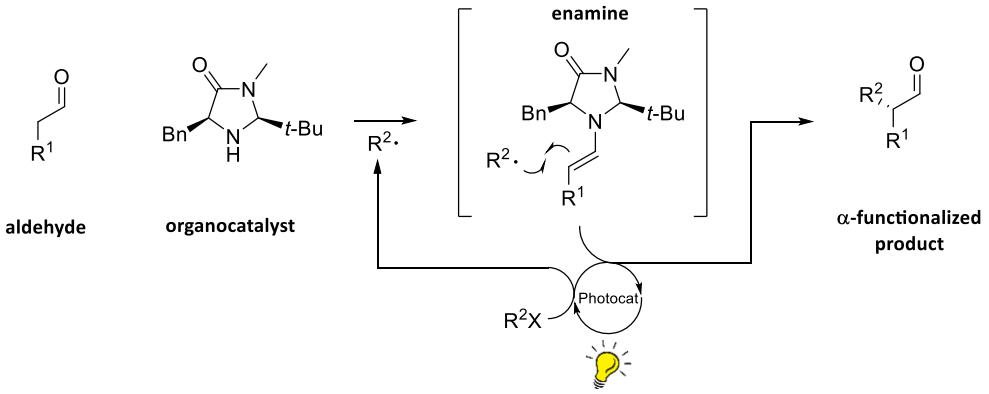
[11] Erkkilä A., Majander I., Pihko P. M., *Chem. Rev.* **2007**, 107, 5416-5470.

[12] Beeson T. D., Mastracchio A., Hong J., Ashton K., MacMillan D. W. C., *Science* **2007**, 316, 582-585.



Scheme 3

The last activation mode is organo-photoredox catalysis[13] (Scheme 4). In this case the reactive radical intermediate is generated in a photochemical manner and represents the electrophile that reacts with the enamine. Organocatalysis and photocatalysis are merged together to afford α-alkylated aldehydes.



Scheme 4

Recently aminocatalysis evolved to the use of primary amines[14] as catalysts too and to the remote functionalization meeting the vinylogy principle.[15]

3. Non-covalent organocatalysis

Non-covalent organocatalysed processes rely on interactions such as hydrogen bonding[16] or the formation of ion pairs.[17]

Hydrogen bonding to an electrophile decreases its electron density (LUMO decreases in energy), activating it toward nucleophilic attack. This principle is

[13] Nicewicz D. A., MacMillan D. W. C., *Science* **2008**, 322, 77-80.

[14] Melchiorre P., *Angew. Chem. Int. Ed.* **2012**, 51, 9748-9770.

[15] (a) Jurberga I. D., Chatterjeea I., Tannerta R., Melchiorre P., *Chem. Commun.* **2013**, 49, 4869-4883; (b) Jianga H, Albrechtab Ł., Jørgensen K. A., *Chem. Sci.* **2013**, 4, 2287-2300; (c) Bertelsen S., Jørgensen K. A., *Chem. Soc. Rev.* **2009**, 38, 2178-2189.

[16] (a) Doyle A. G., Jacobsen E. N., *Chem. Rev.* **2007**, 107, 5713-5743; (b) Taylor M. S., Jacobsen E. N., *Angew. Chem. Int. Ed.* **2006**, 45, 1520-1543.

[17] (a) Brak K., Jacobsen E. N., *Angew. Chem. Int. Ed.* **2013**, 52, 534-561; (b) Brière J., Oudeyer S., Dallab V., Levacher V., *Chem. Soc. Rev.* **2012**, 41, 1696-1707.

employed frequently by enzymes for the acceleration of a variety of chemical processes. Taking example from nature also organic chemists have started to exploit hydrogen bonding as a mechanism for electrophile activation; in particular, chiral hydrogen bond donors (like for example thioureas, BINOL and TADDOL derivatives, etc…) have emerged as a broadly applicable class of organocatalysts for enantioselective synthesis.

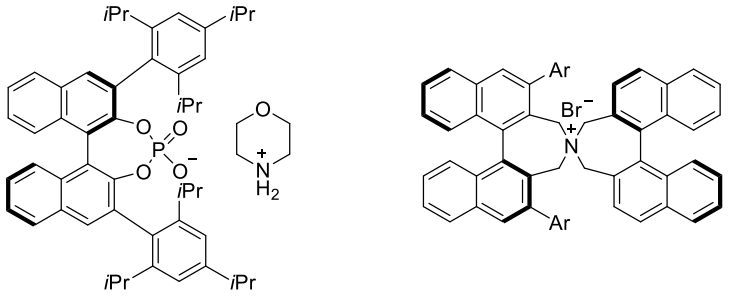
Most of chemical reactions proceed via charged intermediates or transition states; such reactions can be influenced by the counterion, especially if conducted in apolar organic solvents, where ion pairs are inefficiently separated by the solvent.

The use of ion pairing in asymmetric catalysis has been realized in enantioselective phase-transfer catalysis (PTC), which is well-established for reactions proceeding via anionic intermediates.[18] The underlying idea is that these intermediates are necessarily paired to a cation and, if this cation is chiral and a sufficient association can be achieved, reactions can proceed enantioselectively. The use of chiral non racemic salts, like ammonium or phosphonium, as effective phase-transfer catalysts has been intensively studied for the enantioselective carbon-carbon and carbon-heteroatom bond formation under mild biphasic conditions. The rational design of catalysts for targeted reaction is crucial because the generation of a well-defined chiral ion pair is necessary for electrophiles to react in a highly efficient and stereoselective manner. The advantages of this catalysis are its simple experimental procedures, versatility, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations.

Recently, the use of enantiomerically pure counteranions for the induction of asymmetry in reactions proceeding through cationic intermediates has emerged as a new concept, which has been termed asymmetric counteranion-directed catalysis (ACDC).[19] This catalysis refers to the induction of enantioselectivity in a reaction by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst. Examples of PTC and ACDC catalysts are shown in Figure 2.

[18] Ooi T., Maruoka K., *Angew. Chem. Int. Ed.* **2007**, 46, 4222-4266.

[19] Mahlau M., List B., *Angew. Chem. Int. Ed.* **2013**, 52, 518-533.



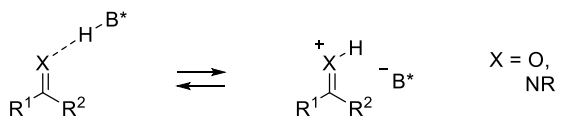
ACDC catalyst **PTC catalyst**

Figure 2

"An ion pair is defined to exist when cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (rt) available to separate them. This means that the ions stay associated longer than the time required for Brownian motion to separate non-interacting species."[20]

Hydrogen bonds can be discussed as a special case of ion pairing between the dipoles of a donor bond and an acceptor atom. This shows that the borders between ion pairing and other interactions are not so clean-cut.

Let's consider for example Brønsted acid organocatalysis where BINOL-derived phosphoric acids are amongst the most widely used motifs.[21] Regarding the activation of reactive electrophiles like imines, the formation of a chiral contact ion pair between the chiral acid and the substrate is generally assumed. In the case of carbonyl activation, the existence of a contact ion pair is less probable because of the low basicity of the oxygen atom; here a sort of equilibrium between the formation of a hydrogen bonding interaction and a contact ion pair complex is more likely. The pKa difference between the Brønsted acid catalyst and the carbonyl function determines which activation mode is more populated in the equilibrium of these two activated species (Scheme 5).

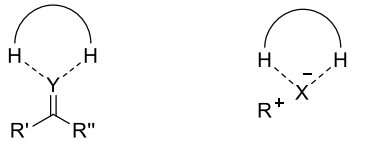


H-bonding interaction **contact ion pair**

Scheme 5

[20] Anslyn E. V., Dougherty D. A., *Modern Physical Organic Chemistry* (**2006**), University Science Books, Sausalito.
[21] Rueping M., Kuenkel A., Atodiresei I., *Chem. Soc. Rev.* **2011**, 40, 4539-4549.

Thioureas (this family of organocatalysts is described in details in Chapter 4) are widely used organocatalysts thanks to their ability to activate neutral electrophiles through hydrogen bonding; furthermore, these catalysts can be used also for anion-binding catalysis (Scheme 6). In this last case is difficult to have a smooth distinction between hydrogen bonding and ion pair catalysis; in fact, the reaction is not proceeding via ion-pairing with a charged chiral catalyst, but through hydrogen bonding to the intermediate ion pair by a chiral neutral catalyst.



Scheme 6

In particular when a bifunctional catalyst, like Takemoto or Soós thioureas, is used hydrogen bonding interactions are present, but also the basic site can deprotonate one of the reactant thus forming an ion pair (Figure 3 – enantioselective addition of acetylacetone to *trans*-β-nitrostyrene).

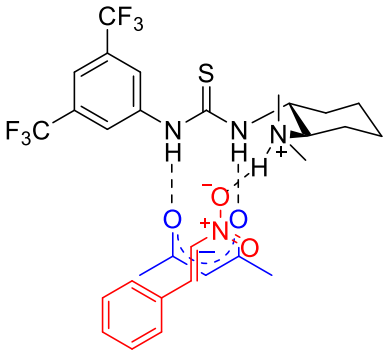


Figure 3

Finally, in the case of non-covalent organocatalysis the activation modes are not so clear-cut as for the covalent one and most of the cases are borderline involving somehow both hydrogen bonding and ion-pairing activation.

Chapter 2

Ion-Tagged Prolines

1. Introduction on proline catalysts

L-Proline is perhaps the most well-known and cheap organocatalyst. Although the natural L-form is normally used, proline is available in both enantiomeric forms, providing an advantage compared to enzymatic catalysis. Proline is the only natural amino acid to own a secondary amine functionality, featuring an enhanced nucleophilicity compared to the other amino acids. Hence, proline is able to act as a nucleophile, in particular with carbonyl compounds or Michael acceptors, to form either an enamine or an iminium ion. In these reactions, the carboxylic function of the amino acid acts as a Brønsted acid binding the acceptor by hydrogen bonding and rendering the proline a bifunctional catalyst.[22]

The high enantioselectivity of proline-mediated reactions can be rationalized by the ability of the molecule to provide highly organized transition states by an extensive hydrogen-bonding network. In all proline-mediated reactions, proton-transfer from the amine or the carboxylic group of proline to the forming alkoxide or imide is essential for charge stabilization and to facilitate C-C bond formation in the transition state.[23]

Since most of the steps in the catalytic cycle of proline catalysed reactions are in equilibrium, the enhanced nucleophilicity of the catalyst can entail a number of equilibrated reactions with the electrophiles present, resulting in a low turnover number.

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[22] (a) Sharma K., Sunoj R. B., *Angew. Chem. Int. Ed.* **2010**, 49, 6373-6377; (b) Schmid M. B., Zeitler K., Gschwind R. M., *Angew. Chem. Int. Ed.* **2010**, 49, 4997-5003; (c) Ajitha M. J., Suresh C. H., *J. Mol. Catal. A-Chem.* **2011**, 345, 37-43; (d) Schmid M. B., Zeitler K., Gschwind R. M., *J. Org. Chem.* **2011**, 76, 3005-3015.

[23] (a) Bahmanyar S., Houk K. N., *Org. Lett.* **2003**, 5, 1249-1251; (b) Bahmanyar S., Houk K. N., Martin H. J., List B., *J. Am. Chem. Soc.* **2003**, 125, 2475-2479; (c) Hoang L., Bahmanyar S., Houk K. N., List B., *J. Am. Chem. Soc.* **2003**, 125, 16-17; (d) Bahmanyar S., Houk K. N., *J. Am. Chem. Soc.* **2001**, 123, 12911-12912; (e) Bahmanyar S., Houk K. N., *J. Am. Chem. Soc.* **2001**, 123, 11273-11283.

Also the choice of the solvent is very limited for solubility reasons. Problems of solubility and poor turn-over number, forced people to use high reaction times and/or high catalyst loading.

Synthetic drawbacks related to proline are also present. For example, in the dimerization or oligomerization of α-unbranched aldehydes, it is difficult to avoid competing pathways. Reactions with acetaldehyde or acetophenone afford generally low yields and selectivity in aldol reactions.

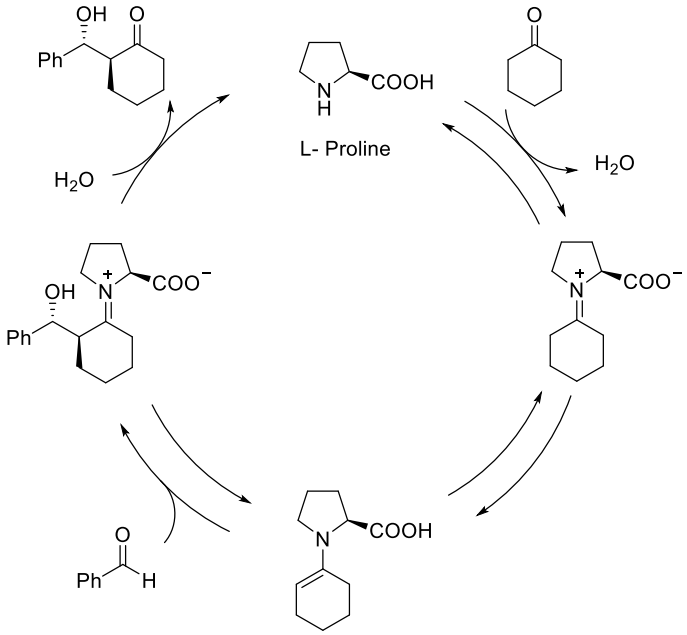
Although proline continues to play a central role in aminocatalysis, new synthetic analogues and more complex oligopeptides were developed to improve proline catalytic performances. Over the last 12 years, an outstanding number of new catalysts were synthesised by modifying proline skeleton, many of these successful efforts were directed to increase catalyst solubility in organic solvents by incorporating lipophilic substituents on proline structure. Skeleton modifications were generally accomplished by adding supplementary groups on the proline carboxylic function or on the hydroxyl group of *trans* or *cis*-4-hydroxy proline.[24] With similar purposes, the hydroxy group of 4-hydroxyproline has been successfully used as a joint to bind proline to soluble polymers[25] and solid matrices.[26]

The first asymmetric organocatalysed reaction using proline as the catalyst was the aldol addition[7] (Scheme 7). It has become the benchmark reaction to test new proline derivatives and demonstrate their efficiency as catalysts,[24] able to provide improved performances.

[24] (a) Aratake S., Itoh T., Okano T., Nagae N., Sumiya T., Shoji M., Hayashi Y., *Chem. Eur. J.* **2007**, 13, 10246-10256; (b) Gu L. Q., Yu M. L., Wu X. Y., Zhang Y. Z., Zhao G., *Adv. Synth. Catal.* **2006**, 348, 2223-2228; (c) Giacalone F., Gruttadauria M., Agrigento P., Lo Meo P., Noto R., *Eur. J. Org. Chem.* **2010**, 5696-5704; (d) Guizzetti S., Benaglia M., Pignataro L., Puglisi A., *Tetrahedron: Asymmetry* **2006**, 17, 2754-2760; (e) Chen X. H., Luo S. W., Tang Z., Cun L. F., Mi A. Q., Jiang Y. Z., Gong L. Z., *Chem. Eur. J.* **2007**, 13, 689-701; (f) Maya V., Raj M., Singh V. K., *Org. Lett.* **2007**, 9, 2593-2595; (g) Cobb A. J. A., Shaw D. M., Longbottom D. A., Gold J. B., Ley S. V., *Org. Biomol. Chem.* **2005**, 3 , 84-96; (h) Giacalone F., Gruttadauria M., Lo Meo P., Riela S., Noto R., *Adv. Synth. Catal.* **2008**, 350, 2747-2760; (i) Notz W., Tanaka F., Barbas III C. F., *Acc. Chem. Res.* **2004**, 37, 580-591; (j) Bellis E., Kokotos G., *Tetrahedron* **2005**, 61, 8669-8676; (k) Hayashi Y., Sumiya T., Takahashi J., Gotoh H., Urushima T., Shoji M., *Angew. Chem.* **2006**, 118, 972-975; (l) List B., Pojarliev P., Castello C., *Org. Lett.* **2001**, 3, 573-575; (m) Huang J., Zhang X., Armstrong D. W., *Angew. Chem. Int. Ed.* **2007**, 46, 9073-9077.

[25] Benaglia M., Cinquini M., Cozzi F., Puglisi A., Celentano G., *Adv. Synth. Catal.* **2002**, 344, 533-542.

[26] (a) Gruttadauria M., Salvo A. M. P., Giacalone F., Agrigento P., Noto R., *Eur. J. Org. Chem.* **2009**, 5437-5444; (b) Gruttadauria M., Giacalone F., Noto R., *Chem. Soc. Rev.* **2008**, 37, 1666-1688; (c) Kehat T., Portnoy M., *Chem. Commun.* **2007**, 2823-2825; (d) Font D., Jimeno C., Pericas M. A., *Org. Lett.* **2006**, 8, 4653-4655.



Scheme 7

2. Electrosteric activation

Ion tagged catalysts own an ionic-tag connected to the catalytic centre through a spacer (Figure 4). The cation is commonly covalently bounded to the catalytic centre and the anion is the counterion.

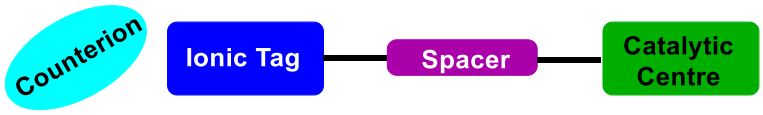


Figure 4

The presence of the counterion is of great importance to determine the solubility profile of the catalyst. Because of their ionic character, ion-tagged catalysts are usually insoluble in non-polar organic solvents, such as hexane or diethyl ether. Conversely, they are usually soluble in polar organic solvents, like for example acetonitrile, dimethylformamide, methanol, and in halogenated solvents, like chloroform or dichloromethane. The solubility in water depends on the nature of the tag: hydrophobicity can be achieved using cations bearing long alkyl chains or using hydrophobic counterions, like hexafluorophosphate (PF_6^-) or bis(trifluoromethylsulfonyl)imide (NTf_2^-).

Ammonium and phosphonium ions are the most common choice for the cation, while halogenated anions such as tetrafluoroborate (BF_4^-), PF_6^- or NTf_2^- are often

chosen as counterions. Among the ammonium ions, imidazolium and pyridinium are the most widely used, because of their stability in many chemical transformations.

The nature of the spacer is fundamental as well, since it must be stable in the reaction conditions. Moreover, the spacer length and flexibility should be properly designed to achieve the best catalytic performances.

The use of an ion-tag as a catalyst recovery strategy displays several attractive advantages: the careful choice of the cation and anion structure enables fine tuning of the solubility, so that immobilization on the supporting phase can be optimized and catalyst leaching reduced. In addition, ion-tags can be employed with common organic solvents, water and ILs, which are commonly addressed as benign solvents from an environmental point of view.[27]

Finally, due to the presence of a charged group, ion-tagged catalysts may display improved catalytic performance compared to their analogous untagged counterparts, when similar experimental conditions are applied.[28] The ionic group can stabilize the transition state, lowering the activation energy of the process thus enhancing the reaction rate. In fact, if the tag ion pair can approach charges that develop along the reaction coordinate with minimal distortion of bond angles and distances, it can lower the free-energy barrier by complementing charge separation in the dipolar transition state (Figure 5). As a consequence, the catalyst loading can be reduced compared to the reference homogeneous catalyst.

[27] Huo C., Chan T. H., *Chem. Soc. Rev.* **2010**, 39, 2977-3006.

[28] Lombardo M., Trombini C., *ChemCatChem* **2010**, 2, 135-145.

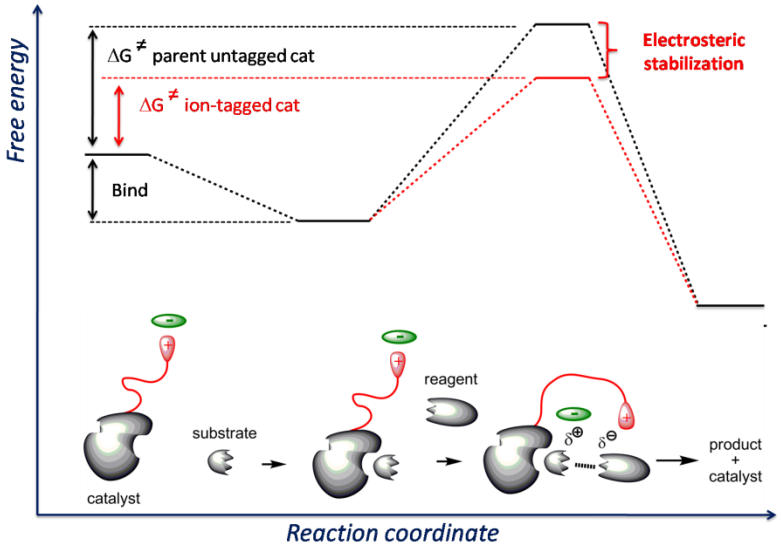


Figure 5

Since organocatalysis mechanistically mimics enzymes with small organic molecules, the electrostatic stabilization of a transition state by an ion tag can be considered a simplified version of the electrostatic activation provided in enzymatic reactions by protein cationic and anionic residues oriented towards the charges of a dipolar transition state. Moreover the presence of the ion pair also determines new steric interactions. Since the overall effect is the result of electrostatic and steric interactions, we defined it as "electrosteric stabilization" of the transition state by the ionic tag, or "electrosteric activation" of the catalytic process.

Provided that interactions between the ionic group and the transition state take place, it is conceivable that the stereochemical outcome of the reaction might be affected as well. Indeed, if parallel reaction pathways leading to stereoisomeric products are accessible, electrosteric interactions may affect competitive transition states to a different extent. However, predicting the effect of the ion-tag on reactivity and selectivity is an extremely challenging issue, since it depends on several factors: the ion covalently bounded to the catalyst, the nature of the potentially exchangeable counter ion, the length and flexibility of the spacer, which must ensure the best charge approach with minimal strain energy. In addition, also the interaction of the solvent with the polar transition state and the ionic group should be taken into account, particularly when polar and highly structured solvents, like water and ILs, are employed.

3. Electrosteric activation by using ion-tagged prolines: a combined experimental and computational investigation

The rate-determining steps in catalytic cycles of proline-catalyzed aldol reactions have been demonstrated to correlate well with those characteristic of class I aldolases, which activate substrates through an iminium ion formation step, followed by conversion to an enamine.[29] The amazing substrate-, site-, and stereo-selectivities characterizing enzymatic catalysis are the result of multiple bonds of the substrate to the active site through hydrogen bonding, hydrophobic, van der Waals, π-stacking, ion–ion and ion–dipole electrostatic interactions, to form the enzyme–substrate complex. This multiple binding is enabled by the presence of aminoacidic residues in the catalytic site of the enzyme that take part in the chemical reaction.[30]

The aim of introducing structural modifications on the proline, exploiting the use of 4-hydroxyproline as starting material for the synthesis of the catalyst, is to provide further interactions, for example extra hydrophobic and van der Waals or new hydrogen-bonding opportunities, in the transition state of the rate-limiting addition of enamine to the acceptor aldehyde.

The synthetic strategy of inserting an ionic group onto the proline original catalyst is aimed to improve its catalytic performance exploiting supplementary electrostatic interactions. The electrostatic stabilization of a transition state by an ion tag could be considered a simplified version of the electrostatic activation of enzymatic reactions, in which cationic and anionic residues are oriented towards the charges of a dipolar transition state.[31] Of course, also new steric interactions have to be considered together with the possibility of the ion tag to affect the stereochemical outcome of the reaction.

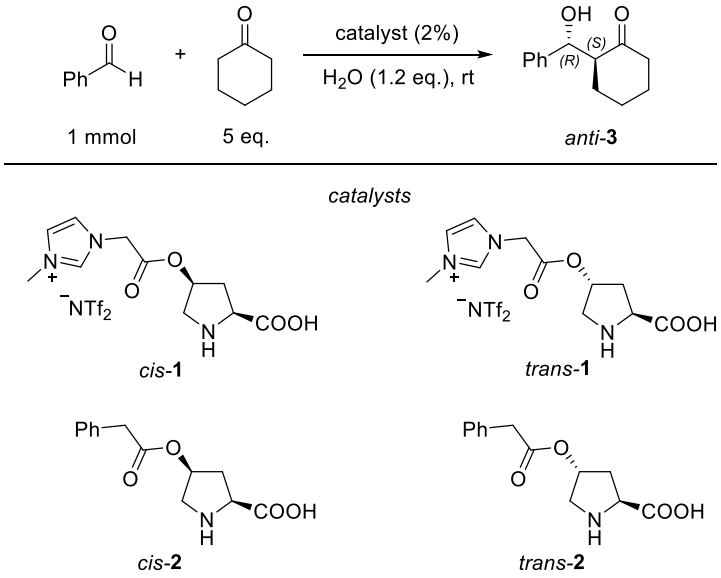
In order to study the electrosteric activation we designed a combined experimental and computational investigation on aldol reaction comparing the use of ion-tagged and tag-free prolines as catalysts (Scheme 8). This reaction was promoted, under the same conditions, by two diastereomeric ion-tagged prolines (*trans*- and *cis*-**1**) and by the

[29] (a) Mase N., Barbas III C. F., *Org. Biomol. Chem.* **2010**, 8, 4043-4050; (b) Barbas III C. F., Heine A., Zhong G., Hoffmann T., Gramatikova S., Bjçrnestedt R., List B., Anderson J., Stura E. A., Wilson I. A., Lerner R. A., *Science* **1997**, 278, 2085-2092.

[30] Bartlett G. J., Porter C. T., Borkakoti N., Thornton J. M., *J. Mol. Biol.* **2002**, 324, 105-121.

[31] Warshel A., Sharma P. K., Kato M., Xiang Y., Liu H., Olsson M. H. M., *Chem. Rev.* **2006**, 106, 3210-3235.

corresponding phenylacetic esters (*trans*- and *cis*-**2**). Catalysts **2** are isoster analogues of the *N*-methylimidazolium-tagged **1**.



Scheme 8

The use of an imidazolium ion as the tag was investigated, owing to its well-known ability to favour supramolecular organization by electrostatic, hydrogen-bonding, and/or aromatic-stacking interactions. It may simulate the role of a catalytic residue in enzyme catalysis through the promotion of supplementary interactions between the reacting species in the transition state.[32]

The reaction conditions for the selected benchmark reaction were identified in the solvent-free protocol previously developed for **1**,[33] in which 5 equivalents of cyclohexanone were used in the presence of an almost stoichiometric amount of water. The role of water in organocatalyzed aldol reactions was discussed recently by Gruttadauria and co-workers[34] and rationalized by Armstrong and Blackmond.[35]

To better evaluate reactivity differences, we decided to use a low loading of the four catalysts *cis*- and *trans*-**1** and *cis*- and *trans*-**2** (2 mol%) and a moderately reactive aldehyde such as benzaldehyde.

[32] Noujeim N., Leclercq L., Schmitzer A. R., *Curr. Org. Chem.* **2010**, 14, 1500-1516.

[33] (a) Lombardo M., Easwar S., Pasi F., Trombini C., *Adv. Synth. Catal.* **2009**, 351, 276-282; (b) Lombardo M., Pasi F., Easwar S., Trombini C., *Synlett* **2008**, 2471-2474.

[34] Gruttadauria M., Giacalone F., Noto R., *Adv. Synth. Catal.* **2009**, 351, 33-57.

[35] Zotova N., Franzke A., Armstrong A., Blackmond D. G., *J. Am. Chem. Soc.* **2007**, 129, 15100-15101.

The reaction was checked in each case by taking samples at different times (after 30 minutes and 1, 2, 3, 4, 7, 8 hours) and analyzing them by reversed-phase HPLC. Conversions were calculated based on the ratio of *anti*-**3** and benzaldehyde peak areas, having previously determined their corresponding response factors by calibration curves on purified samples. The resulting analysis of the conversion during the reaction time is reported in Figure 6.

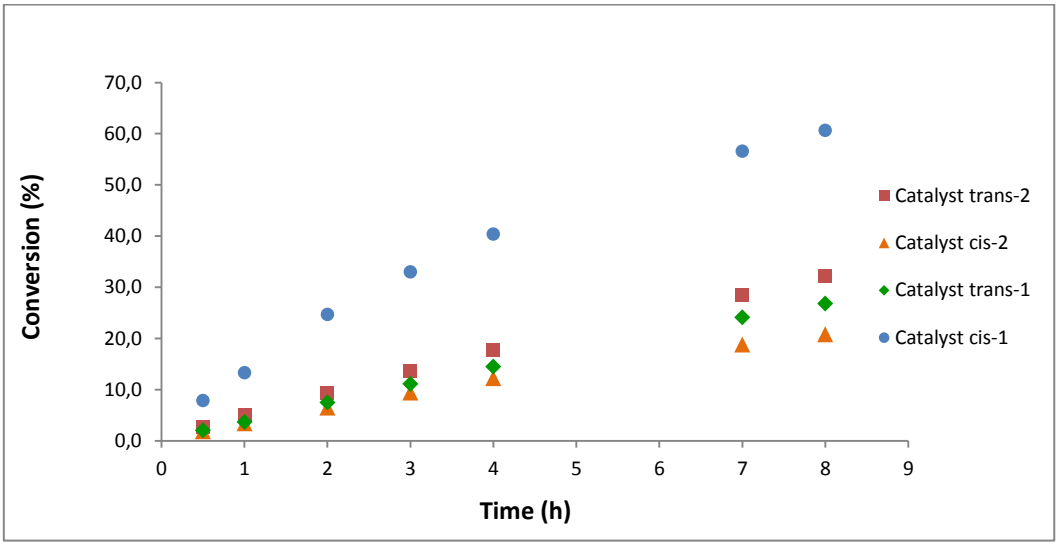


Figure 6

Catalyst *cis*-**1** showed a far superior activity compared to both its tagged analogue *trans*-**1** and the untagged catalysts **2**. In all cases here examined, enantioselectivities were almost complete (*ee*>99%) and diastereomeric ratios were in the 90:10–95:5 range in favor of the *anti*-**3** compound.

To understand in detail the origin of the catalytic effect and stereochemical outcome, in collaboration with the group of Prof. Bottoni and Dr. Miscione, we performed a computational DFT investigation on the reaction reported in Scheme 8 that focused on the rate-limiting step, i.e. the addition of the resulting enamine to the acceptor aldehyde. To this purpose, we considered two different model systems: one to emulate the ion-tagged systems (*trans*-**1** and *cis*-**1**) and the other for untagged ones (*trans*-**2** and *cis*-**2**).

In addition to electrostatic and steric interactions, given the nature of the ion tag and the counterion, other interactions played important roles in stabilizing the transition state of the rate-limiting step, in particular hydrogen bonds and π-stacking interactions. We analyzed in detail the interactions responsible for the superior activity

of *cis*-**1** compared to a simple proline, where the above-mentioned interactions were lacking, and compared to its isomer *trans*-**1** and the species *cis*-**2** and *trans*-**2** with similar steric biases but lacking a neat charge on the substituent at C-4 of the proline ring system.

The strong stabilization of the transition state with *cis*-**1** is the result of a complex interplay of hydrogen bonds, in particular those involving the NTf_2^- oxygen atoms and the hydrogen atoms of the ionic tag. In catalyst *cis*-**1** stabilizing π-stacking interactions between the NTf_2^- π oxygen lone pairs and the π electron cloud of benzaldehyde phenyl ring exist. A further stabilization owes to π-stacking interactions between the imidazole ring and the proline carboxyl group. Furthermore, during its migration the hydrogen atom interacts with the proline nitrogen, so this nitrogen atom can be thought to behave like a proton shuttle that "assists" the hydrogen atom transfer from the carboxyl group of the proline to the oxygen of the benzaldehyde, by stabilizing the corresponding transition state. These interactions are possible only if the system can achieve a suitable folded arrangement of the ionic tag, the spacer, and proline carboxyl group; this is due to the presence of the ion tag in *cis* geometry respect to the carboxyl function of the proline (Figure 7).

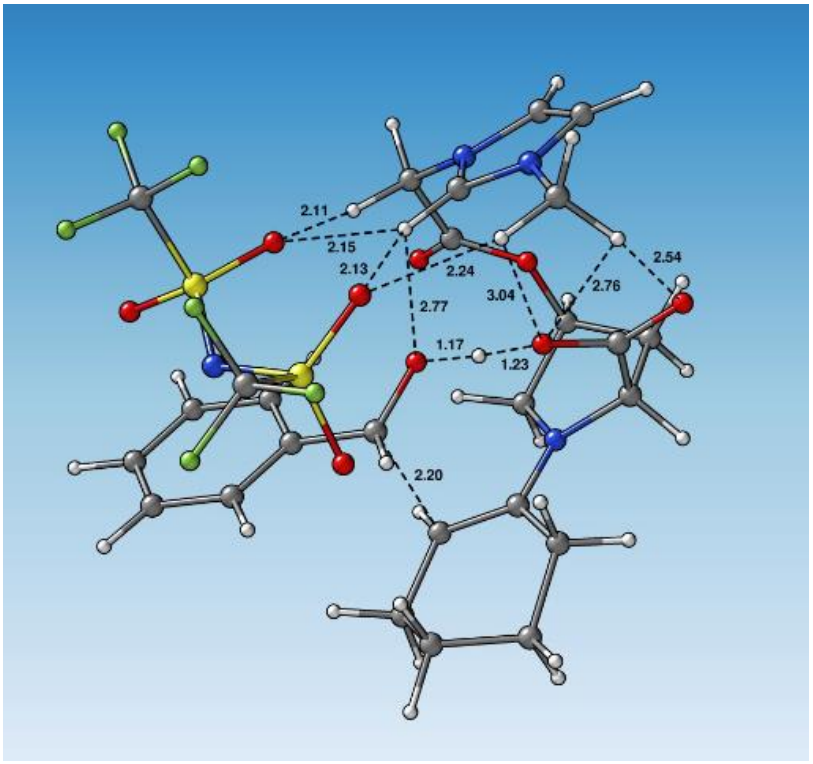


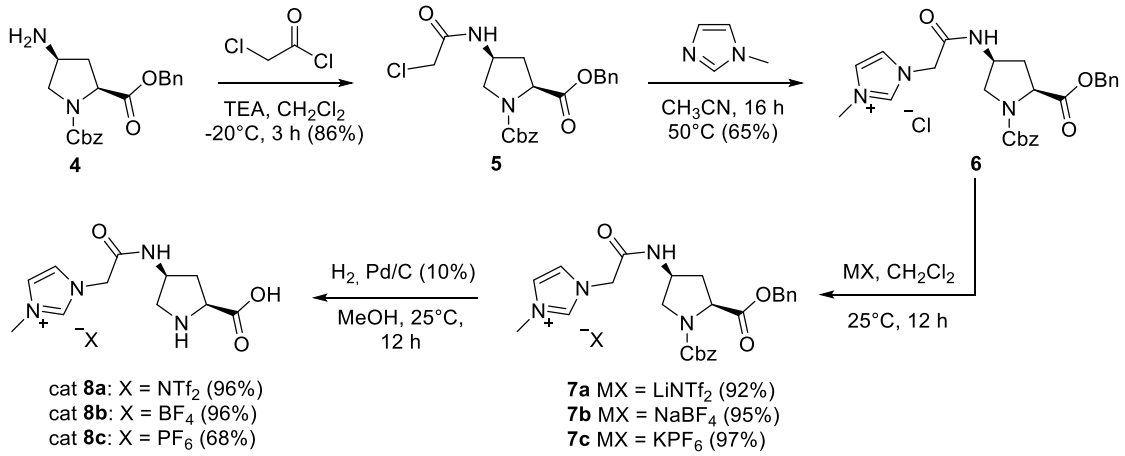
Figure 7

The poorer catalytic effect observed experimentally for catalysts **2** is due to the absence in the tag-free case of the folded enamine structure providing an activation barrier which is larger than the one computed for the ion-tagged system along the *cis* pathway. The folded enamine structure brings the ionic tag and the proline carboxyl group closer and activates stabilizing π-stacking interactions between the two fragments. If a benzene ring replaces the imidazolium group these interactions disappear and are replaced by others between the C-H bond of the aldehyde phenyl ring and the π electron cloud of the benzene ring bonded to proline, which are active only in the preliminary complex and not in the following transition state. Hence, the resulting barrier for the untagged system increases significantly.

This study computationally proved the superior reactivity of *cis*-**1** and, in all the cases examined, was in agreement with the stereochemical outcome of the reaction.

4. A new robust and efficient ion-tagged proline catalyst

A limit in the use of catalysts *cis*- and *trans*-**1** is given by the sensitivity of the ester spacer to hydrolysis. For example, when they were exposed to hydrogenation conditions in methanol, transesterification reactions occured and methanol had to be replaced with ethyl acetate to avoid this problem. Moreover, chromatographic purification was not possible and time-consuming crystallizations at low temperature were needed. A reduced storability (not more than 1 month under argon) was also a consequence of the sensitivity to hydrolysis of the ester linkage. The synthesis of a new, highly efficient *cis*-ion-tagged catalyst (**8**), possessing a robust amide linkage between the imidazolium tag and the proline ring, was developed (Scheme 9).

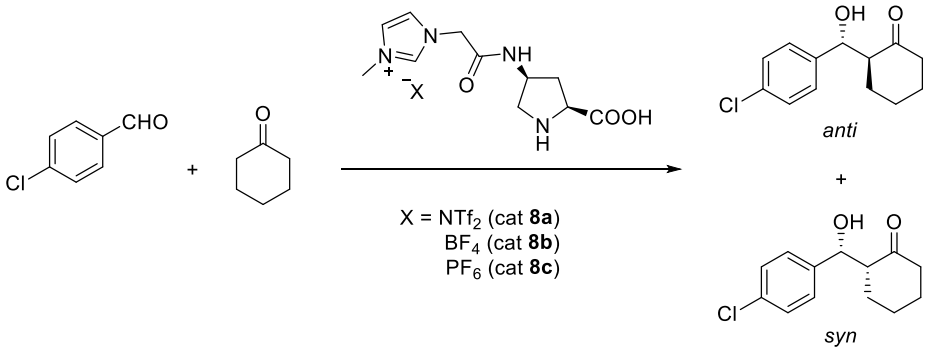


Scheme 9

When exposed to hydrogenolytic conditions (H_2 1 atm, Pd/C) in methanol, compounds **7a-c** were deprotected to **8a-c** with no trace of side reactions, confirming the stability towards hydrolysis of **8**. Moreover all precursors **6** and **7a-c** could be efficiently purified by chromatography on neutral alumina using CH_2Cl_2/MeOH mixtures (98:2 to 95:5 v/v). Furthermore, catalyst **8a** has been stored unaltered for six months without any precautions.

To compare the counterions and establish which was the best one, we tested catalysts **8a-c** in the aldol reaction between 4-chlorobenzadehyde and cyclohexanone in two different protocols: protocol A in ionic liquids and protocol B in solvent-free conditions in the presence of water (Table 1). In protocol B we used 5 equivalents of cyclohexanone which acted also as the reaction medium homogenizing the reaction mixture. This is an essential task when solid catalysts (like **8**) and solid acceptors are employed.

Table 1: Aldol reaction between 4-chlorobenzadehyde and cyclohexanone in two different protocols.[a]



Entry	Protocol	Catalyst	Solvent	Time (h)	Yield[b] (%)	*anti/syn*[c]	*ee* (%)[d]
1	A	**8a**	[bmim][NTf_2]	18	63	83:17	89
2	A	**8b**	[bmim][BF_4]	18	37	71:29	73
3	A	**8c**	[bmim][PF_6]	23	47	75:25	83
4	B	**8a**	-	18	91	97:3	99
5	B	**8b**	-	18	0	-	-
6	B	**8c**	-	23	60	92:8	95

[a] Reaction conditions protocol A: 4-chlorobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), catalyst (5 mol%), solvent (0.3 mL), rt; Reaction conditions protocol B: 4-chlorobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), catalyst (5 mol%), H_2O (0.6 mmol), rt. [b] Yield of the isolated product after flash-chromatography. [c] Determined by ^1H NMR of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC.

The ionic liquid used in protocol A was a 1-butyl-3-methylimidazolium ([bmim]) salt, carrying the same counterion of the selected catalyst. The **8a**/[bmim][NTf_2] system revealed to be the best catalyst/solvent pair compared to the analogous with PF_6 and BF_4 (entries 1-3).

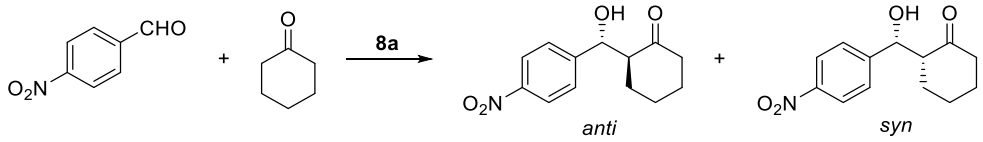
Catalyst **8a** was superior to **8c** also in protocol B (entries 4, 6), while hydrophilic catalyst **8b** failed to react (entry 5) for its lack of solubility in the reaction mixture.

The results reported in entries 1-6 prompted us to choose catalyst **8a** for the aldol reaction.

In the aldol reaction catalysed by prolines 4-nitrobenzaldehyde shows a higher reactivity with respect to 4-chlorobenzaldehyde, the former providing a quantitative yield with a lower catalyst loading in a shorter reaction time.

To verify the effect of the amount of water on the reaction we performed some experiments both employing protocol A and B (Table 2).

Table 2: Study of the effect of water amount.[a]



Entry	H_2O	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	-	8	20	70:30	98
2	1.2	3	99	98:2	>99
3	12	8	5	97:3	97
4	excess[e]	24	45	96:4	58
5[f]	-	18	91	75:25	85
6[f]	1.2	16	99	94:6	94

[a] Reaction conditions protocol B: 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), catalyst (2 mol%), H_2O, rt; [b] Yield of the isolated product after flash-chromatography. [c] Determined by ^1H NMR of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC. [e] Under emulsion conditions using 0.8 mL of water, under efficient stirring. [f] Protocol A: 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), [bmim][NTf_2] (0.3 mL), catalyst (2 mol%), H_2O, rt.

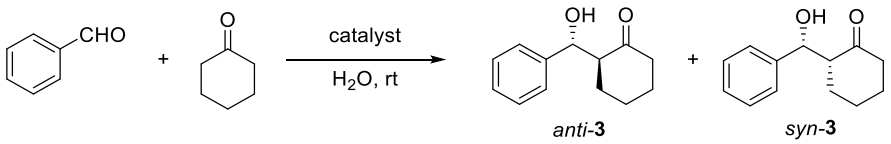
In protocol B without the addition of water (entry 1) a 20% yield was obtained after 8 hours using **8a** (2 mol%), accompanied by a poor diastereocontrol, while under the same conditions in the presence of 1.2 equivalents of water, yield, diastereo- and enantio-selectivity reached remarkable values (entry 2). Increasing the amount of

water (entry 3) or adopting an "on water" protocol (entry 4), that means generating in water microdroplets of the concentrated organic phase consisting of the reactants and the catalyst, had deleterious effects on conversions and enantiocontrol.

The presence of a nearly stoichiometric amount of water was also significant when protocol A was emplyed, not only in terms of an improved yield, but particularly in terms of a remarkable increase of the *anti*-diastereoselectivity and enantiocontrol (entries 5, 6).

The efficiency of catalyst **8a** was also compared to the one of the ester analogues *cis*-**1** and *trans*-**1**, using protocol B and benzaldehyde (Table 3). We chose benzaldehyde because it is less reactive than 4-nitrobenzaldehyde and allowed a more accurate evaluation of reactivity diversity.

Table 3: Comparison between catalytic performances of catalysts **8a** and *cis*-/*trans*-**1** in aldol reaction.[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	**8a**	24	82	95:5	>99
2	*trans*-**1**	24	66	93:7	94
3	*cis*-**1**	19	86	92:8	>99

[a] Reaction conditions: benzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), catalyst (5 mol%), H_2O (0.6 mmol), rt. [b] Yield of the isolated product after flash-chromatography. [c] Determined by ^1H NMR of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC.

After 19-24 hours we analysed the crude reaction mixtures for conversions, dr and *ee*. Catalyst *cis*-**8a** gave results similar to *cis*-**1**, providing a slightly lower yield, an higher dr and the same *ee*. In short, reactivity of **8a** locates very close to that of *cis*-**1**, while *trans*-**1** was less active and stereoselective under these conditions.

To study in detail the activity of these catalysts, we checked the conversion of the reaction during the time obtaining the curves shown in Figure 8.

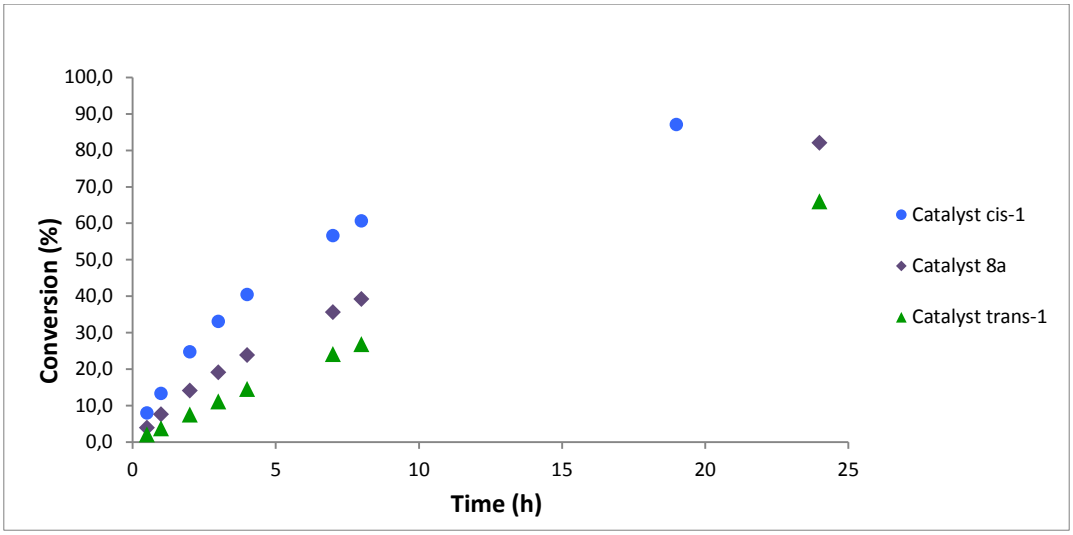
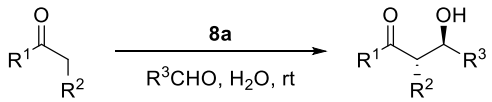


Figure 8

Finally, we explored the scope of the reaction, testing a few different combinations of donor and acceptor carbonyl compounds that included reactive and known poorly reactive substrates (Table 4).

Table 4: Scope of the aldol reaction using catalyst **8a**.[a]



Entry	Aldehyde	Ketone	**8a** (mol%)	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	C_6F_5CHO	cyclohexanone	5	1.5	99	>99:1	99
2	C_6F_5CHO	cyclohexanone	2	24	88	98:2	>99
3	C_6F_5CHO	cyclohexanone	0.1	24	64	98:2	97
4[e]	4-$MeOC_6H_4CHO$	cyclohexanone	5	60	35	80:20	98
5[f]	*n*-pentanal	cyclohexanone	10	50	80	>99:1	>99
6[f]	isobutanal	cyclohexanone	10	60	75	>99:1	>99
7	isobutanal	hydroxyacetone	10	24	60	88:12	99
8	4-$NO_2C_6H_4CHO$	cyclopentanone	1	3	97	83:17	97
9	4-$NO_2C_6H_4$ CHO	cycloheptanone	5	60	35	56:44	54
10	ethyl glyoxalate	cyclopentanone	5	4	99	70:30	77
11	4-$NO_2C_6H_4CHO$	acetone	2	24	91	-	35
12	4-$NO_2C_6H_4CHO$	hydroxyacetone	10	23	70	70:30	84

[a] Reaction conditions: aldehyde (0.5 mmol), ketone (2.5 mmol), catalyst, H_2O (0.6 mmol), rt. [b] Yield of the isolated product after flash-chromatography. [c] Determined by ^1H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC. [e] After 8 hours the conversion was 35%. [f] H_2O (0.65 mmol).

The reaction using pentafluorobenzaldehyde showed an high rate allowing us to decrease the catalyst loading up to 0.1 mol% (entries 1-3). While the result obtained with 4-methoxybenzaldehyde (entry 4), confirmed that electron-poor aldehydes are the preferred acceptors in the aldol reaction catalysed by proline derivatives.

Aliphatic aldehydes, even though less reactive, ensured an excellent *anti*-diastereoselection and a complete enantioselectivity when reacted with either cyclohexanone or hydroxy-acetone (entries 5-7).

Among cycloalkanones, cyclopentanone is the most reactive one (entries 8, 10) allowing us to reduce to 1 mol% the catalyst loading in the reaction with 4-nitrobenzaldehyde with an almost complete conversion in only 3 hours.

In terms of stereochemical control, cycloheptanone and acetone (entries 9 and 11) didn't afford good results.

As far as diastereoselection is concerned, hydroxyacetone presented its known irregular behaviour. Indeed **8a** provided *anti*-adducts (entries 7 and 12) with proline itself,[36] as well as other proline derivatives like C_2-symmetrical bis-prolinamides[37] and small *N*-terminal prolyl peptides.[38] Conversely, a variety of structurally different chiral amines are known to favour the formation of *syn* adducts using hydroxyacetone as donor in aldol reactions.[39]

5. Ion-tagged proline catalyst recycling by using a silica gel bound multilayered ionic liquid phase

A major challenge over the last two decades has been to heterogenize intrinsically homogeneous catalysts by anchoring them on a solid support to allow a simple catalyst–product separation and the recycling of structurally complex and expensive species. However, a decrease in catalyst activity is generally associated with immobilization: the presence of mass transfer limitations, heat transfer, possible lack of homogeneity of the solid support, and other factors make the reaction kinetics very

[36] Notz W., List B., *J. Am. Chem. Soc.* **2000**, 122, 7386-7387.

[37] Samanta S., Liu J., Dodda R., Zhao C., *Org. Lett.* **2005**, 7, 5321-5323.

[38] Tang Z., Yang Z., Cun L., Gong L., Mi A., Jiang Y., *Org. Lett.* **2004**, 6, 2285-2287.

[39] (a) Kumar A., Singh S., Kumar V., Chimni S. S., *Org. Biomol. Chem.* **2011**, 9, 2731-2742; (b) Czarnecki P., Plutecka A., Gawroński J., Kacprzak K., *Green Chem.* **2011**, 13, 1280-1287; (c) Demuynck A. L. W., Peng L., de Clippel F., Vanderleyden J., Jacobs P. A., Selsa B. F., *Adv. Synth. Catal.* **2011**, 353, 725-732; (d) Paradowska J., Rogozińska M., Mlynarski J., *Tetrahedron Lett.* **2009**, 50, 1639-1641; (e). Xu X., Wang Y., Gong L., *Org. Lett.* **2007**, 9, 4247-4249.

complex.[40] Moreover, the weakening of the catalyst support bonds ascribable to the stress of repeated cycles results in the unavoidable leaching of the catalyst.[41]

Liquid–liquid homogeneous conditions are an attractive alternative strategy for combining the advantages of homogeneous and heterogeneous catalysis. These include superlative activities and selectivities under mild homogeneous conditions, simple operations for product-catalyst separation with minimum cross-contamination, and catalyst recycling.[42] A biphasic system consisting of two mutually insoluble solvents is proposed. In one phase the reaction takes place and the solvent entraps the catalyst; in the other phase, reactants and products can be removed from the catalyst-containing solvent. High degrees of dispersion can be obtained through emulsification and the two phases can be separated by conventional means. The main limitation of this approach is the identification of a solvent pair that enables a perfectly complementary catalyst and product partition, which is essential to limit final cross-contamination and ensure efficient catalyst recycling. The advantages are those typical of homogeneous processes, namely faster reactions with higher selectivities, followed by a simple physical operation such as decantation, after which the catalyst-containing phase can be reused directly. Several technical solutions have been proposed for liquid–liquid biphasic homogeneous catalysis.[43] Water, fluorous phases, supercritical fluids, and ionic liquids are possible components of the liquid–liquid biphase.

The main problem with these reactions is to magnify the affinity of the catalyst for one of the two phases. Generally, this is done by the installation of a solvent-recognition element on the structure of the catalyst. For example, if an organic solvent is used in combination with an immiscible ionic liquid, an ion pair can be installed onto the catalyst frame to magnify its solubility into the ionic liquid. One ionic group is covalently bonded to the catalyst, whereas the exchangeable counterion allows the control of the catalyst solubility profile.[44] Literature on the physico-chemical properties

[40] (a) Buchmeiser M. R., *Chem. Rev.* **2009**, 109, 303-321; (b) Fraile J. M., García J. I., Mayoral J. A., *Chem. Rev.* **2009**, 109, 360-417; (c) Trindade A. F., Gois P. M. P., Afonso C. A. M., *Chem. Rev.* **2009**, 109, 418-514; (d) Lu J., Toy P. H., *Chem. Rev.* **2009**, 109, 815-838; (e) Shylesh S., Schünemann V., Thiel W. R., *Angew. Chem. Int. Ed.* **2010**, 49, 3428-3459; (f) Collis E. A. C., Horváth I. T., *Catal. Sci. Technol.* **2011**, 1, 912-919.

[41] Mayr M., Mayr B., Buchmeiser M. R., *Angew. Chem. Int. Ed.* **2001**, 40, 3839-3842.

[42] Lombardo M., Quintavalla A., Chiarucci M., Trombini C., *Synlett* **2010**, 1746-1765.

[43] (a) Keim W., *Chem. Ing. Tech.* **1984**, 56, 850-853; (b) Keim W., *Green Chem.* **2003**, 5, 105-111.

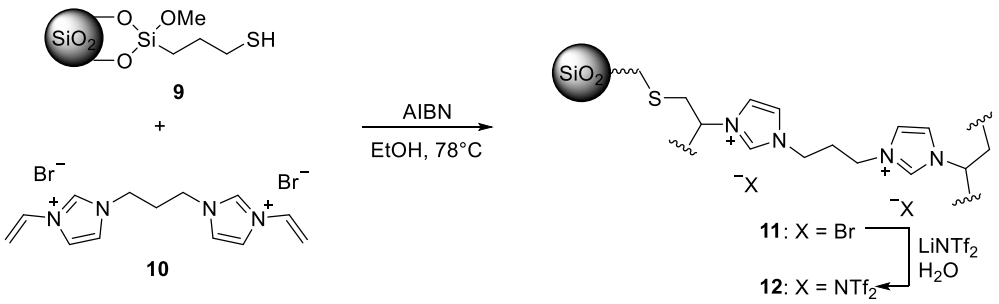
[44] (a) Chiappe C., Pieraccini D., *J. Phys. Org. Chem.* **2005**, 18, 275-297; (b) Weingärtner H., *Angew. Chem. Int. Ed.* **2008**, 47, 654-670; (c) Marciniak A., *Int. J. Mol. Sci.* **2010**, 11, 1973-1990; (d) Werner S., Haumann M., Wasserscheid P., *Annu. Rev. Chem. Biomol. Eng.* **2010**, 1, 203-230.

of ionic liquids has found that the use of Tf_2N^- brings a dramatic decrease of solubility in water.

A major limitation in traditional biphasic ionic liquid-organic solvent systems is the need for relatively large amounts of ionic liquids, which are expensive solvents. In addition, the high viscosity of ionic liquids compared to classical organic solvents can induce mass transfer limitations. Both these drawbacks can be circumvented by immobilizing a thin film of ionic liquid onto a high surface area support.[45] Supported ionic liquid phases (SILP) on porous support material have been prepared by covalent bonding of the ionic liquid to the support or by physisorption, which exploits van der Waals and dipole forces. IL immobilization by covalent bonding is much more robust and the ionic liquid film is not easily leached from the support to polar solvents.

Covalently bonded aromatic ionic liquids offered the best results in terms of reaction performance and recyclability. Notably, the SILP preparation strategy affects the nature of the liquid microlayer. Indeed, the SILP is present as a monolayer if there is covalent bonding to the surface, whereas it appears as a multilayer if the IL is adsorbed.

To overcome this problem, Gruttadauria et al. proposed an innovative approach to prepare a multilayered covalently bonded supported ionic liquids phases (mlc-SILP). This method is shown in Scheme 10, representing the mlc-SILP we used to recycle our catalyst **8a**.



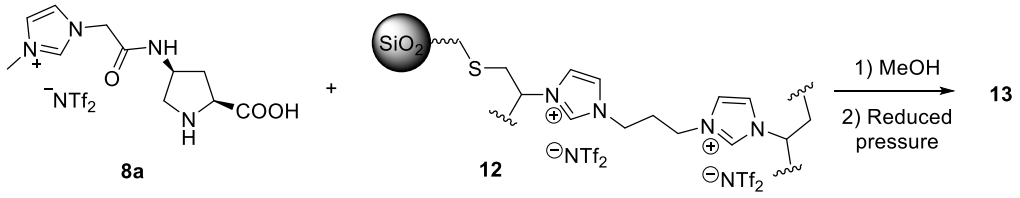
Scheme 10

This approach offers all of the desirable features of a click reaction: high efficiency, simplicity, no side products, relatively fast reaction, and high yield. The reaction led to

[45] (a) Mehnert C. P., *Chem. Eur. J.* **2005**, 11, 50-56; (b) Shi F., Zhang Q., Li D., Deng Y., *Chem. Eur. J.* **2005**, 11, 5279-5288; (c) Riisager A., Fhermann R., Haumann M., Wasserscheid P., *Top. Catal.* **2006**, 40, 91-102; (d) Sievers C., Jimenez O., Müller T. E., Steuernagel S., Lercher J. A., *J. Am. Chem. Soc.* **2006**, 128, 13990-13991; (e) Burguete M. I., Galindo F., Garcia-Verdugo E., Karbass N., Luis S. V., *Chem. Commun.* **2007**, 3086-3088; (f) Mikkola J. T., Virtanen P. P., Kordás K., Karhu H., Salmi T. O., *Appl. Catal. A* **2007**, 328, 68-76.

the near-quantitative anchoring of the employed salt on the surface of the support to yield the mlc-SILP material **11**. As the bisvinylimidazolium salt **10** is added in excess relative to the amount of thiol groups (3.62 $mol_{salt}/mol_{thiol\ group}$), the formation of imidazolium cross-linked networks through self-addition reaction of the double bonds is expected. The multilayered ionic liquid phase is generated through this oligomerization. The obtained material showed a surface area of 128 m^2/g and a cumulative pore volume of 0.2 cm^3/g. Anion metathesis was accomplished to give the supported ionic liquid material **12** with the correct counterion.

The repeated use of a catalyst recycling may give decomposition of it over time, so we chose the *cis*-ion-tagged proline **8a** catalyst since it's characterized by a robust amide linkage between the catalytically active site and the imidazolium tag, with bistriflimide as the counterion. We speculated that the structural similarity between the imidazolium motif and the counterion between mlc-SILP **12** and catalyst **8a** should optimize their mutual interactions, and, hence, the solubility of **8a** in **12**. The absorption of **8a** was accomplished simply by stirring the mlc-SILP **12** with a methanol solution of **8a** and then removing the solvent under reduced pressure. The white powder obtained (**13**) was prepared with a catalyst loading of 13.8 wt% (Scheme 11).



Scheme 11

Given the excellent catalytic performances of **8a** in aldol addition, we decided to recycle it exploiting its adsobtion on **12** and chosing 4-nitrobenzaldehyde and cyclohexanone as the partners of aldol reaction.

Catalyst **8a** was tested in aldol reaction using the previously described protocol B. For the development of the recycling procedure we used the same reaction conditions replacing pure **8a** with the catalytic material **13**.

The process is split into a reaction and a separation stage (Figure 9). In the reaction stage, **13** was first soaked with cyclohexanone and water. The aldehyde was added and the mixture stirred at room temperature for the required time, monitoring the reaction by TLC.

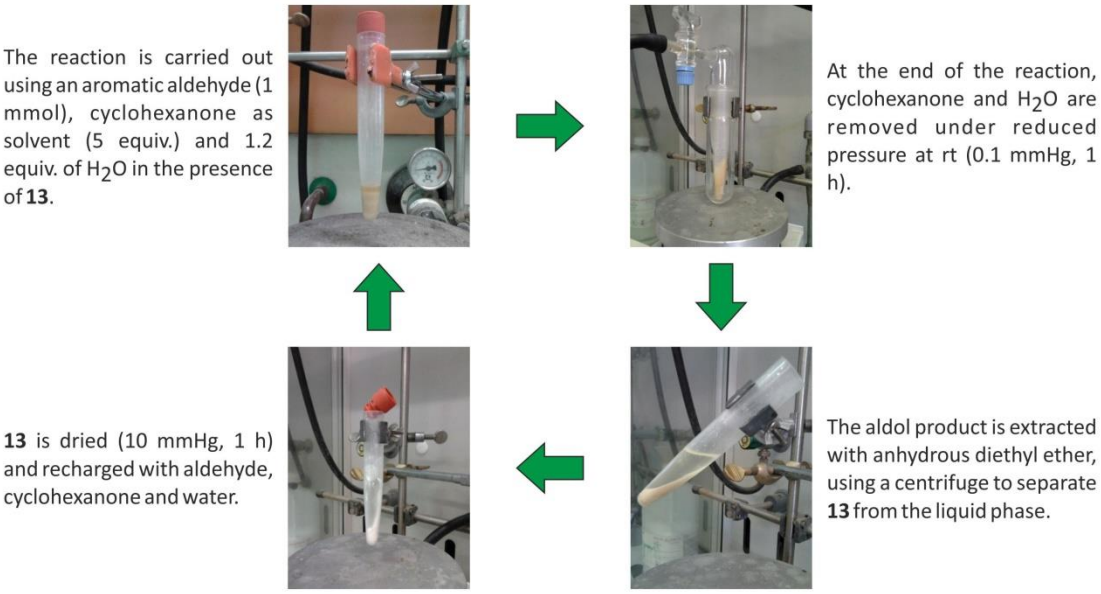
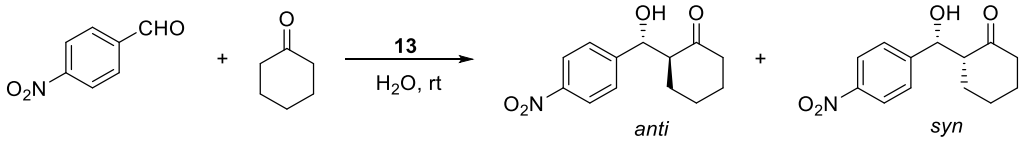


Figure 9

In this first stage, the composite material **13** acts as a catalyst reservoir that delivers **8a** to the cyclohexanone phase, allowing a homogeneous reaction to take place. To better understand the partitioning of catalyst **8a** between the mlc-SILP/cyclohexanone system in this stage, we stirred material **13** (193 mg, 0.05 mmol of **8a**) with cyclohexanone (5 mmol) for 2.5 hours at room temperature. The mixture was then filtered, and the cyclohexanone was evaporated at reduced pressure. Waiting the crude residue and recording a ^{1}H NMR we found out that approximately 50% of catalyst **8a** was extracted by cyclohexanone from mlc-SILP **12**. In the separation stage, cyclohexanone is removed under vacuum and the resulting solid residue is extracted with anhydrous diethylether, which is a catalyst antisolvent. Here, **12** acts as a catalyst sponge redissolving **8a** in its multilayer film and restoring **13**, which can be reused. Product extraction is extremely selective: no trace of catalyst was detected in the product containing phase.

The first experiments reported in Table 5 were aimed to determine the performances achievable with different catalyst loadings.

Table 5: Aldol reaction with different catalyst loadings.[a]



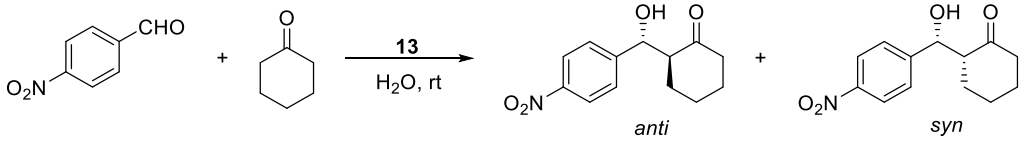
Entry	**13** (mg)	**8a** (%)	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	386	10	2	99	94:6	>99
2	193	5	2	96	96:4	>99
3	77	2	3	99	96:4	99
4	39	1	17	99	97:3	99
5	19	0.5	19	97	98:2	99

[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), cyclohexanone (5 mmol), **13**, H_2O (1.2 mmol), rt. [b] Yield of the isolated product. [c] Determined by ^1H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC.

The reaction proceeded slower decreasing the catalyst loading, but it still worked well using only 0.5 mol% of catalyst. The reactivity recorded using this procedure were the same as in homogeneous conditions.

We performed the recycling procedure of **13** in the model reaction first using 1 mol% of catalyst (Table 6).

Table 6: Recycle of **13** with 1 mol% of catalyst.[a]



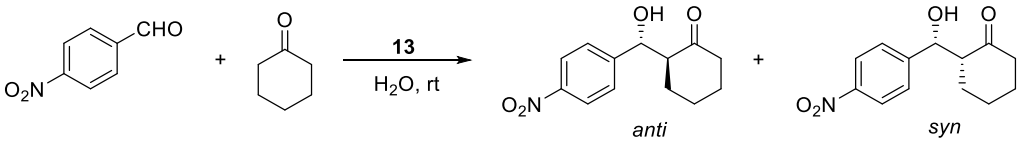
Cycle	**13** (mg)	**8a** (%)	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	39	1	17	99	97:3	99
2	39	1	17	99	98:2	99
3	39	1	17	99	95:5	98
4	39	1	17	97	95:5	97
5	39	1	17	89	94:6	96
6	39	1	17	40	93:7	92

[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), cyclohexanone (5 mmol), **13** (39 mg, **8a** 1 mol%), H_2O (1.2 mmol), rt. [b] Yield of the isolated product. [c] Determined by ^1H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC.

In these conditions we were able to recycle the catalyst, recording a consistent drop of yield only in the 6th cycle.

We performed the same recycling experiment lowering to 0.5 mol% the amount of **8a** (Table 7).

Table 7: Recycle of **13** with 0.5 mol% of catalyst.[a]



Cycle	**13** (mg)	**8a** (%)	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	19	0.5	19	97	98:2	99
2	19	0.5	19	87	96:4	97
3	19	0.5	19	34	96:4	95

[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), cyclohexanone (5 mmol), **13** (19 mg, **8a** 0.5 mol%), H_2O (1.2 mmol), rt. [b] Yield of the isolated product. [c] Determined by ^1H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC

In this case we were able to reuse the catalytic material **13** two times, recording in the 3rd cycle a lowering of the yield. Given the relatively small amount of **13** used, we probably lost some catalytic material during the extaction of the product.

The cumulative productivity P_n and the averaged enantiomeric excess $[EE]_n$ after n cycles, which were performed by using the same molar amount of limiting aldehyde and the same excess of ketone in each run, were calculated by using Equations (1) and (2), as reported by Mandoli et al.,[46] in which y_i is the yield and ee_i the enantiomeric excess of the i^{th} recycle.

$$P_n = \frac{aldehyde\ (mmol)}{catalyst\ (mmol)} \cdot \frac{\sum_{i=1}^{n} y_i(\%)}{100} \qquad (1)$$

$$[EE]_n = \frac{\sum_{i=1}^{n} y_i(\%) \cdot ee_i}{\sum_{i=1}^{n} y_i(\%)} \qquad (2)$$

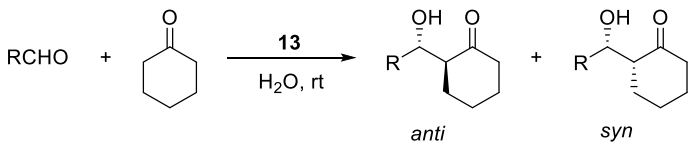
The calculated values for the recycling experiments in Table 6 that used 1 mol% of the catalyst were remarkably high, with P_6=523 and $[EE]_6$=97% and, to the best of our knowledge, unprecedented in this benchmark organocatalysed aldol reaction. Although use of 0.5 mol% of the catalyst resulted in a low yield and stereoselectivity in

[46] Cancogni D., Mandoli A., Jumde R. P., Pini D., *Eur. J. Org. Chem.* **2012**, 1336-1345.

the third recycle (Table 7), the productivity and the averaged enantiomeric excess remained high, with P_3=436 and $[EE]_3$=98%.

Experiments collected in Table 8 were aimed to demonstrate the robustness of the mlc-SILP **12**. By using methanol, we washed out **8a** from the sample of **13** used for the previously reported experiments. Freed solid material **12** was then reloaded with fresh **8a** at a loading of 13.8 wt%, to give a regenerated sample of **13**. This material was then subjected to a longer series of recycling experiments using 5 mol% of catalyst, to allow the use of less-reactive aldehydes.

Table 8: Recycle of **13** with 5 mol% of catalyst changing the aldehyde.[a]



Cycle	Aldehyde	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	4-$NO_2C_6H_4CHO$	2.5	99	94:6	98%
2	4-$NO_2C_6H_4CHO$	2.5	99	93:7	97%
3	4-$NO_2C_6H_4CHO$	2.5	99	94:6	97%
4	4-$NO_2C_6H_4CHO$	2.5	99	93:7	94%
5	4-$NO_2C_6H_4CHO$	2.5	99	93:7	96%
6	4-ClC_6H_4CHO	18	92	97:3	99%
7	4-BrC_6H_4CHO	18	95	97:3	97%
8	4-CNC_6H_4CHO	7	99	93:7	92%
9	4-$NO_2C_6H_4CHO$	2.5	98	93:7	94%
10	Ph-CHO	24	94	90:10	96%
11	4-$NO_2C_6H_4CHO$	2.5	95	93:7	92%
12	4-$NO_2C_6H_4CHO$	2.5	89	92:8	89%
13	4-$NO_2C_6H_4CHO$	2.5	90	90:10	87%
14	4-$NO_2C_6H_4CHO$	2.5	81	90:10	88%
15	4-$NO_2C_6H_4CHO$	2.5	81	89:11	91%

[a] Reaction conditions: aldehyde (1 mmol), cyclohexanone (5 mmol), **13** (193 mg, **8a** 5 mol%), H_2O (1.2 mmol), rt. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC.

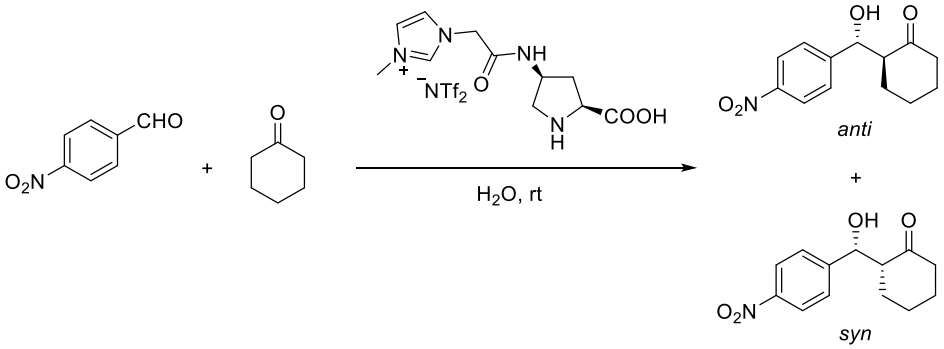
Besides the robustness of mlc-SILP **12**, which can be regenerated and reused for 15 cycles, these experiments showed the efficiency of the reaction workup, which

ensured a very effective catalyst recovery and a quantitative product extraction, as confirmed by the absence of cross-contamination when different aldehydes were used in consecutive runs.

In the long term, iminium intermediates may irreversibly decompose, namely by decarboxylation or oxidation, or they may epimerize with a detrimental effect on maximum turnover numbers or in preservation of stereocontrol with longer reaction times. This may explain the worsening of catalytic performances after 15 cycles, together with a loss of catalytic material.

The role of material **12** in this process revealed to be very important. Indeed, we studied amorphous and C18 silica gels as surrogates of the mlc-SILP in recycling experiments, but they didn't provide the same good resuts. Both silicas were charged with catalyst **8a** at a loading of 13.8 wt% with a methanol solution, followed by stripping of the solvent under vacuum. Applying the same conditions of entry 2 (Table 5) to amorphous silica gel loaded with **8a**, the aldol product was recovered in 36% yield after 2.5 hours with an *anti/syn* diastereomeric ratio of 80:20. The use of C18 silica gel charged with **8a** was more effective. The first reaction in the same conditions delivered the product in 87% yield after 2.5 hours, with an *anti/syn* diastereomeric ratio of 97:3 and *ee* (*anti*)>99%. However, in the second run, the yield decreased to 73 %, indicating that the aliphatic monolayer of this reverse silica gel phase was much less efficient than **12** as a catalyst trap. Conversely to these disappointing resuts, the use of **12** do not show any significant change in catalytic activity and stereocontrol as previously reported, thus demonstrating its importance and efficiency as a catalyst trap. A series of reactions were set up also simply using catalyst **8a** in the absence of mlc-SILP and adopting exactly the same experimental protocol reported in entry 3 in Table 5. The results obtained with 4-nitrobenzaldehyde are reported in Table 9.

Table 9: Recycle of **8a** with 2 mol% of catalyst loading [a]



Cycle	Yield (%)[b]	*anti/syn*[c]	*ee* (%)[d]
1	99	98:2	>99
2	99	98:2	>99
3	76	98:2	>99

[a] Reaction conditions: aldehyde (1 mmol), cyclohexanone (5 mmol), **8a** (2 mol%), H_2O (1.2 mmol), 16 h, rt; [b] Yield of the isolated product. [c] Determined by ^1H NMR and HPLC of the crude mixture. [d] Determined for the *anti* product by CSP-HPLC

In the absence of mlc-SILP **12**, a drastic drop in the yield of the aldol product was observed already in the third cycle, although high values of diastereo- and enantioselectivity were retained. This was probably due to the loss of catalyst during the work up and confirmed the importance of **12** in the catalyst recycling.

6. Conclusions

We studied the concept of electrosteric activation through a combined compuational and experimental investigation analysing the aldol reaction catalysed by ion-tagged and ion-free prolines. From these studies we found out that the better performances of the ion-tagged proline *cis*-**1** were due to the presence of the ionic tag on the same side of the carboxyl group of the proline, thus enabling stabilizing hydrogen bonding and π-stacking interactions in the transition state.

Knowing now the importance of the *cis* geometry for the ion-tagged proline catalysts and the instability of catalyst *cis*-**1** toward hydrolytic conditions, we developed a new ion-tagged catalyst with a robust amide linkage between the imidazolium ion and the proline ring (**8a**). This made the catalyst highly stable to acidic, hydrolytic and reductive conditions. Catalyst **8a** was prepared in a 4-step sequence in 50% total yield from **4** on a multigram scale and, using the reaction protocol "in the

presence of water", **8a** can be considered equal to *cis*-**1** in terms of overall performance.

The robustness of **8a** and its catalytic performances prompted us to develop a recycling procedure of this catalyst in the aldol reaction. We used material mlc-SILP **12**, produced for the first time in Gruttadauria's lab, to charge it with catalyst **8a**; the resulting composite material **13** played a dual role, depending on the nature of the second solvent it was in combination with. For the reaction we used a molar excess of cyclohexanone as partner solvent, while for the work-up we used anhydrous diethyl ether as antisolvent. In these conditions the recycle of the catalytic material **13** was very efficient and productivities above 400–500 were achieved easily using 0.5 or 1 mol% of catalyst **8a**. The robustness of **12**, **8a** and the overall reaction procedure was confirmed further by the 15 cycle for which a regenerated **13** was employed, without any detectable cross-contamination when different aldehydes were used in consecutive runs.

7. Experimental section

General Information:

Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates (Merck 60 F254) were used and compounds were visualized by irradiation with UV light and/or by treatment with a soluition $KMnO_4$ followed by heating. Flash chromatography was performed using silica gel Merck grade Type 9385 230-400, 60 Å purchased from Sigma-Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 and on a Varian Gemini 200. Chemical shifts are reported in d relative to tetramethylsilane (TMS); the coupling constants *J* are given in Hz. Chiral HPLC studies were carried out on a Hewlett-Packard series 1090 instrument.

Preparation of catalysts Catalysts *cis*-1, *trans*-1 and *trans*-2 were prepared according to literatureprocedures.[33,47]

cis-**2**: A solution of diethyl azodicarboxylate (DEAD) (0.824 mL, 1.8 mmol) in anhydrous THF (3 mL) was added dropwise to an icecold solution of triphenylphosphine (0.432 g, 1.65 mmol), phenylacetic acid (0.215 g, 1.58 mmol), and *N*-benzyloxycarbonyl-(2*S*,4*R*)-

[47] Giacalone F., Gruttadauria M., Lo Meo P., Riela S., Noto R., *Adv. Synth. Catal.* **2008**, 350, 2747-2760.

4-hydroxyproline benzyl ester (0.533 g, 1.5 mmol) in anhydrous THF (8 mL). The reaction mixture was allowed to warm to room temperature and stirred for a further 24 h. Concentration of the reaction mixture in vacuo followed by silica-gel column chromatographic purification of the residue (cyclohexane/ethyl acetate 90:10) furnished quantitatively the *cis*-phenyl acetate. $[\alpha]_D^{20}$ =-39.9° (c=0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, two conformational isomers 1:1) δ=2.31–2.38 (m, 2 H), 2.39–2.53 (m, 2 H), 3.29–3.41 (m, 4H), 3.58–3.53 (m, 2H), 3.76–3.87 (m, 2H), 4.55 (dd, *J*=2.1, 9.4 Hz, 1 H), 4.64 (dd, *J*=2.2, 9.3 Hz, 1 H), 5.00–5.08 (m, 2 H), 5.08–5.13 (m, 2 H), 5.13–5.18 (m, 2H), 5.18–5.23 (m, 2H), 5.23–5.30 (m, 2 H), 7.15–7.21 (m, 4H), 7.22–7.41 ppm (m, 26H); ^{13}C NMR (100 MHz, $CDCl_3$, two conformational isomers 1:1) δ=171.3, 171.0, 170.97, 170.87, 154.7, 154.3, 136.4, 135.7, 135.6, 133.4, 129.29, 129.27, 128.65, 128.56, 128.51, 128.45, 128.4, 128.21, 128.16, 128.10, 128.04, 127.96, 127.2, 73.2, 72.2, 67.4, 67.3, 67.0, 66.9, 58.1, 57.8, 52.7, 52.4, 40.9, 36.4, 35.4 ppm; elemental analysis calcd for $C_{28}H_{27}NO_6$ (473.52): C, 71.02; H, 5.75; N, 2.96; found: C, 71.69; H, 5.69; N, 2.95.

The intermediate *cis*-phenyl acetate was dissolved in MeOH, 10% palladium on charcoal (0.160 g, 0.15 mmol) was added and the mixture stirred under hydrogen at room temperature under atmospheric pressure for 24 h. It was then filtered on Celite by washing 5 times with CH_3CN (5 mL). The organic phase was evaporated in vacuo to provide the catalyst *cis*-**2** as a solid (0.334 g, 89% yield). $[\alpha]_D^{20}$ = -16.4° (c=0.61, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ=2.43–2.54 (m, 1H), 2.54–2.64 (m, 1 H), 3.43–3.53 (m, 1 H), 3.53–3.61 (m, 1 H), 3.64 (s, 2 H), 4.13 (dd, *J*=3.6, 9.9 Hz, 1 H), 5.27–5.33 (m, 2H), 7.21–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ= 172.59, 172.55, 135.1, 130.5, 129.5, 128.1, 74.2, 65.6, 52.0, 41.5, 36.1 ppm; elemental analysis calcd for $C_{13}H_{15}NO_4$ (249.26): C, 62.64; H, 6.07; N, 5.62; found: C, 62.32; H, 6.15; N, 5.57.

Aldol reaction

General procedure: Cyclohexanone (0.52 mL, 5 mmol), water (0.022 mL, 1.2 mmol) and benzaldehyde (0.102 mL, 1 mmol) were added to the appropriate catalyst (0.02 mmol) and the mixture was stirred at room temperature. The reaction mixture was quenched by charging it directly onto a silica-gel column and the pure aldol was obtained upon elution with cyclohexane/ethyl acetate 8:2. The *ee* values were determined by using chiral HPLC with a CHIRALCEL OJ column (*n*-hexane/2-propanol 90:10, flow rate=0.5

mL/min, λ=220 nm, T=40°C); t_R *anti* (major)=15.57 min, t_R *syn*=16.50 min, t_R *anti*=18.81 min, t_R *syn* (major)=21.03 min. [33a]

Determination of reaction conversion

A sample of the reaction mixture (10 µL) was diluted in 3 mL of CH_3CN and 5 µL of the resulting solution was injected on HPLC. The retention time for benzaldehyde was 13.6 min and the retention time for the product *anti*-**3** was 22.9 min. HPLC conditions: Eclipse XDB-C18 5 µm column (4.6 mm x 150 mm) with CH_3CN/H_2O 30:70 as the mobile phase and detection at 210 nm, flow rate=0.5 mL/min, T=30°C.

Computational Methods

All computations reported in the paper were performed with the Gaussian09 series of programs. As aryl groups and extended π systems were present on both the aldehyde and the catalyst, a functional capable of describing interactions involving π system was required. It is well-known that this class of interaction (in which medium-range correlation effects are dominant) are not described properly by most popular DFT functionals, for example, B3LYP. However, during the last decade new functionals have been recommended that are capable of treating medium-range correlation effects. Within this family of innovative functionals, we have chosen that recently proposed by Truhlar and Zhao, known as M06-2X, which has been demonstrated to provide a good estimate of π–π interactions and reaction energetics. All atoms have been described by the DZVP basis, which is a local spin densityoptimized basis set of double-zeta quality including polarization functions. The geometries of the various critical points on the potential surface were optimized fully by using the gradient method available in Gaussian 09 and harmonic vibrational frequencies were computed to evaluate the nature of all critical points.

All reagents were purified by distillation or recrystallization before use. (2*S*,4*S*)-*N*-benzyloxycarbonyl-4-aminoproline benzyl ester was prepared following a known literature procedure: M. Tamaki, G. Han, V. J. Hruby, *J. Org. Chem.* **2001**, 66, 1038-1042.

***N*-Benzyloxycarbonyl-(2*S*,4*S*)-4-(2-chloroacetamido)-proline Benzyl Ester (5)**

2-Chloroacetyl chloride (0.83 mL, 10.2 mmol) was added dropwise at -20°C to a solution of (2*S*,4*S*)-*N*-benzyloxycarbonyl-4-aminoproline benzyl ester **4** (3.0 g. 8.47

mmol) and triethylamine (1.53 mL, 11.0 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at this temperature for 3 h after which it was diluted with CH_2Cl_2 (5 mL) and washed with water (10 mL). The organic phase was dried over Na_2SO_4. Concentration of the solvent under vacuum gave an oily residue which was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1). The product was obtained as a colourless oil; yield: 3.14 g (7.29 mmol, 86%); $[\alpha]_D^{20}$: -26.38° (c=0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, two conformational isomers): δ=1.92–2.07 (m, 1H), 2.43–2.58 (m, 1H), 3.54–3.81 (m, 2H), 3.82–4.03 (m, 2H), 4.41–4.56 (ddd, *J*=29.7, 9.8, 2.0 Hz, 1H), 4.61–4.76 (m, 1H), 4.93–5.40 (m, 4H), 7.20–7.42 (m, 10H), 7.42–7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, two conformational isomers): δ=35.47, 36.51, 42.3, 48.0, 49.0, 53.0, 53.4, 57.7, 58.1, 67.41, 67.43, 67.46, 67.49, 127.8, 1, 128.07, 128.14, 128.25, 128.34, 128.42, 128.44, 128.47, 128.55, 128.57, 134.9, 135.1, 136.0, 153.9, 154.5, 165.5, 173.5; anal. calcd. for $C_{22}H_{23}ClN_2O_5$ (430.88): C 61.32, H 5.38, N 6.50; found: C 61.22, H 5.34, N 6.53.

Imidazolium Chloride Salt (6)

1-Methylimidazole (0.64 mL, 8.1 mmol) was added to a solution of the chloroacetamide **5** (2.9 g, 6.7 mmol) in anhydrous CH_3CN (12 mL) and the reaction mixture was heated at 50°C for 16 h. The organic solvent was removed under reduced pressure, the crude hygroscopic product was washed with anhydrous ether (5 x 5 mL) and vacuum dried. The title imidazolium chloride salt was obtained as a low-melting solid after purification by flash-chromatography on neutral alumina, eluting with CH_2Cl_2/methanol 95:5; yield: 2.24 g (4.4 mmol, 65%); $[\alpha]_D^{20}$: -17.48° (c=0.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, two conformational isomers): δ=2.04–2.25 (m, 1H), 2.46–2.59 (m, 1H), 3.28–3.47 (m, 1H), 3.77–3.95 (m, 4H), 4.15–4.45 (m, 2H), 4.81–5.33 (m, 6H), 7.03–7.11 (m, 1H), 7.11–7.33 (m, 10H), 7.39–7.49 (m, 1H), 9.39–9.51 (t, *J*=7.1 Hz, 1H), 9.74 (s, 1H); 13C NMR (100 MHz, $CDCl_3$, two conformational isomers): δ=34.4, 35.3, 36.5, 48.3, 49.0, 50.7, 51.1, 51.5, 57.7, 58.0, 67.10, 67.13, 67.2, 122.20, 122.23, 123.61, 123.66, 127.73, 127.99, 128.04, 128.08, 128.14, 128.20, 128.26, 128.39, 128.48, 128.52, 135.4, 135.6, 136.2, 136.3, 138.2, 153.9, 154.6, 164.9, 171.9, 172.1; anal. calcd. for $C_{26}H_{29}ClN_4O_5$ (512.99): C 60.87, H 5.70, N 10.92; found: C 61.41, H 5.72, N 10.33.

Imidazolium Bis(trifluoromethanesulfonyl)imide Salt (7a)

Lithium bis(trifluoromethanesulfonyl)imide (1.23 g, 4.3 mmol) was added to a solution of the imidazolium chloride salt **6** (2.0 g, 3.6 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight at room temperature, then it was diluted with CH_2Cl_2 (30 mL) and washed with water (5 x 10 mL). The organic layer was dried (Na_2SO_4) and concentred under vacuum to give the title compound **7a** as a gummy solid; yield: 2.72 g (3.9 mmol, 92%); $[\alpha]_D^{20}$: -11.98° (c=0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, two conformational isomers): δ=1.97–2.15 (m, 1H), 2.45–2.64 (m, 1H), 3.38–3.52 (m, 1H), 3.75–3.87 (m, 4H), 4.30–4.51 (m, 2H), 4.71–4.90 (m, 2H), 4.92–5.24 (m, 4H), 7.13–7.39 (m, 12H), 7.70–7.86 (d, *J*=7.0 Hz, 1H), 8.62–8.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, two conformational isomers): δ=33.2, 34.5, 35.5, 36.2, 48.2, 49.0, 50.8, 51.4, 51.7, 57.6, 58.0, 67.18, 67.24, 114.9, 118.0, 121.2, 122.8, 123.7, 124.4, 127.6, 127.7, 127.8, 127.9, 128.05, 128.07, 128.11, 128.2, 128.37, 128.40, 128.44, 128.5, 135.1, 135.3, 136.0, 136.1, 137.1, 154.0, 154.6, 163.8, 172.7, 172.8; anal. calcd. for $C_{28}H_{29}F_6N_5O_9S_2$ (757.68): C 44.39, H 3.86, N 9.24; found: C 44.24, H 3.83, N 9.35.

Imidazolium Tetrafluoroborate Salt (7b)

Following the same procedure reported for **7a**, **6** (0.14 g, 0.28 mmol) was reacted with sodium tetrafluoroborate (0.037 g, 0.34 mmol) to afford **7b** as a solid; yield: 0.15 g (0.27 mmol, 95%); $[\alpha]_D^{20}$: -9.48 (c=0.58, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.87–2.16 (m, 1H), 2.31–2.64 (m, 1H), 3.18–3.50 (m, 1H), 3.57–3.91 (m, 4H), 4.19–4.47 (m, 2H), 4.63–4.88 (s, 2H), 4.89–5.24 (m, 4H), 7.08–7.57 (m, 12H), 8.45–8.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 34.5, 35.4, 36.2, 48.1, 49.0, 50.8, 51.4, 51.6, 53.4, 57.7, 58.0, 67.2, 67.3, 122.78, 122.81, 123.6, 127.7, 127.91, 127.95, 128.00, 128.05, 128.11, 128.2, 128.3, 128.4, 128.5, 128.6, 135.3, 135.5, 136.2, 136.3, 137.4, 154.0, 154.6, 164.5, 164.5, 172.5, 172.7; anal. calcd. for $C_{26}H_{29}BF_4N_4O_5$ (564.34): C 55.34, H 5.18, N 9.93; found: C 55.43, H 5.21, N 9.97.

Imidazolium Hexafluorophosphate Salt (7c)

Following the same procedure reported for **7a**, **6** (0.11 g, 0.21 mmol) was reacted with potassium hexafluorophosphate (0.047 g, 0.26 mmol) to afford **7c** as a solid; yield: 0.13 g (0.20 mmol, 97%); $[\alpha]_D^{20}$: -7.78 (c=0.67, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, two conformational isomers): δ=2.00–2.15 (m, 1H), 2.40–2.60 (m, 1H), 3.40–3.58 (m, 1H), 3.72–3.85 (m, 4H), 4.30–4.54 (m, 2H), 4.59–4.78 (m, 2H), 4.96–5.26 (m, 4H), 7.03–7.15 (m, 2H), 7.17–7.41 (m, 10H), 8.39–8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7,

33.9, 34.6, 35.4, 36.1, 48.1, 49.0, 50.8, 51.6, 51.8, 57.7, 58.0, 67.26, 67.30, 122.9, 123.6, 127.7, 127.9, 128.0, 128.07, 128.11, 128.24, 128.26, 128.38, 128.44, 128.5, 128.6, 135.3, 135.5, 136.2, 136.3, 137.1, 154.0, 154.7, 164.1, 172.8, 172.9; anal. calcd. for $C_{26}H_{29}F_6N_4O_5P$ (622.50): C 50.17, H 4.70, N 9.00; found: C 55.33, H 4.72, N, 8.94.

Imidazolium Bis(trifluoromethylsulfonyl)imide Catalyst (8a)

10% palladium on charcoal (0.19 g, 0.18 mmol) was added to a solution of **7a** (2.7 g, 3.6 mmol) in anhydrous CH_3OH (10 mL). The mixture was stirred under hydrogen at atmospheric pressure overnight. The reaction mixture was then filtered and washed with CH_3OH (10 mL). The organic layer was evaporated under vacuum to provide the catalyst as a solid; yield: 1.83 g (3.56 mmol, 96%); $[\alpha]_D^{20}$: -20.48 (c=0.80, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ=2.24 (dt, *J*= 13.7, 6.0 Hz, 1H), 2.63 (ddd, *J*=13.8, 9.2, 7.0 Hz, 1H), 3.41 (dd, *J*=12.2, 4.9 Hz, 1H), 3.54 (dd, *J*=12.2, 6.7 Hz, 1H), 4.09 (dd, *J*=9.1, 6.5 Hz, 1H), 4.44 (ddd, *J*=11.8, 6.7, 5.1 Hz, 1H), 4.99 (s, 2H), 7.52–7.65 (m, 2H), 8.90 (s, 1H); ^{1}H NMR (400 MHz, DMSO-d6): δ=1.84–1.96 (dt, *J*=13.2, 7.4 Hz, 1H), 2.36–2.53 (m, 1H), 3.00–3.10 (dd, *J*=11.6, 6.5 Hz, 1H), 3.26–3.36 (dd, *J*=11.6, 7.0 Hz, 1H), 3.78–3.86 (t, *J*=8.3 Hz, 1H), 3.86–3.93 (s, 3H), 4.22–4.35 (m, 1H), 4.90–5.02 (d, *J*= 3.5 Hz, 2 H), 7.65–7.72 (m, 2H), 8.88–8.95 (d, *J*=6.5 Hz, 1H), 9.04–9.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ= 34.0, 35.8, 48.6, 48.9, 50.5, 59.4, 123.0, 123.7, 137.7, 165.0, 169.6; anal. calcd. for $C_{13}H_{17}F_6N_5O_7S_2$ (533.42): C 29.27, H 3.21, N 13.13; found: C 29.04, H 3.19, N, 13.14.

Imidazolium Tetrafluoroborate Catalyst (8b)

Following the same procedure reported for **8a**, **8b** was obtained as a solid; yield: 96%; $[\alpha]_D^{20}$: -15.38 (c=0.36, H_2O). ^{1}H NMR (400 MHz, D_2O): δ=2.18–2.34 (dt, *J*=14.2, 6.2 Hz, 1H), 2.65–2.83 (ddd, *J*=14.1, 9.1, 7.0 Hz, 1H), 3.43–3.55 (dd, *J*=12.5, 5.0 Hz, 1H), 3.62–3.73 (dd, *J*=12.6, 6.9 Hz, 1H), 3.90–4.02 (s, 3 H), 4.21–4.36 (dd, *J*=9.1, 6.8 Hz, 1H), 4.44–4.62 (ddd, *J*=12.2, 6.8, 5.4 Hz, 1H), 5.00–5.13 (s, 2H), 7.47–7.51 (s, 1H), 7.51–7.54 (s, 1H), 8.74–8.86 (s, 1H); ^{13}C NMR (50 MHz, CD_3OD): δ=35.2, 36.6, 50.6, 50.7, 51.8, 61.4, 124.5, 125.0, 139.3, 167.2, 173.3; anal. calcd. For $C_{11}H_{17}BF_4N_4O_3$ (340.08): C 38.85, H 5.04, N 16.47; found: C 38.64, H 5.07, N 16.49.

Imidazolium Hexafluorophosphate Catalyst (8c)

Following the same procedure reported for **8a**, **8c** was obtained as a solid; yield: 68%; $[\alpha]_D^{20}$: -14.28 (c=0.32, H_2O). ^{1}H NMR (400 MHz, CD_3OD): δ=2.17–2.29 (dt, *J*=13.0, 6.0 Hz, 1H), 2.56–2.73 (m, 1H), 3.37–3.46 (dd, *J*=12.2, 4.9 Hz, 1H), 3.47–3.58 (dd, *J*=12.2,

6.7 Hz, 1H), 3.91–4.01 (s, 3H), 4.01–4.13 (dd, *J*=9.0, 6.7 Hz, 1H), 4.36–4.52 (m, 1H), 4.93–5.11 (s, 2H), 7.52–7.62 (s, 2H), 8.79–8.94 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ=35.4, 36.5, 50.75, 50.77, 51.8, 61.6, 124.4, 125.0, 138.5, 167.1, 173.6; anal. calcd. for $C_{11}H_{17}F_6N_4O_3P$ (398.24): C 33.18, H 4.30, N 14.07; found: C 33.14, H 4.33, N 14.02.

Typical Procedure using Protocol A (Table 1, Entry 14)

Cyclohexanone (0.10 mL, 1 mmol) was added to a solution of catalyst **8a** (5.3 mg, 0.01 mmol) in [bmim] [NTf2] (0.3 mL) and the mixture was allowed to stir for 10 min at room temperature. 4-Nitrobenzaldehyde (0.075 g, 0.5 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. The product was extracted from ionic liquid with diethyl ether (8 x 2 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The pure aldol product was obtained by flash-chromatography on silica gel eluting with cyclohexane/ethyl acetate (7:3); yield: 0.113 g (0.46 mmol, 91%). The *ee* was determined by chiral HPLC (CHIRALPAK AD column, *n*-hexane/2-propanol=85:15, flow rate: 0.8 mL/min, λ=254 nm): t_R *syn*=11.1 min, t_R *syn*=13.6 min, t_R *anti* (minor)=14.6 min, t_R *anti* (major)=18.8 min.

Typical Procedure using Protocol B (Table 2, Entry 7)

Cyclopentanone (0.22 mL, 2.5 mmol) and water (0.011 mL, 0.6 mmol) were added to the catalyst **8a** (2.7 mg, 0.005 mmol) and the mixture was allowed to stir for 10 min at room temperature. 4-Nitrobenzaldehyde (0.076 g, 0.5 mmol) was then added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by addition of CH_2Cl_2 (1.0 mL) and saturated aqueous NH_4Cl solution (0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The pure aldol was obtained by flash-chromatography on silica gel upon eluting with cyclohexane/ethyl acetate mixtures. The *ee* was determined by chiral HPLC (CHIRALPAK OF column, *n*-hexane/2-propanol=80:20, flow rate: 1.0 mL/min, λ=254 nm): t_R *syn*=11.3 min, t_R *syn*=14.9 min, t_R *anti* (major)=22.3 min, t_R *anti* (minor)=26.1 min.

2-hydroxy(4-nitrophenyl)methyl)cyclohexanone:[33a] Daicel Chiralpak AD column, *n*-hexane/2-propanol = 85:15, flow rate: 0.8 mL/min, λ = 214 nm, t_R (*syn*, major) = 16.09 min, t_R (*syn*, minor) = 17.31 min, t_R (*anti*, minor) = 18.08 min, t_R (*anti*, major) = 22.66 min.

2-hydroxy(pentafluorophenyl)methyl)cyclohexanone:[33a] Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 99:1, flow rate: 0.7 mL/min, λ = 210 nm, t_R (*anti*, major) = 12.42 min, t_R (*anti*, minor) = 15.40 min, t_R (*syn*) = 28.76 min, t_R (*syn*) = 30.30 min.

2-hydroxy(4-chlorophenyl)methyl)cyclohexanone:[33a] Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 93:7, flow rate: 0.5 mL/min, λ = 210 nm, t_R (*anti*, major) = 17.82 min, t_R (*syn*) = 18.90 min, t_R (*anti*, minor) = 20.37 min, t_R (*syn*) = 23.99 min.

2-hydroxy(4-methoxyphenyl)methyl)cyclohexanone:[33a] Daicel Chiralcel OD column, *n*-hexane/2-propanol = 95:05, flow rate: 1.0 mL/min, λ = 214 nm, t_R (*syn*) = 9.92 min, t_R (*syn*) = 10.12 min, t_R (*anti*, major) = 11.97 min, t_R (*anti*, minor) = 14.70 min.

4-hydroxy-4-(4-nitrophenyl)butan-2-one:[33a] Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 90:10, flow rate:1.0 mL/min, λ = 214 nm, t_R (major) = 24.27 min, t_R (minor) = 27.16 min.

2-(hydroxy(4-nitrophenyl)methyl)cycloheptanone:[33a] Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 95:05, flow rate: 1.0 mL/min, λ = 214 nm, t_R (*syn*, minor) = 24.04 min, t_R (*syn*, major) = 28.74 min, t_R (*anti*, major) = 31.04 min, t_R (*anti*, minor) = 32.84 min.

2-(hydroxy(4-nitrophenyl)methyl)cyclopentanone:[33a] Daicel Chiralcel OF column, *n*-hexane/2-propanol = 80:20, flow rate: 1.0 mL/min, λ = 214 nm, t_R (*syn*) = 11.25 min, t_R (*syn*) = 14.90 min, t_R (*anti*, major) = 22.31 min, t_R (*anti*, minor) = 26.07 min.

2-(1-hydroxy-2-methylpropyl)cyclohexanone:[33b] Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 99:01, flow rate: 0.4 mL/min, λ = 214 nm, t_R (*anti*, major) = 12.49 min, t_R (*anti*, minor) = 13.61 min.

2-(1-hydroxypentyl)cyclohexanone: Daicel Chiralcel OJ column, *n*-hexane/2-propanol = 95:05 for 20 min, then 90:10, 85:15 and 80:20 in 5 min intervals, flow rate: 0.5 mL/min, λ = 214 nm, t_R (*anti*, major) = 7.95 min, t_R (*anti*, minor) = 10.10 min.

Ethyl 2-hydroxy-2-(2-oxocyclopentyl)acetate:[48] Daicel Chiralpak AD column, *n*-hexane/2-propanol = 98:02, flow: 0.7 mL/min, λ = 214 nm, t_R (*syn*) = 36.65 min, t_R (*syn*) = 45.89 min, t_R (*anti*, minor) = 56.37 min, t_R (*anti*, major) = 58.40 min.

3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one:[39c] Daicel Chiralpak AD column, *n*-hexane/2-propanol = 80:20, flow rate: 0.9 mL/min, λ = 210 nm, t_R (*syn*) = 8.28 min, t_R (*syn*) = 9.02 min, t_R (*anti*, major) = 10.50 min, t_R (*anti*, minor) = 12.81 min.

[48] Tsuboi S., Nishiyama E., Furutani H., Utaka M., Takeda A., *J. Org. Chem.* **1987**, 52, 1359-1362.

3,4-dihydroxy-5-methylhexan-2-one:[39e] Daicel Chiralpak AS-H column, *n*-hexane/2-propanol = 85:15, flow rate: 0.5 mL/min, λ = 214 nm, t_R (*anti*, major) = 11.75 min, t_R (*anti*, minor) = 13.82 min, t_R (*syn*) = 13.82 min, t_R (*syn*) = 18.60 min.

Synthesis of bis-vinylimidazolium salt 10:

A solution of 1,3-dibromopropane (0.01 mol) and 1-vinylimidazole (0.021 mol) in toluene (10 mL) was heated at reflux for 24 h in an oil bath at 90°C with magnetic stirring. After cooling at room temperature, the mixture was filtered and washed several times with diethyl ether and the resulting solid was dried at 40°C to give a white solid. Yield: 83%; ^{1}H NMR (300 MHz, CD_3OD): δ=2.67–262 (m, 2H), 4.51–4.46 (m, 4H), 5.48 (dd, *J*=8.7, 2.7 Hz, 2H), 5.98 (dd, *J*=15.6,2.7 Hz, 2H), 7.31 (dd, *J*= 15.6, 8.7 Hz, 2H), 7.89 (d, *J*=1.8 Hz, 2H), 8.07 (d, *J*=1.8 Hz, 2H), 9.51 ppm (s, 2H); ^{13}C NMR (CD_3OD): δ=31.1, 47.9, 110.2, 120.9, 124.4, 129.8 ppm; elemental analysis calcd (%) for $C_{13}H_{18}Br_2N_4$ (390.12): C 40.0, H 4.5, Br 41.4, N 14.3; found: C 40.0, H 4.7, Br 41.5, N 14.4.

Synthesis of mlc-SILP materials 11 and 12:

The mercaptopropylmodified silica **9** (1.2 mmol/g), the bis-vinylimidazolium salt **10** (3.62 eq.), AIBN (60 mg), and ethanol (130 mM) were placed in a three-necked, round-bottom flask. The suspension was degassed by bubbling argon for 10 min and the reaction mixture was magnetically stirred under argon. The flask was heated to 78°C to favour the dissolution of the bis-vinylimidazolium salt and the mixture was stirred for 20 h. After cooling to room temperature, the solid was filtered and washed with hot methanol and diethyl ether and then dried at 40°C overnight. Material **11** (1.00 g) was suspended in water (20 mL) and $LiNTf_2$ (1.4 g, 1.5 eq.) was added. The mixture was stirred for 48 h, then filtered and washed with water, methanol, and diethyl ether and dried at 40°C overnight to provide **12**.

Asymmetric aldol reaction, typical procedure (Table 3, run 1): Cyclohexanone (0.516 mL, 5 mmol, 5 eq.) and water (0.022 mL, 1.2 mmol, 1.2 eq.) were added to **13** (193 mg, 13.8 wt% **8a**, 0.05 mmol, 5 mol%) in a centrifuge tube and the heterogeneous mixture was magnetically stirred until a semi-transparent gel was obtained (5–10 min). *p*-Nitrobenzaldehyde (0.151 g, 1 mmol) was then added and the mixture stirred at room temperature for 2.5 h, during which the conversion was monitored by TLC. After the

reaction was complete, cyclohexanone was removed under reduced pressure (≈0.1 mmHg, 1 h) and 2 mL of anhydrous diethyl ether were added. The two phases were separated by using a centrifuge (2000 rpm, 1 min), and diethyl ether was removed and collected. Extractions were repeated 4–6 times until TLC evidenced the complete disappearance of product and unreacted reagents, if present. The combined organic phases were evaporated at reduced pressure and the residue was purified by silica gel chromatography with a cyclohexane/ethyl acetate (7:3) eluent. *ee* was determined by chiral HPLC using a Chiralpak AD column (*n*-hexane/2-propanol= 85:15, flow rate=0.8 mL/min, λ =230 nm); t_R (*syn*)=13.5 min, t_R (*syn*)=16.8 min, t_R (*anti*, minor)=18.0 min, t_R (*anti*, major)=23.4 min. The catalytically active material **13** was dried under vacuum (≈10 mmHg, 1 h, rt), then charged with the reactants and water using the same reaction and workup conditions described previously.

A New Family of Bicyclic Diarylprolinol Silyl Ethers as Organocatalysts

1. Introduction

A long-standing goal in the development of new catalytic systems is the discovery of general catalysts, able to promote a large number of enantioselective reactions, via multiple activation modes, with good substrate tolerance and high stereoselectivity.

Relevant examples are the amino acid proline **1** and MacMillan's imidazolidinones **2** (Figure 10), which have often been described as fairly general and efficient amine-based catalysts.

L-Proline
1

MacMillan's
catalysts
2

Figure 10

Enamine catalysis using **1** has been applied to both intermolecular and intramolecular nucleophilic addition reactions with a variety of electrophiles.[49] In these processes the configuration of the final adducts is generally controlled by a hydrogen-bond interaction between the acidic proton of proline and the incoming electrophile. Thus, this interaction, whilst activating the electrophile, guides its approach from the upper face of the enamine. A similar pattern is generally followed by catalysts bearing a hydrogen-bond donor at the α position of the pyrrolidine nitrogen.[49d,e]

[49] (a) List B., *Tetrahedron* **2002**, 58, 5573-5590; (b) List B., *Acc. Chem. Res.* **2004**, 37, 548-557; (c) List B., *Chem. Commun.* **2006**, 819-824; (d) Marigo M., Jørgensen K. A., *Chem. Commun.* **2006**, 2001-2011; (e) Guillena G., Ramón D. J., *Tetrahedron: Asymmetry* **2006**, 17, 1465-1492.

MacMillan's imidazolidinone-based catalysts are even more general,[50] but although applicable to a variety of reactions, a fine-tuning of the substituents is often required to reach the desired selectivities.

Recently, other pyrrolidine derivatives and diarylprolinol have emerged as potentially general organocatalysts. Although (*S*)-2,2-diphenylprolinol may promote reactions with a good level of stereocontrol, the processes are characterized by low catalyst turnover. This fact has been mainly ascribed to the formation of the relatively stable and unreactive hemiaminal species, which removes a significant amount of the catalyst from the catalytic cycle. To avoid the hemiaminal formation, trimethylsilyl (TMS) ethers **3** have been developed (Figure 11).

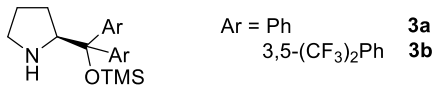


Figure 11

The α,α-L-diaryl prolinol silyl ethers **3a** and **3b**, originally developed by Hayashi's[51] and Jørgensen's[52] groups, can be considered the most important and employed ones, since they are able to promote several functionalizations of carbonyl compounds with excellent stereocontrol.[53] Moreover, the absolute configuration of the newly formed stereogenic centres is predictable on the basis of the steric shielding exerted by the *O*-protecting group on one face of the conformationally preferred enamine or iminium ion formed during the process. Hence the electrophile approach takes place at the lower face of the enamine, thus affording products of opposite configuration compared to those obtained with L-proline as catalyst.

Based on the diarylprolinol silyl ether system, several studies on enamine-mediated transformations of saturated carbonyl compounds were able to provide the introduction of different functionalities into the α-position in a highly stereoselective manner. This activation mode was later extended to α,β-unsaturated aldehydes, which after condensation with the aminocatalyst generate a dienamine species able to give

[50] Lelais G., MacMillan D. W. C., *Aldrichimica Acta* **2006**, 39, 79-87.

[51] Hayashi Y., Gotoh H., Hayashi T., Shoji M., *Angew. Chem. Int. Ed.* **2005**, 44, 4212-4215.

[52] Marigo M., Wabnitz T. C., Fielenbach D., Jørgensen K. A., *Angew. Chem. Int. Ed.* **2005**, 44, 794-797.

[53] (a) Jensen K. L., Dickmeiss G., Jiang H., Albrecht Ł., Jørgensen K. A., *Acc. Chem. Res.* **2012**, 45, 248-264; (b) Palomo C., Mielgo A., *Angew. Chem. Int. Ed.* **2006**, 45, 7876-7880; (c) Palomo C., Mielgo A., *Chem. Asian J.* **2008**, 3, 922-948; (d) Meninno S., Lattanzi A., *Chem. Commun.* **2013**, 49, 3821-3832.

stereoselective Diels-Alder reactions and provide an effective functionalization of the γ-position. Recently, this activation principle was further developed to include 2,4-dienals, which form trienamine intermediates upon condensation with the aminocatalyst, which effectively react with carbon-centered dienophiles. Because of the concerted nature of the reaction and the efficient catalyst shielding of the β-position, the stereoinduction is achieved at the remote ε-position of the original aldehyde.

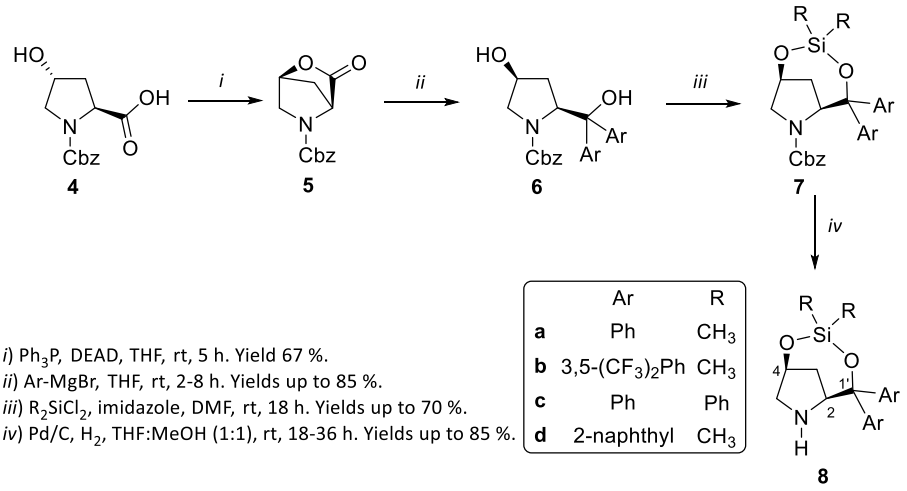
Complementary to the enamine-mediated activations, α,β-unsaturated aldehydes can also be efficiently functionalized by applying the diarylprolinol silyl ether systems in the conjugate addition through iminium ion mediated processes. In such reactions, the aminocatalyst not only effectively shields one of the enantiotopic faces of the enal, but it also ensures excellent chemoselectivity, affording only 1,4-adducts. Several different carbon and heteroatom nucleophiles can be added in a highly stereoselective fashion.

The ability of these catalysts to participate in various enamine and iminium ion mediated processes also makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner.

Due to the ease of their preparation, the wide versatility of their applications and the almost invariable high stereochemical efficiency, Jørgensen-Hayashi's diarylprolinol silyl ethers certainly play a central role when iminium/enamine-based reactivity is considered.

2. Synthesis and applications of conformationally constrained bicyclic diarylprolinol silyl ethers as organocatalysts

We rationally designed a new family of bicyclic diarylprolinol silyl ethers **8a–d** characterised by a 2,4-dioxa-3-sila-7-azabicyclo[4.2.1]nonane scaffold, which were easily obtained in good yields from commercially available *N*-Cbz-*trans*-4-L-hydroxyproline **4** in a four synthetic steps (Scheme 12).



i) Ph_3P, DEAD, THF, rt, 5 h. Yield 67 %.
ii) Ar-MgBr, THF, rt, 2-8 h. Yields up to 85 %.
iii) R_2SiCl_2, imidazole, DMF, rt, 18 h. Yields up to 70 %.
iv) Pd/C, H_2, THF:MeOH (1:1), rt, 18-36 h. Yields up to 85 %.

	Ar	R
a	Ph	CH_3
b	3,5-$(CF_3)_2$Ph	CH_3
c	Ph	Ph
d	2-naphthyl	CH_3

Scheme 12

Catalysts **8a–d** are bench-stable solids that can be stored for long time at room temperature in a simple vial, without noticeable decomposition, whereas commercially purchased catalysts **3** may contain up to 10–15% of their deprotected analogues. Zeitler and Gschwind quantitatively assessed the entity of the desilylation reaction of **3**. They recorded different ^{1}H NMR spectra of **3** in the presence of PhCOOH as additive (100 mol%, 50 mM) in DMSO-d6 at different times.[54] They found out that, when catalyst **3a** was subjected to these experimental conditions, 50% of the desilylated compound was observed after only about 45 minutes and an almost complete (nearly 90%) desilylation reaction occurred within 5 hours. Conversely, in the same conditions we did not observe any trace of the desilylated product deriving from **8a**, even after more than 48 hours, as shown in the ^{1}H NMR spectra reported in Figure 12.

[54] Haindl M. H., Schmid M. B., Zeitler K., Gschwind R. M., *RSC Advances* **2012**, 2, 5941-5943.

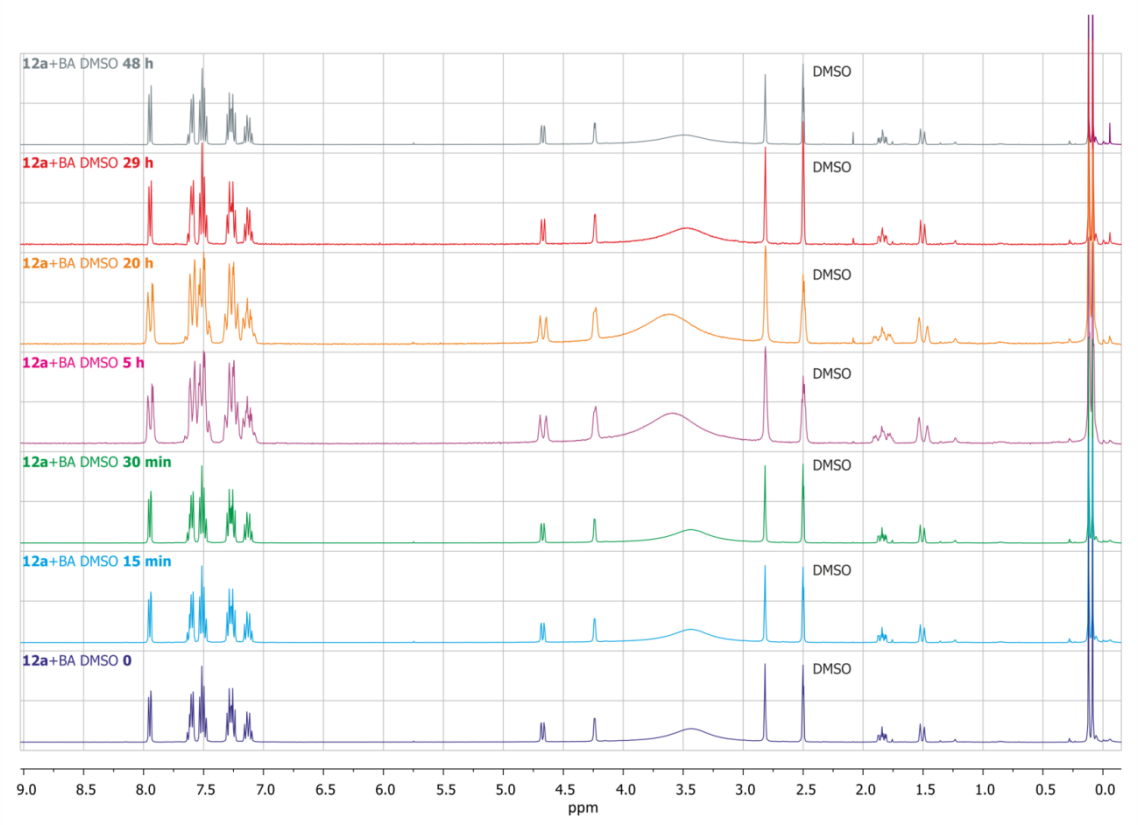


Figure 12

The bicyclic structure of these catalysts prevent the free rotation around the exocylic C(2)-C(1') bond, therefore directing an aromatic ring, and not the *O*-protected group as in the case of catalysts **3**, towards one face of the reacting intermediate. The effect of the substituents on the aromantic ring responsible of shielding one face of the reacting intermediate has already been studied by Mayr and Gilmour for MacMillan catalysts.[55] They demonstated that the rational modulation of this substitution pattern can improve the catalytic performances. Hence, also in our case it is possible in principle to fine tune the efficiency and the selectivity of these catalysts by changing nature, number and position of the substituents on the aromatic rings.

This bridge between the C-2 and C-4 carbon atoms blocks also the ring puckering of the pyrrolidine, forcing the ring in the "down"[56] envelope conformation and thus exposing the less hindered convex bottom face to the attack of the reaction partner. The B3LYP/6-31G(d) optimised geometry for the cinnamoylidene imminium adduct of catalyst **8d** is reported in Figure 13.

[55] Holland M. C., Paul S., Schweizer W. B., Bergander K., Mück-Lichtenfeld C., Lakhdar S., Mayr H., Gilmour R., *Angew. Chem. Int. Ed.* **2013**, 52, 7967-7971.

[56] Schmid M. B., Zeitler K., Gschwind R. M., *Chem. Sci.* **2011**, 2, 1793-1803.

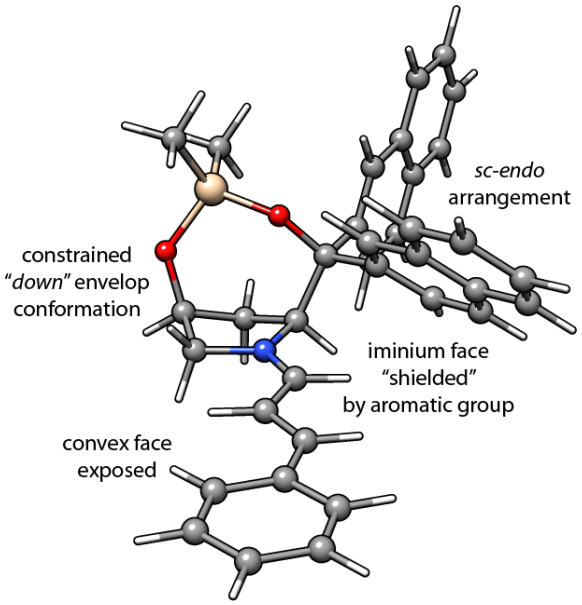


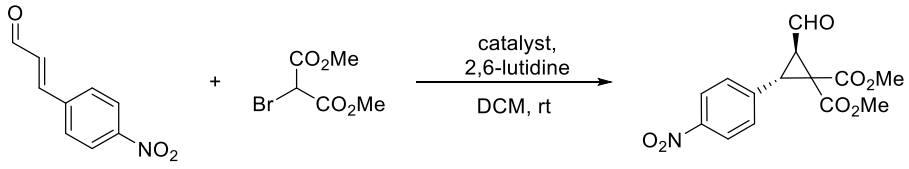
Figure 13

We tested our new catalysts in different transformations in which Jørgensen–Hayashi catalysts **3** were reported to afford excellent results.

We first examined the cyclopropanation reaction of 4-nitrocynnamaldehyde with dimethyl bromomalonate in the conditions recently reported by Wang and co-workers.[57] This reaction allowes the formation of two new C-C bonds, two new stereogenic centers and one quaternary carbon atom.

The results obtained with this reaction protocol are reported in Table 10.

Table 10: Organocatalytic cyclopropanation reaction of *trans*-4-nitrocinnamaldehyde with dimethyl bromomalonate.[a]



Entry	Catalyst	Time (h)	Conv. (%)[b]	Yield (%)[c]	dr *(anti/syn)*[b]	*ee* (%)[d]
1		4	74			
	3a			73	>30:1	91
2		6	82			

[57] Xie H., Zu L., Li H., Wang J., Wang W., *J. Am. Chem. Soc.* **2007**, 129, 10886-10894.

Entry	Catalyst	Time (h)	Conv. (%)[b]	Yield (%)[c]	dr *(anti/syn)*[b]	*ee* (%)[d]
3		4	84			
	8a			76	>30:1	94
4		6	86			
5		3	0			
6	**8b**	24	10	18	>30:1	80
7		51	24			
8		5	73			
	8c			74	>30:1	92
9		6	80			
10		4	84			
	8d			83	>30:1	95
11		6	89			

[a] Reaction conditions: dimethyl bromomalonate (0.12 mmol), 4-nitrocinnamaldehyde (0.14 mmol), 2,6-lutidine (0.13 mmol), catalyst (10 mol%), dichloromethane (DCM, 0.5 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Conversions calculated with respect to dimethyl bromomalonate. [c] Yield of the isolated product after flash-chromatography. [d] Determined by CSP-HPLC.

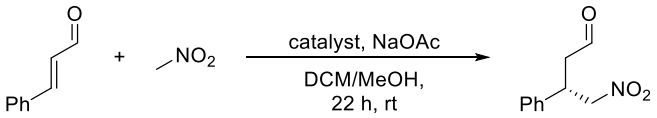
Catalyst **8c** afforded more or less the same activity and selectivity as **3a** (entries 8 and 9), while catalysts **8a** and **8d** proved to be slightly better, providing both higher conversions and *ee*s in the same reaction time (entries 3, 4, 10, and 11). Catalyst **8b** afforded lower *ee*s and also showed an evident decrease of reactivity (entries 5-7). Also Wang et al. reporting the use of catalyst **3b** in the cyclopropanation reaction, using TEA as the base obtained a very low yield (<20%) and thus the *ee* was not determined. It is noteworthy that both **3b** and **8b** possess two CF_3 groups in the *meta* positions of the phenyl rings; these are probably reasponsible of this decrease of efficiency.

We investigated the performances of our catalysts also in the conjugate addition of nitromethane to (*E*)-cinnamaldehyde. This reaction was reported by many groups using Jørgensen-Hayashi catalysts **3** in rather different reaction conditions.[58] We chose the conditions reported by Ye and co-workers, involving the use of 5 mol% of catalyst,

[58] (a) Hayashi Y., Itoh T., Ishikawa H., *Angew. Chem. Int. Ed.* **2011**, 50, 3920-3924; (b) Ghosh S. K., Zheng Z., Ni B., *Adv. Synth. Catal.* **2010**, 352, 2378-2382; (c) Mager I., Zeitler K., *Org. Lett.* **2010**, 12, 1480-1483; (d) Wang Y., Li P., Liang X., Zhang T. Y., Ye J., *Chem. Commun.* **2008**, 1232-1234; (e) Zu L., Xie H., Li H., Wang J., Wang W., *Adv. Synth. Catal.* **2007**, 349, 2660-2664; (f) Palomo C., Landa A., Mielgo A., Oiarbide M., Puente A., Vera S., *Angew. Chem. Int. Ed.* **2007**, 46, 8431-8435.

catalytic amounts of NaOAc (30 mol%) in a 9:1 mixture of DCM and methanol as the solvent.[58d] The results obtained are collected in Table 11.

Table 11: Organocatalytic Michael addition of nitromethane to (*E*)-cinnamaldehyde.[a]



Entry	Catalyst	Yield (%)[b]	*ee* (%)[c]
1	**3a**	76	97
2	**8a**	40	96
3	**8b**	16	94
4	**8c**	44	96
5	**8d**	70	98

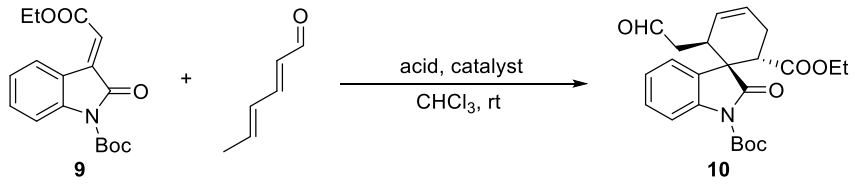
[a] Reaction conditions: cinnamaldehyde (0.3 mmol), nitromethane (0.9 mmol), sodium acetate (30 mol%), catalyst (5 mol%), DCM/MeOH (9:1, 0.6 mL), rt. [b] Yield of the isolated product after flash-chromatography. [c] Determined by CSP-HPLC.

Again catalyst **8b** revealed to be the least reactive one, even if in this reaction it afforded a very good enantiocontrol (entry 3). The other three catalysts (**8a, c, d**) provided *ee*s comparable with catalyst **3a** (entries 2, 4 and 5), but only **8d** gave similar reactivity. Since catalyst **8b** furnished poor results and catalysts **8a** and **8c** showed so far almost the same stereoselectivity and reactivity, we decided to continue the screening of catalysts performances using only **8a** and **8d**.

These catalysts were used in some recent Diels–Alder reactions based on trienamine activation mode.[59] First we analysed the organocatalytic Diels-Alder reaction between (2*E*,4*E*)-hexadienal and 3-ylidene oxindole **9**, which afforded the spirocyclic oxidole **10** as a single diastereoisomer (Table 12).

[59] Jia Z., Jiang H., Li J., Gschwend B., Li Q., Yin X., Grouleff J., Chen Y., Jørgensen K. A., *J. Am. Chem. Soc.* **2011**, 133, 5053-5061.

Table 12: Organocatalytic Diels–Alder reaction of (2*E*,4*E*)-hexadienal with 3-yilidene oxindole **9**.[a]



Entry	Catalyst	Acid	Time (h)	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	**3c**[e]	OFBA	4	99	92	98
2	**8a**	OFBA	24	32	28	93
3	**8d**	OFBA	48	45	38	96
4	**8a**	CA	4	76	64	94
5	**8a**	CA	24	99	84	94
6	**8a**	MNBA	9	85	73	94
7	**8a**	DFPA	9	99	86	95
8	**8d**	DFPA	9	99	87	96

[a] Reaction conditions: 3-yilidene oxindole **9** (0.1 mmol), (2*E*,4*E*)-hexadienal (0.15 mmol), acid (20 mol%), catalyst (20 mol%), chloroform (1 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Conversions calculated with respect to **9**. [c] Yield of the isolated product after flash-chromatography. [d] Determined by CSP-HPLC. [e] **3** wih Ar=Ph and TES group instead of TMS group.

The best results obtained by Jørgensen and co-workers in this reaction were achieved in the presence of 20 mol% *o*-fluorobenzoic acid (OFBA) as the additive and installing triethyl silyl group instead of trimethyl silyl group on the diphenylprolinol **3c** (entry 1).

In the same reaction conditions **8a** and **8d** displayed a slightly diminished stereoselectivity compared to the catalyst used by Jørgensen and co-workers, but also remarkable reduced reactivities (entries 1-3).

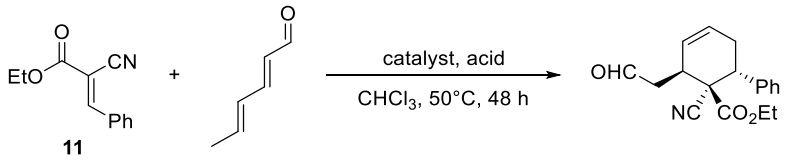
Acid additives play a central role in secondary amine organocatalysts activity. Seebach and Hayashi recently demonstrated that the acid additive may play many different roles in the organocatalytic cycle and that a strong relationship exists between acid strength and catalyst activity.[60] So we tested the former Diels–Alder

[60] Patora-Komisarska K., Benohoud M., Ishikawaa H., Seebach D., Hayashi Y., *Helv. Chim. Acta* **2011**, 94, 719-745.

reaction in the presence of different acid additives. In particular we increased the acidity of the additive trying chloroacetic acid (CA), 4-methyl-2-nitrobenzoic acid (MNBA) and α,α-difluorophenylacetic acid (DFPA). Using **8a** we found an apparent direct relationship between catalyst activity and acid additive pKa, obtaining higher conversions in shorter reaction times when stronger acids were used (entries 2, 4–7). With α,α-difluorophenylacetic acid we obtained quantitative conversions and very high stereoselectivities for both **8a** and **8d**, although these results are still slightly lower than those provided by **3c** (entries 1, 7 and 8).

We used **8d** in a second Diels–Alder addition between (2*E*,4*E*)-hexadienal and the ethyl (*E*)-2-cyano-3-phenylacrylate **11** (Table 13). This reaction, reported by Jørgensen, required a much more encumbered organocatalyst **3d** (Ar=4-OMe-3,5-(di-*t*Bu)C_6H_2 and TES instead of TMS) and higher temperatures to give good conversions and acceptable *ee*s.[59]

Table 13: Organocatalytic Diels–Alder reaction of (2*E*,4*E*)-hexadienal with ethyl (*E*)-2-cyano-3-phenylacrylate **11**.[a]



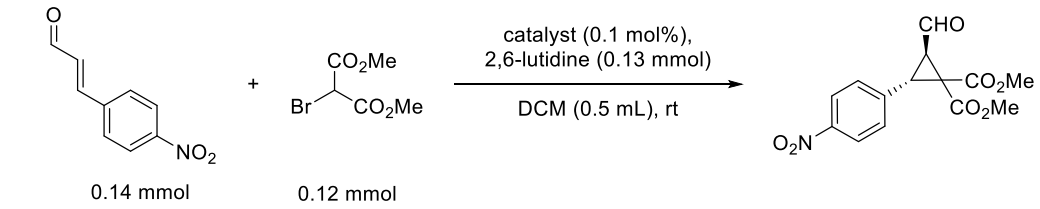
Entry	Catalyst	Additive	Yield (%)[b]	*ee* (%)[c]	dr[d]
1	**3d**[e]	OFBA	87	86	80:20
2	**8d**	OFBA	83	89	80:20
3	**8d**	CA	58	92	80:20

[a] Reaction conditions: ethyl (*E*)-2-cyano-3-phenylacrylate **11** (0.1 mmol), (2*E*,4*E*)-hexadienal (0.2 mmol), acid (20 mol%), catalyst (20 mol%), chloroform (0.5 mL), 50°C. [b] Yield of the isolated product after flash-chromatography. [c] Determined by CSP-HPLC. [d] Determined by ^{1}H NMR of the crude mixture. [e] **3** with Ar=4-OMe-3,5-(di-*t*Bu)C_6H_2 and TES instead of TMS.

In this case the use of OFBA was sufficient for **8d** to afford a comparable conversion and better stereochemical control with respect to those obtained with **3d** (entries 1, 2). Conversely, CA afforded this time a much lower yield, but still a very good *ee* value (entry 3).

Among the reactions in which we tested our bicyclic diaryl prolinol silyl ethers, the cyclopropanation was the one that provided us the best results (Table 10). These performances together with the stability of our catalysts prompted us to carry out the

reaction in the same conditions, but lowering the catalyst loading. First we used 5 mol% of catalyst **8a**, chosen for these experiments, and we obtained a complete conversion, determined by ^{1}H NMR of the crude mixture, after 21 hours. Then, we decreased the amount of catalyst to 1 mol% and we recorded 91% of conversion in 21 hours. Encouraged by these results we performed the reaction using only 0.1 mol% of **8a** and we checked the conversion during the reaction time. We also carried out the reaction in the same conditions and catalytic loading using Hayashi's catalyst **3a** in order to compare the activity of the two systems. The results obtained are shown in Figure 14.



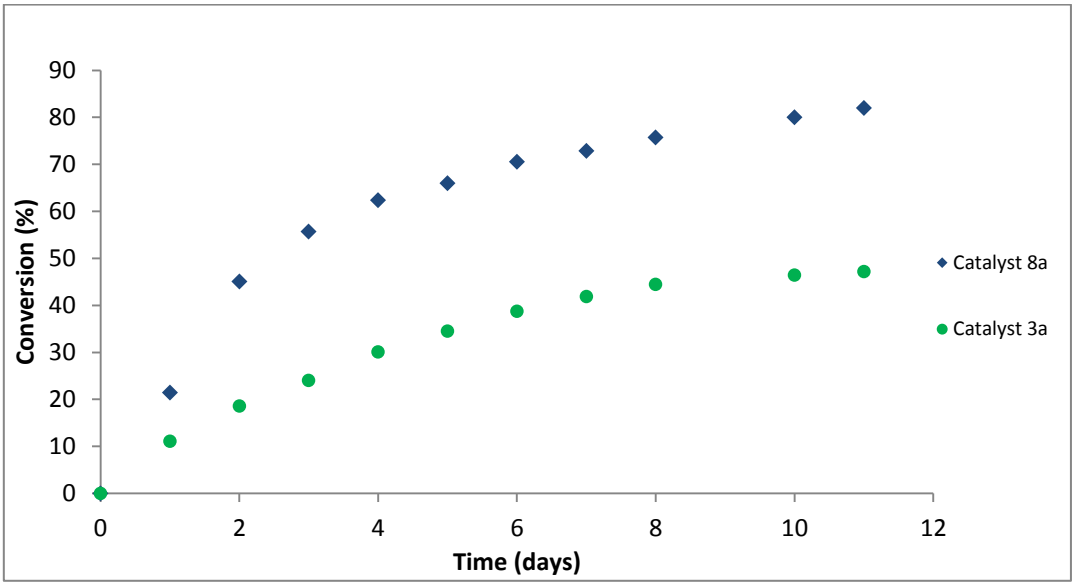


Figure 14

It is noteworthy that after 11 days catalyst **8a** provided 81% of conversion, while catalyst **3a** didn't reach 50%, thus demonstrating the major reactivity of our catalyst and confirming its stability.

3. Conclusions

These new bicyclic diarylprolinol silyl ethers are easily accessible in good yields using simple synthetic procedures. They are much more stable to hydrolytic conditions

and so more easily stored and handled compared to Jørgensen-Hayashi catalysts maintaining comparable activity and selectivity.

Using these new catalysts the stereochemical outcomes of the reactions mainly depend on the nature of the aromatic rings and not on the bulky *O*-protected diarylmethanol group; this opens up the possibility to further modulate their efficacy and activity by varying the nature and the substitution pattern of the aromatic rings.

The cyclopropanation reaction performed using only 0.1 mol% of catalyst proved that this family of organocatalysts may be successfully employed in organocatalytic transformations with a very low catalyst loading. These performances are possible thanks to the reactivity and stability of these new catalysts. Further studies on these low loading organocatalytic reactions are still in progress.

The stability and reactivity of these new catalysts, together with their structural modulability make them possible alernatives to widen the choice of catalysts available for asymmetric organocatalytic transformations.

4. Experimental section

General information

^{1}H and ^{13}C NMR were recorded on a Varian Inova 400 and on a Varian Gemini 200; chemical shifts (δ) are reported in ppm relative to TMS. Chiral HPLC studies were carried out on a Agilent Technologies Series 1200 instrument. HPLC-MS were recorded using a Agilent Technologies HP1100 instrument (column ZOBRAX-Eclipse XDB-C8 Agilent Technologies, mobile phase: H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 25 min, 0.4 mL/min) coupled with Agilent Technologies MSD1100 single-quadrupole mass spectrometer (full-scan mode from m/z 50 to m/z 2600, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow 11.5 mL/min, fragmentor voltage 20 V). Optical rotations were measured with a Perkin-Elmer 343 polarimeter. Reactions were monitored by TLC (Merck 60 F254). Flash-chromatography was carried out using Merck silica gel 60 (230-400 mesh particle size). All reagents were commercially available and were used without further purification, unless otherwise stated.

Synthesis of the catalysts

(1*S*,4*S*)-benzyl 3-oxo-2-oxa-5 -azabicyclo[2.2.1]heptane-5-carboxylate (5)

A solution of DEAD 40% in toluene (5.5 mL, 12 mmol) was added dropwise at 0°C to a solution of Z-Hyp-OH (2.65 g, 10 mmol) and triphenylphosphine (3.16 g, 12.06 mmol) in anhydrous THF (40 mL) under argon atmosphere. The reaction was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and then diethyl ether (20 mL) was added to the residue in order to precipitate triphenylphosphine oxide that was filtered away. The solution was concentred under reduced pressure and the residue was purified by flash-chromatogaphy on silica gel (diethyl ether/DCM 95:5). The product was obtained as a white solid (1.65 g, 6.67 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 5.28 – 5.03 (m, 3H), 4.67 (bs, 1H), 3.62 (dd, *J* = 10.9, 1.3 Hz, 1H), 3.54 (d, *J* = 11.1 Hz, 1H), 2.25 (ddt, *J* = 10.8, 2.6, 1.3 Hz, 1H), 2.04 (d, *J* = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 38.9, 49.9, 57.3, 67.4, 78.2, 127.8, 128.1, 128.4, 135.8, 154.2, 170.6. HPLC-MS: $[M+Na]^+$ =270.2 m/z. Anal. Calcd for $C_{13}H_{13}NO_4$ (247.25): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.59; H, 5.28; N, 5.70.

(2*S*,4*S*)-benzyl 4-hydroxy-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (6a,c)

Compound **5** (0.52 g, 2.1 mmol) was dissolved in 13 mL of anhydrous THF under argon atmosphere and a 3 M solution of phenylmagnusium bromide in diethyl ether (2.1 mL, 6.3 mmol) was added dropwise over 30 minutes at 0°C. The reaction was allowed to reach room temperature. After stirring for 8 h the reaction was quenched with a saturated solution of ammonium chloride (20 mL) and extracted with diethyl ether (15 mL). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 1:1). The product was obtained as a white solid (0.6 g, 1.5 mmol, 70%). $[\alpha]_D^{20}$ = 95.8° (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.02 (m, 15H), 5.04 (d, *J* = 8.9 Hz, 1H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.52 – 4.38 (m, 1H), 4.18 – 4.06 (m, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.45 – 2.25 (m, 1H), 1.91 (d, *J* = 14.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.2, 57.3, 64.9, 66.9, 69.9, 81.2, 126.8, 127.1, 127.2, 127.7, 127.8, 127.9, 128.3, 136.4, 144.6, 144.7, 155.3. HPLCMS: $[M\text{-}OH^-]^+$ =386.3 m/z; $[M+Na]^+$ =426.4 m/z. Anal. Calcd for $C_{25}H_{25}NO_4$ (403.47): C, 74.42; H, 6.25; N, 3.47. Found: C, 74.18; H, 6.21; N, 3.44.

(1*S*,6*S*)-benzyl 3,3-dimethyl-5,5-diphenyl-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane-7-carboxylate (7a)

To a solution of compound **6a,c** (0.3 g, 0.74 mmol) and imidazole (0.12 g, 1.78 mmol) in anhydrous DMF (3 mL) under argon atmosphere was added dichlorodimethylsilane (0.11 mL, 0.89 mmol) dropwise at 0°C. The reaction was stirred at room temperature for 19 h, then quenched with a phosphate buffer pH=7 (5 mL) and extracted with ethyl acetate (8 mL). The organic phase was washed with a 5% aqueous solution of lithium chloride (5 mL × 3). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9:1). The product was obtained as a gummy white solid (0.24 g, 0.52 mmol, 70%). $[\alpha]_D^{20}$ = 139.8° (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.01 (m, 15H), 5.21 (bs, 1H), 4.89 (d, *J* = 12.3 Hz, 1H), 4.68 (t, *J* = 5.8 Hz, 1H), 3.96 (dd, *J* = 13.1, 6.5 Hz, 1H), 3.68 (d, *J* = 12.7 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.34 (d, *J* = 14.8 Hz, 1H), 0.35 (s, 3H), -0.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9, 1.6, 39.0, 58.3, 64.9, 66.6, 72.7, 84.6, 126.4, 126.9, 127.1, 127.4, 127.6, 127.8, 127.9, 128.0, 128.2, 136.7, 144.9, 155.1. HPLC-MS: $[M+H]^+$ =460.4 m/z. Anal. Calcd for $C_{27}H_{29}NO_4Si$ (459.61): C, 70.56; H, 6.36; N, 3.05. Found: C, 70.36; H, 6.41; N, 3.03.

(1*S*,6*S*)-3,3-dimethyl-5,5-diphenyl-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane (8a)

Compound **7a** (0.18 g, 0.4 mmol) was dissolved in a mixture of anhydrous THF and methanol 1:1 (4 mL). Then palladium on charcoal 10% (0.043 g, 0.040 mmol) was added to the solution and the reaction was stirred under hydrogen at atmospheric pressure for 36 h. The reaction mixture was then filtered and washed with ethyl acetate (15 mL). The organic layer was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 7:3). The product was obtained as a white solid (0.11 g, 0.34 mmol, 85%). $[\alpha]_D^{20}$ = -67.6° (c = 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.45 (m, 4H), 7.36 – 7.22 (m, 4H), 7.21 – 7.09 (m, 2H), 4.61 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.43 – 4.35 (m, 1H), 3.05 (d, *J* = 9.4 Hz, 1H), 2.91 (dd, *J* = 9.4, 2.3 Hz, 1H), 1.93 – 1.87 (m, 2H), 1.71 (bs, 1H), 0.23 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.5, 2.9, 36.3, 54.5, 62.4, 73.9, 84.3, 125.6, 125.9, 126.27, 126.31, 128.0, 128.1, 146.6, 146.8. HPLC-MS: $[M+H]^+$ =326.1 m/z. Anal. Calcd for $C_{19}H_{23}NO_2Si$ (325.48): C, 69.94; H, 7.14; N, 4.33. Found: C, 70.36; H, 6.41; N, 3.03.

(2*S*,4*S*)-benzyl 2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (6b)

Bromo-3,5-bis(trifluoromethyl)benzene (1.0 mL, 6 mmol) in 4 mL of anhydrous THF was added dropwise to a suspension of magnesium (0.15 g, 6.3 mmol) in anhydrous THF (2 mL) under argon atmosphere. The reaction was refluxed for 30 minutes. After cooling to room temperature the reaction mixture was added dropwise to a solution of compound **5** (0.5 g, 2 mmol) in anhydrous THF (4 mL) at 0°C under argon atmosphere. The reaction was left to reach room temperature and stirred for 17 h. The reaction was quenched with a saturated solution of ammonium chloride (15 mL) and extracted with diethyl ether (10 mL). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 8:2). The product obtained was obtained as a white solid (0.69 g, 1.0 mmol, 50%). $[\alpha]_D^{20}$ = 83.0° (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.91 (s, 2H), 7.88 (s, 1H), 7.71 (s, 1H), 7.36 – 7.28 (m, 3H), 7.14 (s, 2H), 6.33-6.28 (m, 1H), 5.17 (d, *J* = 9.1 Hz, 1H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.65-4.55 (m, 1H), 4.08-3.96 (m, 1H), 3.62 (d, *J* = 12.9 Hz, 1H), 3.03 (bs, 1H), 2.41 (ddd, *J* = 15.3, 9.4, 6.3 Hz, 1H), 1.82 (d, *J* = 14.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 57.1, 65.0, 67.5, 70.1, 79.1, 119.1, 119.3, 121.21, 121.25, 121.29, 121.32, 121.78, 121.81, 121.85, 121.89, 121.93, 121.96, 124.49, 124.67, 126.80, 126.84, 127.02, 127.20, 127.38, 127.98, 128.12, 128.26, 128.33, 128.36, 128.42, 128.44, 128.47, 128.51, 131.0 (q, *J* = 33.2 Hz), 132.1 (q, *J* = 33.5 Hz), 135.7, 146.2, 147.8, 155.3. HPLC-MS: $[M+OH^-]^+$ =658.3 m/z. Anal. Calcd for $C_{29}H_{21}F_{12}NO_4$ (675.46): C, 51.57; H, 3.13; N, 2.07. Found: C, 69.90; H, 6.42; N, 3.01.

(1*S*,6S)-benzyl 5,5-bis(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl-2,4-dioxa-7-aza-3-sila bicyclo[4.2.1]nonane-7-carboxylate (7b)

To a solution of compound **6b** (0.69 g, 1.0 mmol) and imidazole (0.17 g, 2.5 mmol) in anhydrous DMF (4 mL) under argon atmosphere was added dichlorodimethylsilane (0.15 mL, 1.2 mmol) dropwise at 0°C. The reaction was stirred at room temperature for 19 h, then quenched with a phosphate buffer pH=7 (5 mL) and extracted with ethyl acetate (8 mL). The organic phase was washed with a 5% aqueous solution of lithium chloride (5 mL × 3). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9:1). The product was obtained as a gummy white solid (0.49 g, 0.67 mmol, 65%). $[\alpha]_D^{20}$ = 138.8° (c = 1.05,

$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 2H), 7.92 (s, 1H), 7.72 (s, 3H), 7.40 – 7.29 (m, 3H), 7.22 – 7.11 (m, 2H), 5.26 (d, *J* = 9.1 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.68 (t, *J* = 5.4 Hz, 1H), 3.88 – 3.75 (m, 1H), 3.72 (d, *J* = 12.5 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.10 (d, *J* = 14.8 Hz, 1H), 0.46 (s, 3H), -0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0, 1.2, 38.4, 58.2, 65.0, 67.4, 73.0, 83.8, 118.9, 119.2, 121.29, 121.33, 121.37, 121.40, 121.44, 121.64, 121.95, 122.12, 122.16, 122.20, 122.23, 122.27, 124.35, 124.66, 126.90, 126.94, 126.98, 127.02, 127.06, 127.24, 127.27, 127.31, 127.36, 128.06, 128.17, 128.20, 128.28, 128.41, 128.42, 128.45, 128.47, 132.1 (q, *J* = 33.6), 130.9 (q, *J* = 33.3), 136.0, 146.6, 146.7, 155.8. HPLC-MS: $[M+H]^+$ =732.3 m/z. Anal. Calcd for $C_{31}H_{25}F_{12}NO_4Si$ (731.60): C, 50.89; H, 3.44; N, 1.91. Found: C, 51.23; H, 3.47; N, 1.92.

(1*S*,6*S*)-5,5-bis(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethyl-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane (8b)

Compound **7b** (0.49 g, 0.67 mmol) was dissolved in a mixture of anhydrous THF and methanol 1:3 (4 mL). Then palladium on charcoal 10% (0.071 g, 0.067 mmol) was added to the solution and the reaction was stirred under hydrogen at atmospheric pressure for 24 h. The reaction mixture was then filtered and washed with ethyl acetate (15 mL). The organic layer was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2). The product was obtained as a white solid (0.22 g, 0.37 mmol, 55%). $[\alpha]D^{20}$ = -35° (c = 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.99 (s, 2H), 7.79 (s, 1H), 7.77 (s, 1H), 4.70 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.51 – 4.41 (m, 1H), 3.10 (dd, *J* = 9.4, 2.2 Hz, 1H), 3.00 (dd, *J* = 9.4, 2.4 Hz, 1H), 2.04 (ddd, *J* = 14.2, 10.2, 3.9 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.65 (bs, 1H), 0.32 (s, 3H), 0.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.1, 2.7, 36.6, 54.4, 62.5, 73.5, 83.9, 119.09, 119.11, 121.17, 121.21, 121.25, 121.28, 121.34, 121.38, 121.42, 121.46, 121.49, 121.80, 121.82, 124.50, 124.53, 125.75, 125.79, 125.83, 126.05, 126.09, 127.21, 127.24, 131.48, 131.50, 131.81, 131.83, 132.15, 132.16, 132.47, 132.49, 147.7, 148.2. HPLC-MS: $[M+H]^+$ =598.1 m/z. Anal. Calcd for $C_{23}H_{19}F_{12}NO_2Si$ (597.47): C, 46.24; H, 3.21; N, 2.34. Found: C, 46.28; H, 3.18; N, 2.36.

(1*S*,6*S*)-benzyl 3,3,5,5-tetraphenyl-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane-7-carboxylate (7c)

Dichlorodiphenylsilane (0.088 mL, 0.43 mmol) was added dropwise at 0°C to a solution of compound **6a,c** (0.14 g, 0.36 mmol) and imidazole (0.058 g, 0.85 mmol) in

anhydrous DMF (3 mL) under argon atmosphere. The reaction was stirred at room temperature for 21 h, then quenched with a phosphate buffer pH=7 (5 mL) and extracted with ethyl acetate (8 mL). The organic phase was washed with a 5% aqueous solution of lithium chloride (5 mL × 3). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9:1). The product was obtained as a gummy white solid (0.18 g, 0.31 mmol, 87%) that was characterized by HPLC-MS and used directly in the next reaction. HPLC-MS: $[M+H]^+$ =584.2 m/z.

(1*S*,6*S*)-3,3,5,5-tetraphenyl-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane (8c)

Compound **7c** (0.25 g, 0.42 mmol) was dissolved in a mixture of anhydrous THF and methanol 1:1 (4 mL). Then palladium on charcoal 10% (0.045 g, 0.042 mmol) was added to the solution and the reaction was stirred under hydrogen at atmospheric pressure for 18 h. The reaction mixture was then filtered and washed with ethyl acetate (15 mL). The organic layer was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9:1). The product was obtained as a white solid (0.12 g, 0.27 mmol, 63%). $[\alpha]_D^{20}$ = -88.8° (c = 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.05 (m, 20H), 4.67 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.58 – 4.53 (m, 1H), 3.04 (d, *J* = 9.3Hz, 1H), 2.81 (dd, *J* = 9.4, 1.9 Hz, 1H), 2.09 – 1.89 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.1, 53.6, 60.7, 73.7, 85.1, 125.5, 126.4, 126.8, 127.1, 127.5, 127.8, 127.9, 128.1, 128.2, 128.4, 129.0, 130.3, 133.0, 134.3, 134.4, 134.5, 134.6, 138.5, 139.5, 146.5, 146.6. HPLC-MS: $[M+H]^+$ =450.2 m/z. Anal. Calcd for $C_{29}H_{27}NO_2Si$ (449.62): C, 77.47; H, 6.05; N, 3.12. Found: C, 77.17; H, 6.09; N, 3.09.

(2*S*,4*S*)-benzyl 4-hydroxy-2-(hydroxydi(naphthalen-2-yl)methyl)pyrrolidine-1-carboxylate (6d)

2-Bromonaphtalene (0.62 g, 3.0 mmol) in 4 mL of anhydrous THF was added dropwise to a suspension of magnesium (0.077 g, 3.15 mmol) in anhydrous THF (2 mL) under argon atmosphere. The reaction was refluxed for 45 minutes. After cooling to room temperature the reaction mixture was added dropwise to a solution of compound **5** (0.25 g, 1.0 mmol) in anhydrous THF (4 mL) at 0°C under argon atmosphere. The reaction was left to raise to room temperature and stirred for 3 h. The reaction was

quenched with a saturated solution of ammonium chloride (10 mL) and extracted with diethyl ether (10 mL). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 7:3). The product was obtained as a gummy white solid (0.43 g, 0.85 mmol, 85%). $[\alpha]_D^{20}$ = 132.1° (c = 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 – 7.78 (m, 4H), 7.78 – 7.66 (m, 2H), 7.65 – 7.59 (m, 2H), 7.58 – 7.47 (m, 3H), 7.47 – 7.36 (m, 2H), 7.25 – 7.10 (m, 3H), 6.85 (s, 2H), 5.24 (d, *J* = 8.7 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.40 – 4.29 (m, 1H), 4.04 (dd, *J* = 12.6, 7.1 Hz, 1H), 3.55 (d, *J* = 13.0 Hz, 1H), 2.34 (ddd, *J* = 14.5, 9.2, 7.2 Hz, 1H), 1.97 (d, *J* = 14.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 57.3, 64.9, 66.8, 69.9, 81.3, 125.2, 125.4, 125.5, 125.8, 125.9, 126.2, 126.3, 127.1, 127.3, 127.5, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 132.3, 132.4, 132.7, 132.9, 136.1, 142.2, 142.3, 155.3. HPLC-MS: $[M+OH^-]^+$ =486.4 m/z. Anal. Calcd for $C_{33}H_{29}NO_4$ (503.59): C, 78.71; H, 5.80; N, 2.78. Found: C, 79.08; H, 5.81; N, 2.80.

(1*S*,6*S*)-benzyl 3,3-dimethyl-5,5-di(naphthalen-2-yl)-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane-7-carboxylate (7d)

Dichlorodimethylsilane (0.11 mL, 0.94 mmol) was added dropwise at 0°C to a solution of compound **6d** (0.34 g, 0.78 mmol) and imidazole (0.13 g, 1.87 mmol) in anhydrous DMF (2 mL) under argon atmosphere. The reaction was stirred at room temperature for 21 h, then quenched with a phosphate buffer pH=7 (5 mL) and extracted with ethyl acetate (8 mL). The organic phase was washed with a 5% aqueous solution of lithium chloride (5 mL × 3). The organic phase was dried over sodium sulphate, then filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 7:3). The product was obtained as a gummy white solid (0.32 g, 0.58 mmol, 74%). $[\alpha]_D^{20}$ = 309.5° (c = 1.66, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 – 7.65 (m, 7H), 7.64 – 7.29 (m, 8H), 7.23 – 7.08 (m, 2H), 6.96 – 6.76 (m, 2H), 5.47 (bs, 1H), 4.83 – 4.55 (m, 2H), 4.02 (dd, *J* = 12.9, 6.4 Hz, 1H), 3.76 (d, *J* = 12.4 Hz, 1H), 2.79 – 2.41 (m, 2H), 0.44 (s, 3H), -0.30 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.0, 1.6, 39.1, 58.4, 64.8, 66.5, 72.8, 84.9, 125.3, 125.56, 125.62, 126.0, 126.3, 126.4, 126.5, 126.9, 127.4, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.5, 132.3, 132.5, 132.6, 132.8, 136.5, 142.3, 143.3, 155.2. HPLC-MS: $[M+H]^+$

=560.5 m/z. Anal. Calcd for $C_{35}H_{33}NO_4Si$ (559.73): C, 75.10; H, 5.94; N, 2.50. Found: C, 75.22; H, 5.92; N, 2.51.

(1*S*,6*S*)-3,3-dimethyl-5,5-di(naphthalen-2-yl)-2,4-dioxa-7-aza-3-silabicyclo[4.2.1]nonane (8d)

Compound **7d** (0.29 g, 0.52 mmol) was dissolved in a mixture of anhydrous THF and methanol 1:1 (4 mL). Then palladium on charcoal 10% (0.056 g, 0.052 mmol) was added to the solution and the reaction was stirred under hydrogen at atmospheric pressure for 26 h. The reaction mixture was then filtered and washed with ethyl acetate (15 mL). The organic layer was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2). The product was obtained as a white solid (0.17 g, 0.4 mmol, 76%). $[\alpha]_D^{20}$ = -69.8° (c = 0.64, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (s, 2H), 8.06 – 7.60 (m, 8H), 7.60 – 7.34 (m, 4H), 4.86 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.58 – 4.34 (m, 1H), 3.10 (d, *J* = 9.3 Hz, 1H), 2.96 (d, *J* = 9.4 Hz, 1H), 2.20 – 1.76 (m, 2H), 0.39 (s, 3H), 0.29 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.6, 2.9, 36.6, 54.7, 62.3, 73.9, 84.7, 124.2, 124.6, 124.9, 125.7, 125.9, 126.0, 127.4, 127.5, 127.7, 128.0, 128.2, 128.3, 132.2, 133.2, 143.8, 144.0. HPLC-MS: $[M+H]^+$ =426.4 m/z. Anal. Calcd for $C_{27}H_{27}NO_2Si$ (425.59): C, 76.20; H, 6.39; N, 3.29. Found: C, 76.40; H, 6.39; N, 3.32.

Organocatalytic Cyclopropanation Reaction of *trans*-4-Nitrocinnamaldehyde with Dimethyl α-Bromomalonate (Table 10)

To a solution of catalyst (10 mol%) in DCM (0.5 mL) was added dimethyl bromomalonate (0.12 mmol, 0.018 mL), 2,6-lutidine (0.13 mmol, 0.015 mL) and finally 4-nitrocinnamaldehyde (0.14 mmol, 0.025 mg). The reaction was stirred at room temperature for the specified time. The product was purified by flash-cromatography on silica gel (cyclohexane/ethyl acetate 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.59 (d, *J*= 3.8 Hz, 1H), 8.19 (d, *J*=8.8 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 3.88–3.83 (m, 4H), 3.54 (s, 3H), 3.47 (dd, *J*=7.6, 3.8 Hz, 1H). Conversions were determined by ^{1}H NMR using the doublet at 8.19 ppm of the product and the singlet at 4.87 ppm of the dimethyl bromomalonate. The racemic product was synthesised under the same conditions with racemic proline (10 mol%). The enantiomeric excess was determined after derivatisation of the product with Ph_3P=CHCOOEt. Separation conditions in chiral

HPLC: AD 90:10 *n*-Hex/IPA for 15 min then 80:20 in 10 min, 0.7 mL/min, 40°C, λ=230 nm, t_r (major) = 25.0 min , t_r (minor) = 26.8 min.

Organocatalytic Enantioselective Michael Addition of Nitromethane to (*E*)-Cinnamaldehyde (Table 11)

To a solution of catalyst (5 mol%) in a DCM/MeOH mixture (9:1, 0.6 mL) was added cinnamaldehyde (0.3 mmol, 0.038 mL), nitromethane (0.9 mmol, 0.048 mL) and finally sodium acetate (30 mol%, 7.4 mg). The reaction was stirred at room temperature for 22 h. The mixture was diluted with DCM and extracted with water. The water was washed two times with DCM and the organic phases were collected, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash-cromatography on silica gel (cyclohexane/ethyl acetate 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.69 (s, 1H), 7.22–7.35 (m, 5H), 4.60–4.69 (m, 2H), 4.06–4.08 (m, 1H), 2.94 (d, *J*=3.5 Hz, 2H). Conversions were determined by ^{1}H NMR using the doublet at 2.94 ppm of the product and the dd at 6.69 ppm of cinnamaldehyde. The racemic product was synthesised under the same conditions with racemic Jørgensen–Hayashi catalyst (20 mol%). The enantiomeric excess was determined after reduction of the product with $NaBH_4$ in ethanol. Separation conditions in chiral HPLC: IB 90:10 *n*-Hex/IPA, 0.5 mL/min, 40°C, λ=230 nm, t_r (minor) = 25.0 min , t_r (major) = 27.5 min.

Organocatalytic Diels–Alder Reaction of (2E,4E)-Hexadienal with 3-Ylidene Oxindole (Table 12)

To a solution of catalyst (20 mol%) and acid (20 mol%) in $CHCl_3$ (1 mL) were added the dienophile (0.1 mmol, 0.032 g) and the aldehyde (0.15 mmol, 0.017 mL). The reaction was stirred at room temperature for the specified time. The product was purified by flash-cromatography on silica gel (cyclohexane/ethyl acetate from 9:1 to 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.69 (s, 1H), 7.89 (d, *J*=8.2 Hz, 1H), 7.33–7.28 (m, 1H), 7.26–7.21 (m, 1H), 7.10–7.03 (m, 1H), 6.02–5.95 (m, 1H), 5.80–5.71 (m, 1H), 3.93 (q, *J*=7.2 Hz, 2H), 3.32–3.19 (m, 2H), 3.02–2.93 (m, 1H), 2.86–2.73 (m, 1H), 2.63–2.51 (m, 1H), 2.41 (dd, *J*=18.5, 5.0 Hz, 1H), 1.64 (s, 9H), 1.05 (t, *J*=7.1 Hz, 3H). The conversions were determined by ^{1}H NMR using the multiplet at 5.83–5.70 ppm of the product and the doublet at 8.69 ppm of the isatin derivative. The racemic product was synthesised under the same conditions with pyrrolidine (20 mol%). The enantiomeric excess was

determined after derivatisation of the product with Ph_3P=CHCOOEt. Separation conditions in chiral HPLC: AD 95:5 *n*-Hex/IPA, 1 mL/min, 40°C, λ=230 nm, t_r (minor) = 6.6 min , t_r (major) = 8.0 min.

Organocatalytic Diels–Alder Reaction of (2*E*,4*E*)-Hexadienal with (*E*)-Ethyl 2-Cyano-3-phenylacrylate (Table 13)

To a solution of catalyst (20 mol%) and acid (20 mol%) in $CHCl_3$ (0.5 mL) were added the dienophile (0.1 mmol, 0.020 g) and the aldehyde (0.2 mmol, 0.022 mL). The reaction was stirred at 50°C for the specified time. The product was purified by flash-cromatography on silica gel (cyclohexane/ethyl acetate from 9:1 to 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.68 (s, 1H), 7.51–7.22 (m, 5H), 6.01–5.92 (m, 1H), 5.77–5.70 (m, 1H), 3.97–3.85 (m, 2H), 3.65–3.57 (m, 1H), 3.26 (dd, *J*= 11.3, 5.5 Hz, 1H), 3.15 (dd, *J*=19.0, 8.5 Hz, 1H), 2.72–2.63 (m, 1H), 2.59 (dd, *J*=18.8, 4.7 Hz, 1H), 2.51–2.40 (m, 1H), 1.00 (t, *J*=7.1 Hz, 3H). Conversions were determined by ^{1}H NMR using the multiplets at 5.77–5.70 ppm and 5.58–5.53 ppm of the two diastereoisomers of the product and the singolet at 8.27 ppm of the ethyl cyanophenylacrylate. The dr was determined by ^{1}H NMR using the multiplets at 5.77–5.70 ppm and 5.58–5.53 ppm of the two diastereoisomers of the product. The racemic product was synthesised under the same conditions with pyrrolidine (20 mol%). The enantiomeric excess was determined after derivatisation of the product with Ph_3P=$CHCOCH_3$. Separation conditions in chiral HPLC: OD 80:20 *n*-Hex/IPA for 11 min at 0.7 mL/min then to 1 mL/min in 1 min, 40 °C, λ = 230 nm, t_r (minor) = 9.3 min , t_r (major) = 11.6 min.

Chapter 4

Conjugate Addition of Nitrocompounds to 3-Ylidene Oxindoles: Sequential and Domino Reactions

1. Thiourea-based bifunctional catalysis

Ureas and thioureas are able to donate two hydrogen bonds thus accelerating reactions by giving LUMO-lowering of electrophiles or stabilising developing negative charges at heteroatoms in the transition state.

In 1998, Sigman and Jacobsen disclosed that chiral urea or thiourea derivatives (Figure 15) could efficiently transfer stereochemical information promoting highly enantioselective Strecker reactions of *N*-allyl aldimines.[61]

Schreiner et al. were the first to show how profoundly catalyst activity can be tuned by simply varying the *N*-aryl substituent. They introduced the *N*-trifluoromethylphenyl substituent which increased both the solubility and N–H acidity, i.e. hydrogen-bond donating ability, of these compounds[62] (Figure 15).

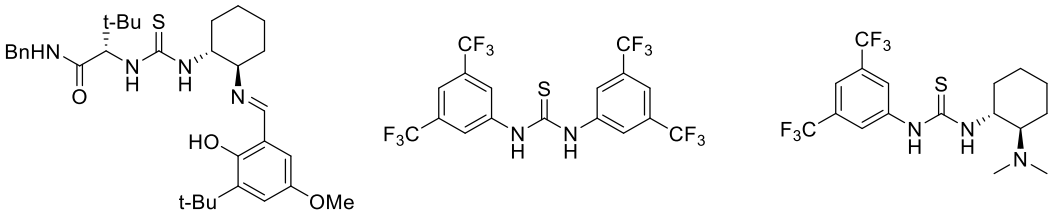
In 2003, Takemoto and co-workers introduced the 1,2-*trans*-cyclohexyldiamine-derived thiourea catalyst (Figure 15). This molecule represents a logical extension of Jacobsen's and Schreiner's ideas, with the advantage of double functionality,[63] including both a Brønsted base that activate the nucleophile and a hydrogen bond donor for the activation of the electrophile. The authors demonstrated the catalyst

[61] Sigman M. S., Jacobsen E. N., *J. Am. Chem. Soc.* **1998**, 120, 4901-4902.

[62] (a) Schreiner P. R., Wittkopp A., *Org. Lett.* **2002**, 4, 217-220; (b) Schreiner P. R., Wittkopp A., *Chem. Eur. J.* **2003**, 9, 407-414.

[63] (a) Siau W., Wang J., *Catal. Sci. Technol.* **2011**, 1, 1298-1310; (b) Ting A., Goss J. M., McDougal N. T., Schaus S. E., "Brønsted Base Catalysts", *Topics in Current Chemistry*, **2010**, Springer, 145-200.

operates via a bifunctional mechanism in the enantioselective Michael addition of dimethylmalonate to nitroalkenes at room temperature.[64]



Jacobsen's thiourea **Schreiner's thiourea** **Takemoto's thiourea**

Figure 15

The first catalytic enantioselective conjugate addition was documented in Wynberg's[65] seminal work on *Cinchona* alkaloid catalysed addition of cyclic β-ketoesters to methyl vinyl ketone. *Cinchona* alkaloids possess relatively rigid structures in which the basicity of the quinuclidine nitrogen combined with the Brønsted acidic C(9)–OH, confers them a bifunctional catalytic property (Figure 16). Acting as bifunctional organocatalysts or ligands, *Cinchona* alkaloids are very useful in asymmetric transformations.

The *Cinchona* alkaloids are provided by nature in pseudoenantiomeric pairs that can be employed to generate either enantiomer of chiral product. The absolute configuration of the alcohol can be readily inverted if required, this way the influence of the relative stereochemistry at the Lewis basic and Lewis acidic groups can change both activity and selectivity.

Also cupreine and cupreidine are pseudoenantiomers of *Cinchona* alkaloids in which the quinoline C(6')–OCH_3 is replaced with an OH–group. The result is the availability of an additional hydrogen-bonding moiety.

[64] Okino T., Hoashi Y., Takemoto Y., *J. Am. Chem. Soc.* **2003**, 125, 12672-12673.

[65] Wynberg H., Heider R., *Tetrahedron Lett.* **1975**, 16, 4057-4060.

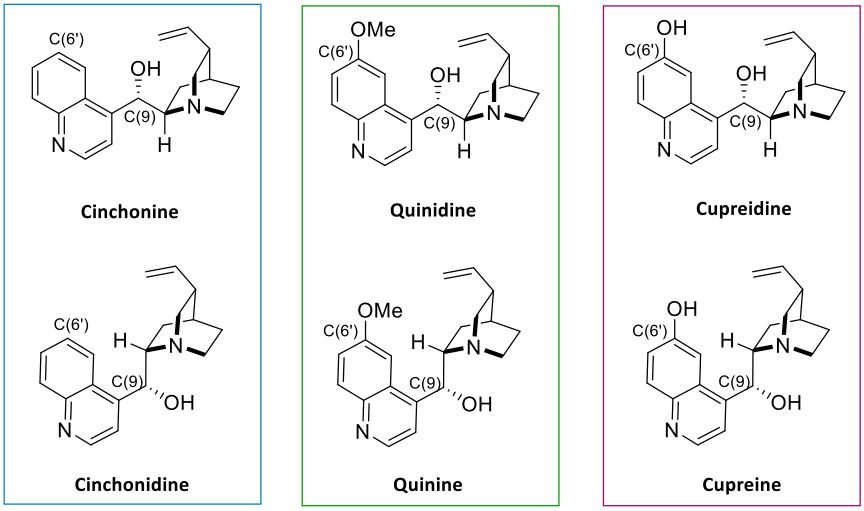


Figure 16

After the introduction of Takemoto's bifunctional catalyst and given the wide applicability of *Cinchona* alkaloids, the development of *Cinchona* derived thiourea catalysts (Figure 17) was the next step.[66]

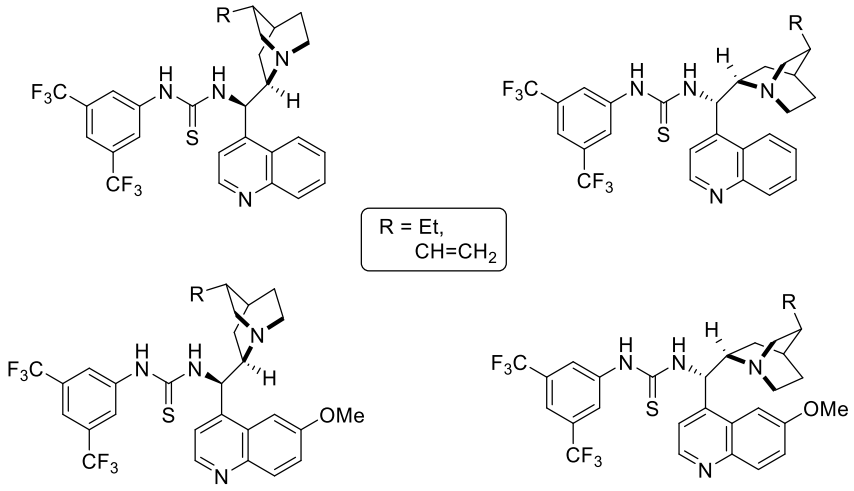


Figure 17

The C-9 secondary alcohol can readily be transformed into a urea or thiourea derivative via the corresponding primary amine. Thus four research groups began working independently with these new catalytic systems and reported their results with half a year of distance between each other. The first report came from Chen and

[66] Connon S. J., *Chem. Commun.* **2008**, 2499-2510.

co-workers,[67] then Soós and co-workers[68] and finally, a short time later, Connon's and then Dixon's groups.[69]

Thiourea-based bifunctional catalysis has been applied in a variety of different reactions like for example Michael addition for C-C, C-O, C-N and C-S bond formation, 1,2 addition, Morita-Baylis-Hillman reaction and Diels-Alder reaction. These catalysts were used also in cascade transformations, dynamic kinetic resolutions and desymmetrization reactions.

2. Oxindole derivatives

Oxindoles are aromatic heterocyclic organic compounds with a bicyclic structure. A 2-oxindole molecule consists of a six-membered benzene ring fused to a five-membered ring containing nitrogen. Its structure is based on the indoline frame where a carbonyl is situated at the 2-position of the five-membered ring. Isatin (or 1H-indole-2,3-dione) is an indole derivative (Figure 18).

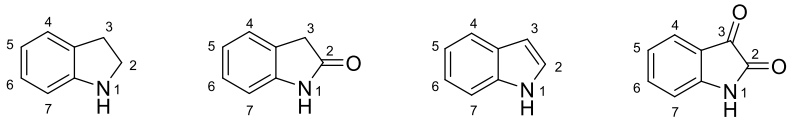


Figure 18

A variety of biological activities are associated with isatins like for instance analgesic, anticonvulsant, antidepressant, antiinflammatory, antimicrobial, etc. Also oxindoles have a wide range of applications and are reported to exhibit many biological effects which include the antiviral, antifungal, antibacterial, antiproliferative,

[67] Li B., Jiang L., Liu M., Chen Y., Ding L., Wu Y., *Synlett* **2005**, 603-606.

[68] Vakulya B., Varga S., Csámpai A., Soós T., *Org. Lett.* **2005**, 7, 1967-1969.

[69] (a) McCooey S. H., Connon S. J., *Angew. Chem. Int. Ed.* **2005**, 44, 6367-6370; (b) Ye J., Dixon D. J., Hynes P. S., *Chem. Commun.* **2005**, 4481-4483.

anticancer, antiinflammatory, antihypertensive, anticonvulsant and antimalaric activities[70] (Figure 19).

Since the chemistry of oxindoles is very interesting and they show biological activity, these compounds became very important in synthetic organic and medicinal chemistry. Indeed, some of the most important spirocycles isolated from natural sources are spirooxindole and spiroindoline alkaloids. These natural products were the target of total syntheses from several groups[71], particularly because several of them possess interesting biological activities, furthermore spirocycles still remain a challenging motif for synthetic chemists.

[70] (a) Millemaggi A., Taylor R. J. K., *Eur. J. Org. Chem.* **2010**, 4527-4547; (b) Bhrigu B., Pathak, D., Siddiqui N., Alam M. S., Ahsan, W., *Int. J. Pharm. Sci. Drug Res.* **2010**, 2, 229-235; (c) Fensome A., Adams W. R., Adams A. L., Berrodin T. J., Cohen J., Huselton C., Illenberger A., Kern J. C., Hudak V. A., Marella M. A., Melenski E. G., McComas C. C., Mugford C. A., Slayden O. D., Yudt M., Zhang Z., Zhang P., Zhu Y., Winneker R. C., Wrobel J. E., *J. Med. Chem.* **2008**, 51, 1861-1873; (d) Canner J., Sobo M., Ball S., Hutzen B., DeAngelis S., Willis W., Studebaker A. W., Ding K., Wang S., Yang D., Lin J., *Br. J. Cancer* **2009**, 101, 774-781; (e) Shangary S., Qin D., McEachern D., Liu M., Miller R. S., Qiu S., Nikolovska-Coleska Z., Ding K., Wang G., Chen J., Bernard D., Zhang J., Lu Y., Gu Q., Shah R. B., Pienta K. J., Ling X., Kang S., Guo M., Sun Y., Yang D., Wang S., *Proc. Natl. Acad. Sci. U. S. A.* **2008**, 105, 3933-3938; (f) Rottmann M., McNamara C., Yeung B. K. S., Lee M. C. S., Zou B., Russell B., Seitz P., Plouffe D. M., Dharia N. V., Tan J., Cohen S. B., Spencer K. R., González-Páez G. E., Lakshminarayana S. B., Goh A., Suwanarusk R., Jegla T., Schmitt E. K., Beck H., Brun R., Nosten F., Renia L., Dartois V., Keller T. H., Fidock D. A., Winzeler E. A., Diagana T. T., *Science* **2010**, 329, 1175-1180.

[71] (a) Albrecht B. K., Williams R. M., *Org. Lett.* **2003**, 5, 197-200; (b) Lin H., Danishefsky S. J., *Angew. Chem. Int. Ed.* **2003**, 42, 36-51; (c) Greshock T. J., Grubbs A. W., Jiao P., Wicklow D. T., Gloer J. B., Williams R. M., *Angew. Chem. Int. Ed.* **2008**, 47, 3573-3577; (d) Reisman S. E., Ready J. M., Weiss M. M., Hasuoka A., Hirata M., Tamaki K., Ovaska T. V., Smith C. J., Wood J. L., *J. Am. Chem. Soc.* **2008**, 130, 2087-2100; (e) Galliford C. V., Scheidt K. A., *Angew. Chem. Int. Ed.* **2007**, 46, 8748-8758; (f) Marti C., Carreira E. M., *Eur. J. Org. Chem.* **2003**, 2209-2219; (g) Trost B. M., Brennan M. K., *Synthesis* **2009**, 18, 3003-3025.

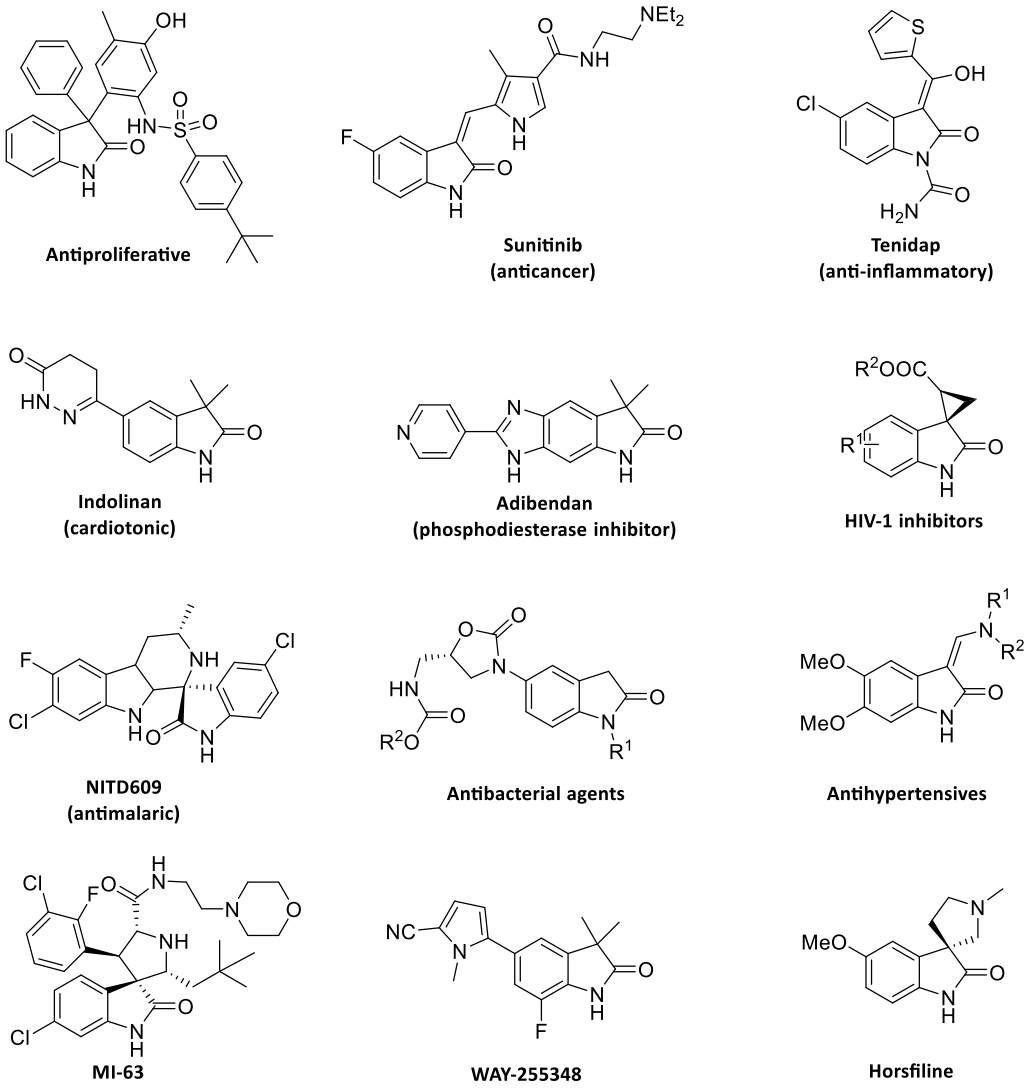


Figure 19

The importance of enantiopure compounds with oxindole scaffold gave birth to the development of different asymmetric approaches both metal-[72] and organo-[73] catalysed. There has been significant focus on the synthesis of 3,3'-disubstituted oxindoles (often as spirocycles) particularly because their biological properties make them good targets for drug candidates and clinical pharmaceuticals. These

[72] (a) Ma S., Han X., Krishnan S., Virgil S. C., Stoltz B. M., *Angew. Chem. Int. Ed.* **2009**, 48, 8037-8041; (b) Trost, B. M., Zhang Y., *Chem. Eur. J.* **2011**, 17, 2916-2922; (c) Trost B. M., Cramer N., Silverman S. M., *J. Am. Chem. Soc.* **2007**, 129, 12396-12397; (d) Kato Y., Furutachi M., Chen Z., Mitsunuma H., Matsunaga S., Shibasaki M., *J. Am. Chem. Soc.* **2009**, 131, 9168-9169; (e) Antonchick A. P., Gerding-Reimers C., Catarinella M., Schürmann M., Preut H., Ziegler S., Rauh D., Waldmann H., *Nat. Chem.* **2010**, 2, 735-740.

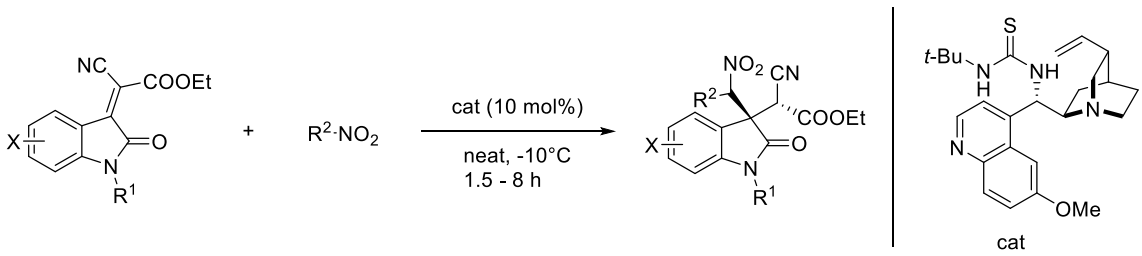
[73] (a) Dalpozzo R., Bartoli G., Bencivenni G., *Chem. Soc. Rev.* **2012**, 41, 7247-7290; (b) Ball-Jones N. R., Badillo J. J., Franz A. K., *Org. Biomol. Chem.* **2012**, 10, 5165-5181; (c) Singh G. S., Desta Z. Y., *Chem. Rev.* **2012**, 112, 6104-6155; (d) Hong L., Wang R., *Adv. Synth. Catal.* **2013**, 355, 1023-1052; (e) Zhou F., Liu Y., Zhou J., *Adv. Synth. Catal.* **2010**, 352, 1381-1407.

compounds, together with the quaternary stereocenter[74] in the oxindole 3-position, often have a sequence of contiguous stereocenters. These synthetic challenging features caught the attention of many organic chemists who started to exploit achiral or racemic oxindole derivatives as starting materials for asymmetric transformations generating complex structures, often making use of consecutive, one-pot, multi-component or domino reactions.

3. Reaction design: sequential transformations

Among all the organocatalysed asymmetric transformations involving oxindole derivatives, we focused our attention on the ones involving bifunctional thioureas as catalyst, in particular we decided to study the reaction concerning the addition of nitroalkanes.

Even if nitrocompounds are commonly used in organocatalysis,[75] in the literature there were only two papers in which a bifunctional thiourea catalysed attack of nitroalkanes to 3-ylidene oxindole derivatives is described. In the first case[76] (Scheme 13) the nitroalkane attacks the oxindole compound in a 1,4 addition respect to the cyano and ester groups.



Scheme 13

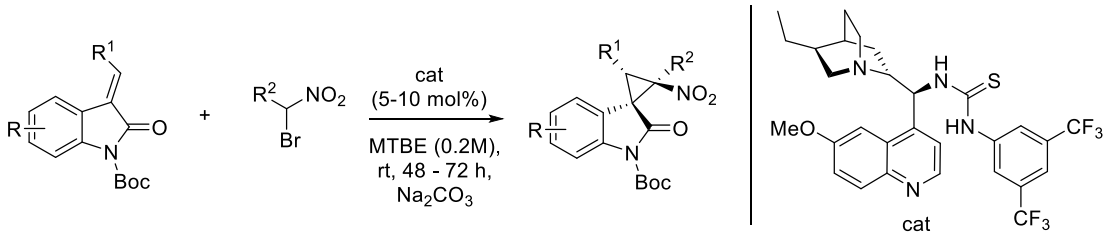
In the second work the nitrocyclopropanation of oxindoles achieved via domino reaction is discussed[77] (Scheme 14).

[74] (a) Corey E. J., Guzman-Perez A., *Angew. Chem. Int. Ed.* **1998**, 37, 388-401; (b) Douglas C. J., Overman L. E., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5363-5367; (c) Peterson E. A., Overman L. E., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 11943-11948; (d) Trost B. M., Jiang C., *Synthesis* **2006**, 3, 369-396; (e) Bella M., Gasperi T., *Synthesis* **2009**, 10, 1583-1614.

[75] Aitken L. S., Arezki N. R., Dell'Isola A., Cobb A. J. A., *Synthesis* **2013**, 45, 2627-2648.

[76] Liu L., Wu D., Zheng S., Li T., Li X., Wang S., Li J., Li H., Wang W., *Org. Lett.* **2012**, 14, 134-137.

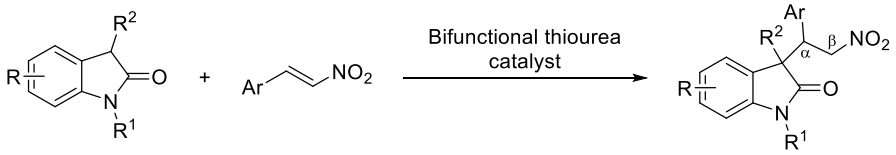
[77] Pesciaioli F., Righi P., Mazzanti A., Bartoli G., Bencivenni G., *Chem. Eur. J.* **2011**, 17, 2842-2845.



Scheme 14

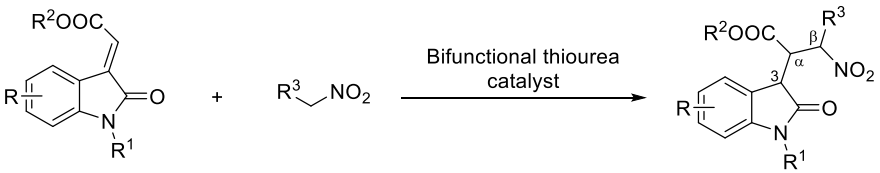
Also the Henry reaction to isatin is described,[78] but in these cases bifunctional thioureas are not the catalysts of choice.

In order to introduce a nitro group in the β-position of oxindole using bifunctional thiourea catalysis, only reactions with oxindoles as nucleophiles and nitrostyrenes as electrophiles were known[79] (Scheme 15).



Scheme 15

Since the reactions of nitroalkanes with oxindole derivatives were not particularly explored, we decided to study the Michael addition of these nitrocompounds to 3-ylidene oxindoles mediated by thiourea-based bifunctional organocatalysts (Scheme 16). In this reaction we observed a different regioselectivity compared to the work reported by Wang et al.[76] because of the highest electron-withdrawing power of the oxindole compared to the ester on the β terminus of the double bond.



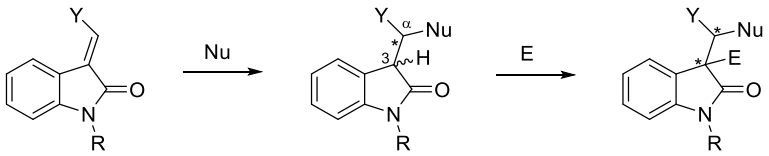
Scheme 16

[78] (a) Liu L., Zhang S., Xue F., Lou G., Zhang H., Ma S., Duan W., Wang W., *Chem. Eur. J.* **2011**, 17, 7791-7795; (b) Zhang Y., Li Z. J., Xu H. S., Zhang Y., Wang W., *RSC Advances* **2011**, 1, 389-392; (c) Li M., Zhang J., Huang X., Wu B., Liu Z., Chen J., Li X., Wang X., *Eur. J. Org. Chem.* **2011**, 5237-5241; (d) Prathima P. S., Srinivas K., Balaswamy K., Arundhathi R., Reddy G. N., Sridhar B., Rao M. M., Likhar P. R., *Tetrahedron: Asymmetry* **2011**, 22, 2099-2103.

[79] (a) Chen X., Zhu W., Qian W., Feng E., Zhou Y., Wang J., Jiang H., Yao Z., Liu H., *Adv. Synth. Catal.* **2012**, 354, 2151-2156; (b) Retini M., Bergonzini G., Melchiorre P., *Chem. Commun.* **2012**, 48, 3336-3338; (c) Li X., Zhang B., Xi Z., Luo S., Cheng J., *Adv. Synth. Catal.* **2010**, 352, 416-424; (d) Bui T., Syed S., Barbas III C. F., *J. Am. Chem. Soc.* **2009**, 131, 8758-8759; (e) Cui B., Han W., Wu Z., Zhang X., Yuan W., *J. Org. Chem.* **2013**, 78, 8833-8839.

There are very few studies on organocatalytic asymmetric intermolecular additions to the β-carbon of 3-ylidene oxindoles. Xiao and co-workers[80] reported the conjugate addition of acetylacetone to 3-ylidene oxindoles recording excellent enantioselectivities, but moderate diastereomeric ratios. In one reaction they tested also nitromethane as Michael donor: the expected product was obtained in high yield and enantiocontrol at C-α, but the two diastereoisomers were formed in almost identical amounts due to lack of control at C-3.

We took advantage of the stereolability problem of oxindole C-3 exploiting its nucleophilicity for a further functionalization[81] generating an all-carbon quaternary stereocenter (Scheme 17).



Scheme 17

The most frequently exploited approach present in literature to solve this stereolability problem is spirocyclization, treated in details in paragraph 5 of this chapter.

4. Organocatalytic conjugate addition of nitroalkanes to 3-ylidene oxindoles: a stereocontrolled diversity oriented route to oxindole derivatives

Protecting groups screening

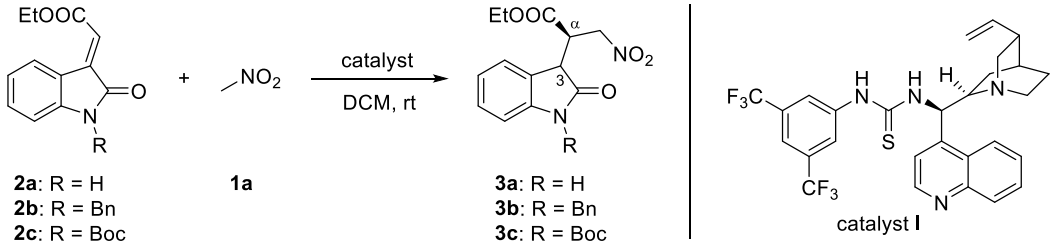
We decided to start the study of the addition of nitroalkane to 3-yilidene-oxindoles performing the reaction between nitromethane (**1a**) and differently *N*-substituted (*E*)-ethyl 2-(2-oxoindolin-3-ylidene)acetates (**2a-c**). We choose a bifunctional thiourea derived from *Cinchona* alkaloid as organocatalyst.

[80] Duan S., Lu H., Zhang F., Xuan J., Chen J., Xiao W., *Synthesis* **2011**, 12, 1847-1852.

[81] For some examples of C-3 acting as nucleophile, see: (a) Ohmatsu K., Kiyokawa M., Ooi T., *J. Am. Chem. Soc.* **2011**, 133, 1307-1309; (b) Ogawa S., Shibata N., Inagaki J., Nakamura S., Toru T., Shiro M., *Angew. Chem. Int. Ed.* **2007**, 46, 8666-8669; (c) Jiang K., Peng J., Cui H., Chen Y., *Chem. Commun.* **2009**, 3955-3957; (d) Tian X., Jiang K., Peng J., Du W., Chen Y., *Org. Lett.* **2008**, 10, 3583-3586; (e) He R., Ding C., Maruoka K., *Angew. Chem. Int. Ed.* **2009**, 48, 4559-4561; (f) Li X., Luo S., Cheng J., *Chem. Eur. J.* **2010**, 16, 14290-14294; (g) Zhang T., Cheng L., Hameed S., Liu L., Wang D., Chen Y., *Chem. Commun.* **2011**, 47, 6644-6646.

Since many reactions with oxindole derivatives catalysed by bifunctional thioureas are strongly dependent on the protecting group, we first focused our attention on their screening (Table 14).

Table 14. *N*-protecting groups screening in the organocatalysed asymmetric conjugate addition of **1a** to 3-ylidene oxindoles (**2a-c**).[a]



2a: R = H
2b: R = Bn
2c: R = Boc

1a

3a: R = H
3b: R = Bn
3c: R = Boc

Entry	Substrate	Time (h)	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1	**2a**	1.5	92	51:49	93/92
2	**2b**	1.75	99	49:51	92/93
3	**2c**	1	99	55:45	99/>99

[a] Reaction conditions: **2** (0.1 mmol), **1a** (1 mmol), catalyst (10 mol%), dichloromethane (DCM, 0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Conversion calculated with respect to **2**. [c] Determined by CSP-HPLC of **3**, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers.

The reaction gave good reactivity (better than in Xiao's conditions:[80] 90% yield after 15 hours) and enantioselectivity with every substituent we tested. As expected, the two diastereoisomers were formed in almost the same amount providing very poor diastereomeric ratios, this is due to the stereolability of C-3 in the reaction conditions.

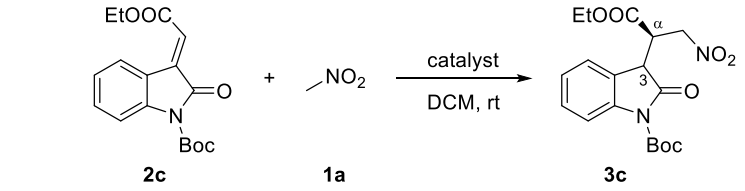
We were very pleased to see that also the unprotected starting material (**2a**) provided very good reactivity and enantioselectivity (entry 1), indeed most of the reactions reported in literature work well only on *N*-protected substrates.

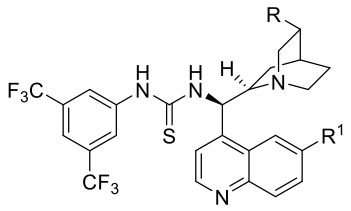
The best enantioselectivity was obtained for *N*-Boc substrate **2c** (entry 3), so further optimizations were performed on it.

Catalysts screening

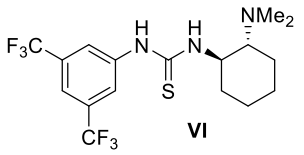
Other bifunctional organocatalysts were tested in the model reaction between **1a** and **2c** (Table 15).

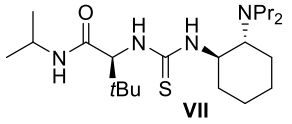
Table 15: Catalysts screening in the organocatalysed asymmetric conjugate addition of **1a** to **2c**.[a]

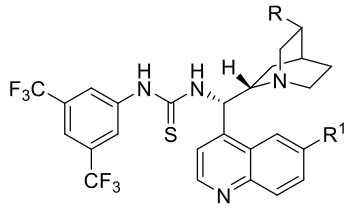




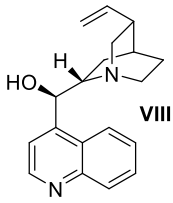
I: R = $CH{=}CH_2$, R^1 = H
III: R = CH_2CH_3, R^1 = H
V: R = $CH{=}CH_2$, R^1 = OMe

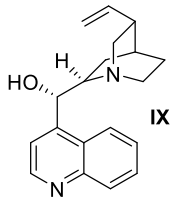






II: R = $CH{=}CH_2$, R^1 = H
IV: R = CH_2CH_3, R^1 = H





Entry	Catalyst	Time (h)	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1	**I**	1	99	55:45	99/>99
2	**II**	1.5	91	48:52	97/98[d]
3	**III**	1.75	99	48:52	95/96
4	**IV**	1.5	99	55:45	97/97[d]
5	**V**	1.5	99	57:43	98/98
6	**VI**	1	99	52:48	99/>99
7	**VII**	1.5	99	54:46	59/64
8	**VIII**	1.5	99	55:45	82/86
9	**IX**	2	99	53:47	83/86[d]

[a] Reaction conditions: **2c** (0.1 mmol), **1a** (1 mmol), catalyst (10 mol%), dichloromethane (DCM, 0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Conversion calculated with respect to **2c**. [c] Determined by CSP-HPLC of **3c**, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers. [d] Opposite enantiomers were formed.

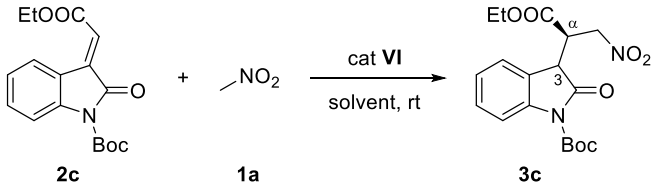
High conversions in short reaction times were invariably observed (entries 2-9), while diastereo- and enantioselectivities did not undergo significant changes when *Cinchona*-derived thioureas (**II**-**V**) and Takemoto's thiourea (**VI**) were used (entries 2-

6). Conversely significant lower *ee*s were recorded employing *Cinchona* alkaloids **VIII** and **IX** (entries 8 and 9) and, particularly, the Jacobsen's thiourea **VII** (entry 7). The best results in terms of reaction rate and stereocontrol were obtained with catalysts **I** and **VI**, thus we chose Takemoto's thiourea **VI** (TUC) as the catalyst for the reaction since it is low cost commercially available.

Optimization of the reaction conditions

A short screening of solvents was carried out (Table 16) confirming dichloromethane as the solvent of choice, even if all the solvents tested afforded good results.

Table 16: Solvents screening in the organocatalysed asymmetric conjugate addition of **1a** to **2c**.[a]



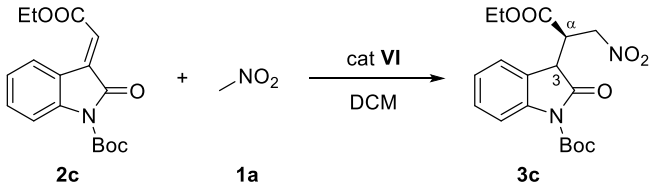
2c **1a** **3c**

Entry	Solvent	Time (h)	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1	DCM	1.5	99	52:48	99/>99
2	THF	1.5	99	49:51	99/>99
3	Toluene	1.5	99	50:50	99/99
4	MeOH	1.5	99	53:47	97/97
5	MeCN	1.5	99	52:48	98/98

[a] Reaction conditions: **2c** (0.1 mmol), **1a** (1 mmol), catalyst **VI** (2.5 mol%), solvent (0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Conversion calculated with respect to **2c**. [c] Determined by CSP-HPLC of **3c**, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers.

Also other reaction conditions were deeply investigated in order to verify the effects of the decrease of nitromethane equivalents, catalyst loading and temperature on both rate and stereoselection (Table 17).

Table 17: Optimization of the reaction conditions for the organocatalysed asymmetric conjugate addition of **1a** to **2c**.[a]



Entry	**1a** (eq.)	**VI** (mol %)	*T* (°C)	Time (h)	Conv. (%)[b]	dr[b]	*ee* (%)[c]
1	2.5	10	rt	1	99	57:43	97/>99
2	10	1	rt	1.5	99	52:48	>99/99
3	5	5	rt	1	99	53:47	99/99
4	2.5	2.5	rt	2	99	52:48	98/98
5	2	1	rt	5.5	72	52:48	95/95
6	5	5	0	1.5	99	49:51	>99/>99
7	5	5	-20	120	72	47:53	>99/>99

[a] Reaction conditions: **2c** (0.1 mmol), catalyst **VI**, DCM (0.15 mL). [b] Determined by ^{1}H NMR of the crude mixture. Conversion calculated with respect to **2c**. [c] Determined by CSP-HPLC of **3c**, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers.

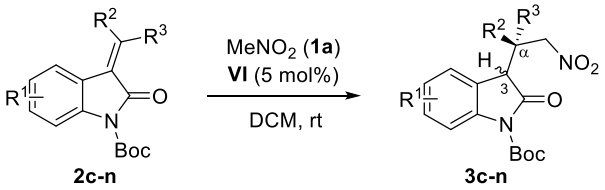
When nitromethane amount (entry 1) and catalyst loading (entry 2) were individually lowered, and also when they were simultaneously decreased up to 2.5 equivalents of **1a** and 2.5 mol % of **VI** (entries 3 and 4) we still got excellent results. The reaction time increased (only up to 5.5 hours) using 2 equivalents of **1a** and only 1 mol % of catalyst (entry 5). Finally we lowered the temperature (entries 6 and 7) in order to have an improvement of diastereoselectivity, but it remained unchanged. From these results we can infer that our reaction system did not allow a stereoselective C-3 protonation. Indeed the C(3)-H acidity of 3-alkyl substituted oxindoles might be significantly influenced by the *N*-protecting group.[82] Electron-withdrawing protecting groups increase the acidity of the C-3 position, for instance the pKa of *N*-acetyloxindole is around 13. Hence the *N*-Boc protection could favor a C-3 epimerization in our reaction conditions. The temperature effect on the diastereoselectivity was investigated also on substrate **2b**: when the model reaction was performed at −20°C, the conversion was complete in 14 hours but the dr was still 1/1. The same reaction at −40°C did not proceed.

[82] Bordwell F. G., Fried H. E., *J. Org. Chem.* **1991**, 56, 4218-4223.

Scope of the reaction

To expand the reaction scope, we employed the reaction conditions that provided the best balance between reaction rate and stereocontrol for the different substrates; these were identified in 5 equivalents of **1a** and 5 mol % of catalyst **VI**. We applied our protocol to a variety of 3-ylidene oxindoles (**2c-n**) and we were delighted to find that the process well tolerated different substitution patterns (Table 18).

Table 18: Organocatalysed asymmetric conjugate addition of **1a** to 3-ylidene oxindoles **2c-n**.[a]



Entry	Substrate	R^1	R^2	R^3	Product	Time (h)	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	**2c**	H	CO_2Et	H	**3c**	1	80	53:47	99/99
2	**2d**	5-Cl	CO_2Et	H	**3d**	3.5	83	60:40	>99/>99
3	**2e**	5-Br	CO_2Et	H	**3e**	3.5	72	53:47	>99/>99
4	**2f**	6-Cl	CO_2Et	H	**3f**	1.5	92	56:44	98/98
5	**2g**	7-Br	CO_2Et	H	**3g**	1	82	59:41	95/94
6	**2h**	5-OMe	CO_2Et	H	**3h**	1	89	55:45	>99/>99
7	**2i**	H	CO_2Bn	H	**3i**	2	72	55:45	>99/>99
8	**2j**	H	CO_2tBu	H	**3j**	2	99	57:43	>99/>99
9	**2k**	H	Ph	H	**3k**	2	52	59:41	60/64
10	**2l**	H	*p*NO_2Ph	H	**3l**	2	98	60:40	31/33
11	**2m**	H	*t*Bu	H	**3m**	26	62	69:31	26/29
12	**2n**	H	CO_2Et	Me	**3n**	2	57	60:40	94/92

[a] Reaction conditions: **2** (0.1 mmol), **1a** (0.5 mmol), catalyst **VI** (5 mol%), DCM (0.15 mL), rt. [b] Yield of the isolated product after flash-chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by CSP-HPLC of products **3**, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers.

The reaction was not affected by the presence of substituents, both electron-withdrawing (entries 2-5) and electron-donating (entry 6), on the aromatic ring proceeding in short reaction times and with excellent enantiocontrol. Also the substituent position on the ring did not significantly affect the efficiency of the process (cf. entries 2 and 4, entries 3 and 5). The ethyl ester could be replaced with benzyl- (entry 7) and *tert*-butyl (entry 8) esters preserving complete enantioselectivity.

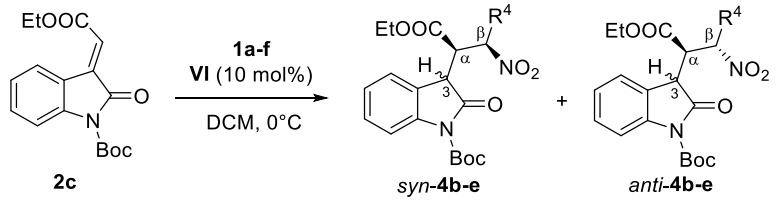
Significant changes, mainly in the enantiocontrol, were observed when, instead of the ester function, aromatic or aliphatic groups were located at the exocyclic double bond. For the phenyl derivative **3k** the *ee* dropped to 60% (entry 9) and the addition of an electron-withdrawing substituent on the phenyl ring provided even worse results (entry 10). The last attempt was conducted introducing an aliphatic group on the double bond, however obtaining very poor *ee*s and longer reaction times (entry 11). The latter data suggested that a crucial role for the enantioselectivity was played by the presence of an ester on the 3-ylidene oxindole. According to the dual activation model[83] proposed by Takemoto, Deng and theoretical calculations performed by Pápai, the bifunctional organocatalyst should simultaneously activate both Michael donor and acceptor, thus controlling the approach of the nitroalkane to the 3-ylidene oxindole. The oxindole reasonably interacts with the thiourea moiety via multiple hydrogen bonds, enhancing the electrophilicity of the reacting carbon center. Concurrently, the nitro compound coordinates to the tertiary amine group. The poor enantiocontrol observed when the methyleneindolinone was directly connected to an aryl or alkyl group may suggest that the ester moiety can affect the coordination between catalyst and substrate, enabling a high enantiocontrol. On the other hand, the interaction between the *N*-Boc carboxyl group and the catalyst in our system seems to be present but not strictly necessary, as evidenced by the small differences in enantioselectivity recorded for substrates **2a**, **2b** and **2c** (Table 14).

The substrate scope was also extended to the challenging construction of a quaternary stereocenter on the C-α position applying our protocol to substrate **2n**, characterized by a tetrasubstituted exocyclic double bond (Table 18, entry 12). Once again the reaction quickly provided the desired product with high *ee*s for both the diastereoisomers.

The next step in our investigation was to explore the use of other nitroalkanes (Table 19), with the aim to introduce a further stereocenter.

[83] (a) Okino T., Hoashi Y., Furukawa T., Xu X., Takemoto Y., *J. Am. Chem. Soc.* **2005**, 127, 119-125; (b) Li H., Wang Y., Tang L., Wu F., Liu X., Guo C., Foxman B. M., Deng L., *Angew. Chem. Int. Ed.* **2005**, 44, 105-108; (c) Hamza A., Schubert G., Soós T., Pápai I., *J. Am. Chem. Soc.* **2006**, 128, 13151-13160.

Table 19: Organocatalysed asymmetric conjugate addition of nitroalkanes **1a-f** to **2c**.[a]

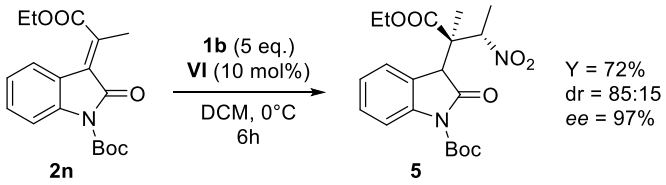


Entry	R^4	Product	Time (h)	Yield (%)[b]	*anti/syn*[c]	*ee anti* (%)[d]
1[e]	**1a** = $MeNO_2$	**3c**	1	80	-	99/99
2[e]	Me (**1b**)	**4b**	2	78	76:24	97/98
3[f]	Me (**1b**)	**4b**	48	73	99:1	>99/>99
4	Me (**1b**)	**4b**	3	71	95:5	>99/>99
5	Et (**1c**)	**4c**	7	76	92:8	>99/>99
6	$(CH_2)_2CO_2Me$ (**1d**)	**4d**	4	83	91:9	>99/>99
7	CH_2Ph (**1e**)	**4e**	4	72	90:10	>99/>99
8	**1f** = *i*$PrNO_2$	**4f**	144	traces	-	-

[a] Reaction conditions: **2c** (0.1 mmol), **1** (0.5 mmol), catalyst **VI** (10 mol%), DCM (0.15 mL), 0°C. [b] Yield of the isolated product after flash-chromatography. [c] Determined by CSP-HPLC of the crude mixture; stereochemical notation *anti:syn* refers to the Cα-Cβ relationship. [d] Determined by CSP-HPLC of the products, isolated as mixture of two C-3 epimers; *ee* values refer to the two C-3 epimers. [e] Reaction performed at rt with 5 mol % of **VI**. [f] Reaction performed at -10°C.

We first applied the conditions optimized for nitromethane **1a** (entry 1). Nitroethane **1b** quickly provided the desired product **4b** in good yield and excellent stereocontrol at C-α, but with modest control of the C-β stereochemistry (entry 2). We tried to improve the *anti*/*syn* ratio (relative to the Cα-Cβ relationship) by lowering the temperature; performing the reaction at -10°C the diastereocontrol was almost complete (entry 3). However, the reaction time was much longer, so that the best trade-off between reactivity and stereoselectivity was reached employing 10 mol% of catalyst at 0°C. In these conditions, after 3 hours **4b** was obtained in good yield, high diastereomeric ratio and excellent *ee*s (entry 4). The protocol was successfully applied to nitroalkanes **1c-e** (entries 5-7), while the isopropyl derivative **1f** did not afford the corresponding product (entry 8), probably because of the steric hindrance at the α-nitro position. With this protocol the configurations of the two stereocenters directly generated in the conjugate addition were highly defined, while the C-3 configuration was, as usual, out of control. With the aim to introduce a quaternary and two tertiary

contiguous stereocenters on the oxindole scaffold, we extended the addition of nitroethane **1b** to substrate **2n** (Scheme 18).



Scheme 18

The product **5** was obtained in good yield and high *ee*. In this case the two C-3 epimers were not equally present (dr = 85:15), probably because the steric crowding and the substituents distribution on the adjacent stereocenters partially affect the C-3 configuration.

Concluding this first part, we developed an asymmetric organocatalytic protocol for the conjugate addition of nitroalkanes to 3-ylidene oxindoles, which proceeds with good yields and excellent enantioselectivities.

Further functionalization: all-carbon C-3 quaternary stereocenter construction

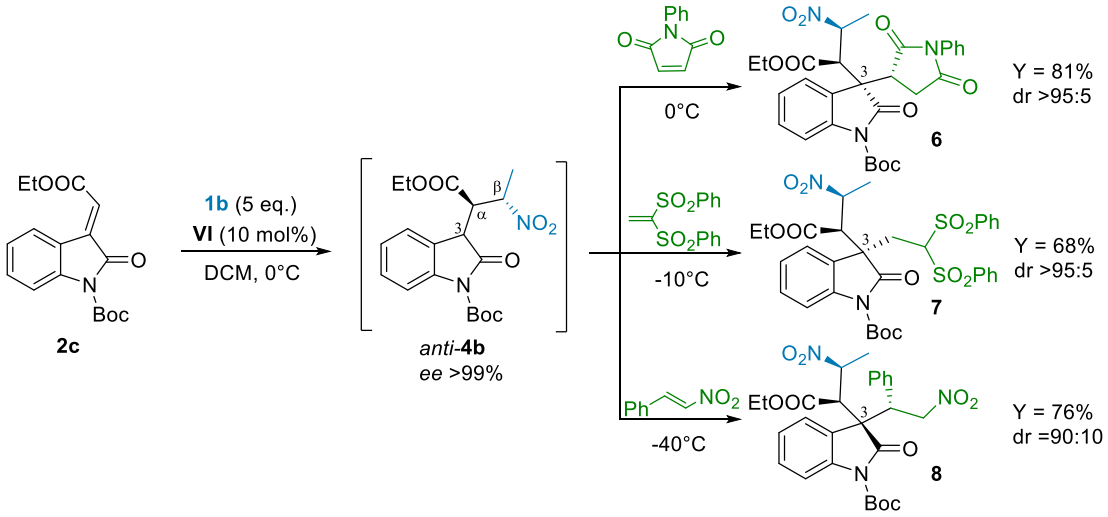
Although it was not possible to control the absolute configuration of the C-3 stereocenter, this limitation can become an opportunity of an all-carbon quaternary stereocenter construction by reacting the β-nitro oxindole **4** with an electrophile, thus increasing the structural complexity. The β-nitro indolin-2-one scaffold **4** could represent a useful precursor for the asymmetric synthesis of 3,3'-disubstituted oxindoles with more substitution variants.

The first attempts were made using *N*-phenylmaleimide,[84] 1,1-bis(benzenesulfonyl)-ethylene[85] and *trans*-β-nitrostyrene[86,79c,d] as electrophiles, in the presence of the same thiourea-catalyst used for the preliminary Michael addition (Scheme 19).

[84] Liao Y., Liu X., Wu Z., Cun L., Zhang X., Yuan W., *Org. Lett.* **2010**, 12, 2896-2899.

[85] (a) Zhu Q., Lu Y., *Angew. Chem. Int. Ed.* **2010**, 49, 7753-7756; (b) Lee H. J., Kang S. H., Kim D. Y., *Synlett* **2011**, 1559-1562.

[86] (a) Li X., Li Y., Peng F., Wu S., Li Z., Sun Z., Zhang H., Shao Z., *Org. Lett.* **2011**, 13, 6160-6163; (b) Ding M., Zhou F., Liu Y. L., Wang C., Zhao X., Zhou J., *Chem. Sci.* **2011**, 2, 2035-2039; (c) Liu X., Wu Z., Du X., Zhang X., Yuan W., *J. Org. Chem.* **2011**, 76, 4008-4017.



Scheme 19

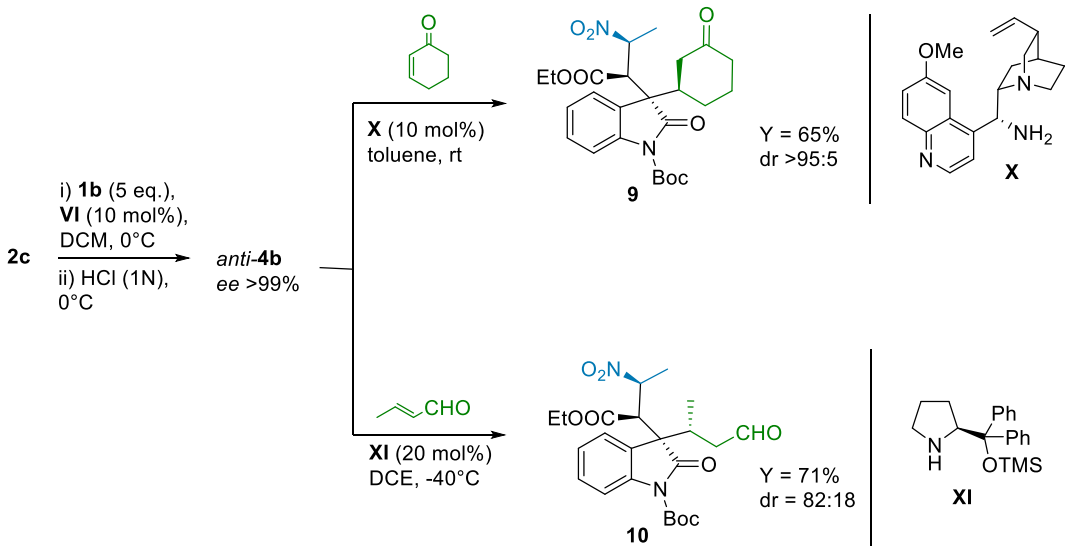
The reaction with *N*-phenylmaleimide smoothly proceeded, affording product **6** as single stereoisomer in good yield. In this one pot three-component tandem reaction four contiguous stereocenters, including the desired C-3 all-carbon quaternary one, were enantioselectively generated.

To introduce structural diversity, the reactivity of **4b** was also tested in the Michael addition to 1,1-bis(benzenesulfonyl)-ethylene. Compound **7**, containing three adjacent stereocenters, was efficiently isolated with excellent stereoenrichment. The organocatalysed conjugate addition of 3-substituted racemic oxindole derivatives to vinyl sulfones is known to proceed with good stereocontrol if an aryl substituent on C-3 is present, while 3-alkyl oxindoles generally afford the corresponding adducts in low yields and poor enantioselectivity; for this reason, Lu and co-workers[85a] and Kim and co-workers[85b] were forced to develop specifically modified organocatalysts. In our case, thanks to the matched induction of pre-existing stereocenters and catalyst, the asymmetric Michael reaction smoothly proceeded on 3-alkyl oxindole **4b** employing the readily available Takemoto's catalyst **VI**.

The last application of the hydrogen-bonding catalysis involved the addition of **4b** to *trans*-β-nitrostyrene, further confirming the versatility of the β-nitro indolin-2-one scaffold as synthetic precursor of optically active 3,3'-disubstituted oxindoles.

One of the advantages of the proposed one-pot tandem reactions was that a single catalyst sequentially promoted two different transformations, so that the addition of other catalysts was not necessary.

To further expand the opportunities of structural diversification, we explored a second activation mode employing covalent amino-catalysis for the reaction of **4b** with 2-cyclohexen-1-one[87] and with crotonaldehyde[88] (Scheme 20). Catalyst **VI** was easily removed by means of an acidic work up, allowing to carry out the subsequent Michael reaction directly on the crude reaction mixture containing **4b**.



Scheme 20

Primary amine **X** and secondary amine **XI** were used, respectively, for the α,β-unsaturated ketone and the α,β-unsaturated aldehyde, affording the corresponding products **9** and **10** in good yields. Once again 3,3'-disubstituted oxindoles bearing four contiguous stereocenters were obtained with good to excellent stereocontrol.

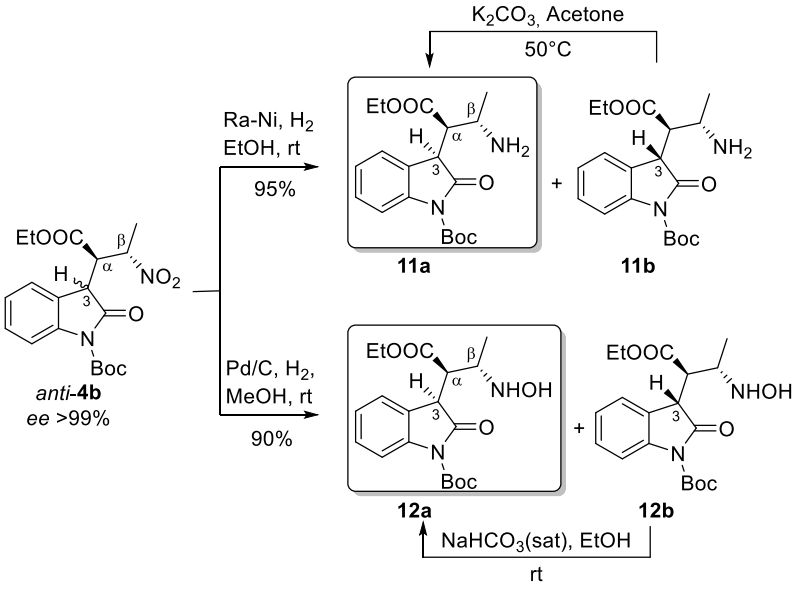
A notable synthetic application of the β-nitro oxindole scaffold lies in its easy conversion to the corresponding β-amino derivative, present in many bioactive compounds. The reduction with Raney Nickel of **4b** quantitatively provided the expected β-amino indolin-2-one **11** (Scheme 21).

We tried also to carry out the reduction with palladium on carbon and, surprisingly, the couple of products observed was different from the one obtained using Raney

[87] (a) Pesciaioli F., Tian X., Bencivenni G., Bartoli G., Melchiorre P., *Synlett* **2010**, 11, 1704-1708; (b) Wang L., Peng L., Bai J., Huang Q., Xu X., Wang L., *Chem. Commun.* **2010**, 46, 8064-8066.

[88] (a) Bencivenni G., Wu L., Mazzanti A., Giannichi B., Pesciaioli F., Song M., Bartoli G., Melchiorre P., *Angew. Chem. Int. Ed.* **2009**, 48, 7200-7203; (b) Jiang K., Jia Z., Chen S., Wu L., Chen Y., *Chem. Eur. J.* **2010**, 16, 2852-2856; (c) Jiang K., Jia Z., Yin X., Wu L., Chen Y., *Org. Lett.* **2010**, 12, 2766-2769; (d) Galzerano P., Bencivenni G., Pesciaioli F., Mazzanti A., Giannichi B., Sambri L., Bartoli G., Melchiorre P., *Chem. Eur. J.* **2009**, 15, 7846-7849; (e) Companyó X., Zea A., Alba A. R., Mazzanti A., Moyano A., Rios R., *Chem. Commun.* **2010**, 46, 6953-6955; (f) Noole A., Oseka M., Pehk T., Öeren M., Järving I., Elsegood M. R. J., Malkov A. V., Lopp M., Kanger T., *Adv. Synth. Catal.* **2013**, 355, 829-835.

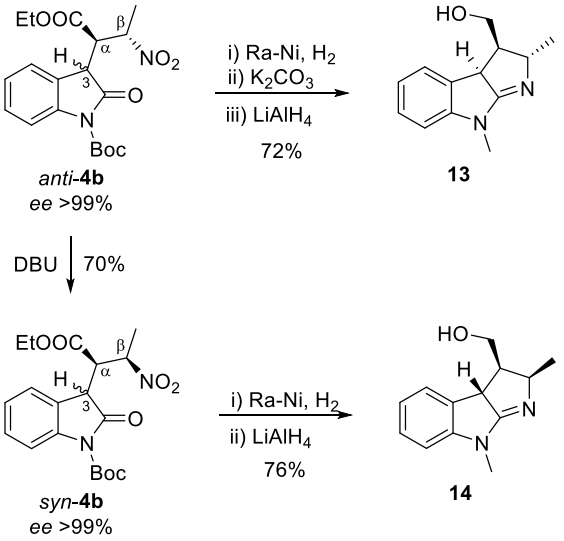
Nickel. A careful analysis of the HPLC-MS and NMR spectra allowed us to establish that the palladium catalyst reduced the β-nitro oxindole **4b** only partially, providing the corresponding β-hydroxylamino oxindole **12**. As expected, the β-amino and the β-hydroxylamino derivatives were both isolated as mixture of two C-3 epimers (**11a,b** and **12a,b** respectively), but, when subjected to basic conditions, both compound **11** and **12** converged to a single stereoisomer (Scheme 21). As previously mentioned about compound **5**, the C-3 configuration could be affected by the stereochemical features and the ability to form specific interactions of the substituents on C-α and C-β. In this case, probably the higher thermodynamic stability of **11a** and **12a** acts as driving force in the base-promoted stereoconvergent C-3 epimerization.



Scheme 21

Finally, the optically active conjugate adduct *anti*-**4b** (>99% *ee*) was first reduced and then cyclized to compound **13**, featured by a core structure similar to those of many important natural products with biological activity (Scheme 22). The possibility to obtain stereochemically different scaffolds starting from the same substrate could be synthetically very useful, providing the opportunity to obtain a platform of diastereomeric derivatives to better evaluate the effect of relative stereochemistry on bioactivity. With this aim, exploiting the acidity on the C-β position, we subjected *anti*-**4b** to basic conditions (1,5-diazabiciclo[5.4.0]undec-5-ene, DBU, 30 mol %) and *syn*-**4b** was isolated in good yield without compromising the optical purity. The previously described reductive protocol allowed us to obtain product **14**, characterized by a

different relative stereochemistry from that of compound **13**. The C-α, whose absolute configuration is controlled by the chiral thiourea during the conjugate addition, is the only stereocenter that remains unchanged, while the stereochemistry at the other centres can be manipulated by means of stereoconvergent transformations, depending on the desired target molecule.



Scheme 22

1D NOESY experiments on compounds **13** and **14** allowed us to establish the relative configuration of the three stereocenters. The more relevant and diagnostic nOe signals are represented in Figure 20.

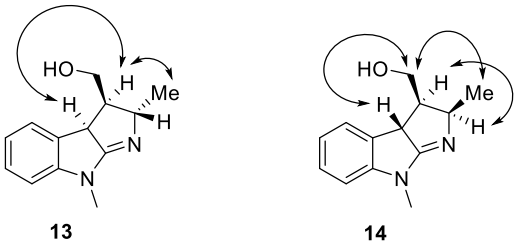


Figure 20

The absolute configuration of compound **13** has been determined by theoretical calculation of its electronic circular dichroism (ECD) spectrum and of its optical rotation (OR), using TD-DFT method.

5. Reaction design: domino spirocyclization

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, a process in which

several bonds are formed in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents would be much more efficient.

A domino reaction[89] involves two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.

This type of reactions, compared to stepwise reactions, allow the minimization of waste, of the amount of solvents, reagents, adsorbents, work and energy. Thus, these reactions would allow a more ecologically and economically favourable production. These domino reactions dramatically increase the structural complexity in only one process.

A significant advantage of many organocatalysts is the capability of promoting several types of reactions through different activation modes, this ability makes an organocatalyst ideal for application in domino reactions.[90] Organocatalytic domino reactions are highly efficient and somehow biomimetic, since the same principles are often found in the biosynthesis of natural products. Domino reactions avoid time-consuming and costly protection/deprotection steps as well as the purification of intermediates; furthermore they often proceed with excellent stereoselectivities. For all these reasons organocatalytic domino reactions are used also in total synthesis.[91]

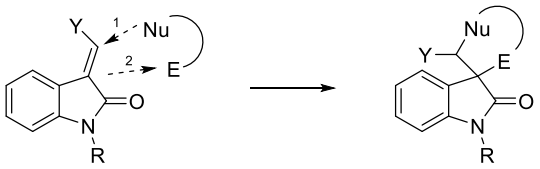
Of particular interest is the use of organocatalytic domino reactions for the synthesis of 3,3'-spirocyclic oxindoles.[92] As already mentioned, after the conjugate addition of a nucleophile to 3-ylidene oxindoles, the C-3 stereocenter is labile and can act as a nucleophile; so introducing on the same reacting molecule both a nucleophile which reacts for first in the 1,4 addition with the oxindole derivative, and an electrophile which reacts in a second time, is possible to have spirocyclization (Scheme 23).

[89] Tietze L. F., *Chem. Rev.* **1996**, 96, 115-136.

[90] For reviews on organocatalytic domino reactions, see: (a) Enders D., Grondal C., Hüttl M. R. M., *Angew. Chem. Int. Ed.* **2007**, 46, 1570-1581; (b) Pellissier H., *Adv. Synth. Catal.* **2012**, 354, 237-294.

[91] Grondal C., Jeanty M., Enders D., *Nat. Chem.* **2010**, 2, 167-178.

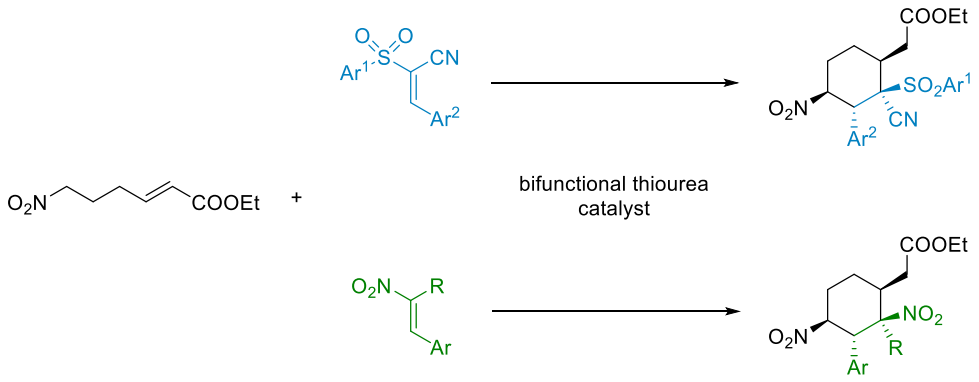
[92] Honga L., Wang R., *Adv. Synth. Catal.* **2013**, 355, 1023-1052.



Scheme 23

Another target that caught the attention in the field of organocatalytic domino reactions is the enantioselective synthesis of six-membered carbocycles.[93]

We decided to merge together these fields for the synthesis of 3,3'-spirocyclohexane oxindoles. In order to do this we decided to expand the study of the addition of nitroalkane to 3-ylidene oxindoles adding to the nitrocompound structure an electrophile. We got inspired by a previous project developed in our group[94] for the choice of an α,β-unsaturated ester as the electrophile for our domino spirocyclization. Later two new reactions using nitro-α,β-unsaturated ester were reported by Cobb and co-workers [95] (Scheme 24).



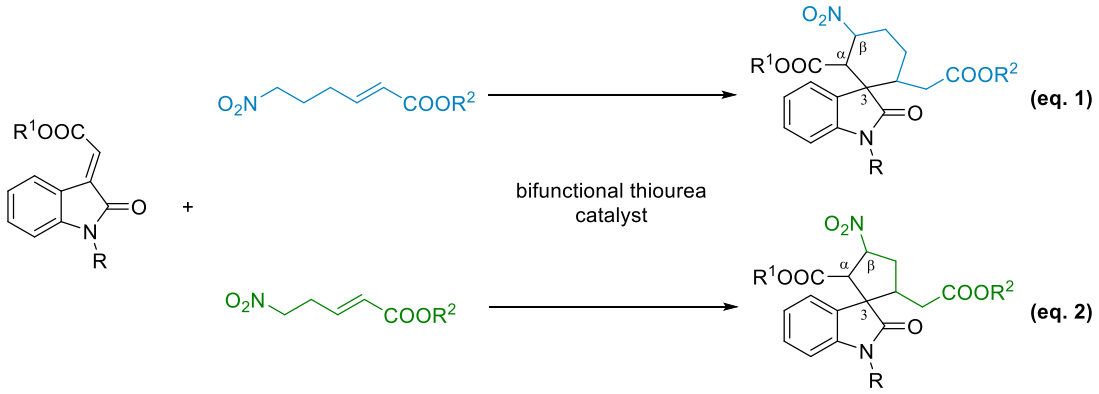
Scheme 24

Using ε-nitro-α,β-unsaturated ester is possible to obtain a 3,3'-spirocyclohexane oxindole (Scheme 25, eq. 1), while using δ-nitro-α,β-unsaturated ester a 3,3'-spirocyclopentane oxindole is provided (Scheme 25, eq. 2).

[93] Goudedranche S., Raimondi W., Bugaut X., Constantieux T., Bonne D., Rodriguez J., *Synthesis* **2013**, 45, 1909-1930.

[94] Quintavalla A., Lombardo M., Sanap S. P., Trombini C., *Adv. Synth. Catal.* **2013**, 355, 938-946.

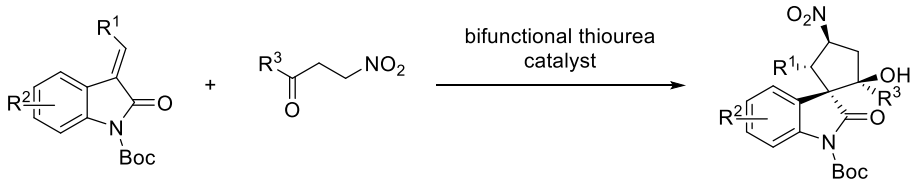
[95] (a) Rajkumar S., Shankland K., Brown G. D., Cobb A. J. A., *Chem. Sci.* **2012**, 3, 584-588; (b) Rajkumar S., Shankland K., Goodman J. M., Cobb A. J. A., *Org. Lett.* **2013**, 15, 1386-1389.



Scheme 25

Spirocyclohexane oxindoles with a nitro group in β-position are present in literature, but they are synthesised in completely different ways, always using Hayashi catalyst and conjugated nitroolefins like nitrostyrene.[96]

Spirocyclopentane oxindoles with a nitro group in β-position are also present in literature, but obtained with different catalytic systems and still employing conjugated nitroolefins as source for nitro group.[97] There is only one recent example in which a bifunctional thiourea catalyst is used with nitroalkanes (Scheme 26), but the electrophilic group that provides the spirocyclization is a ketone.[98]



Scheme 26

The method we designed for bifunctional thiourea catalysed spirocyclization between 3-ylidene-oxindole and nitro-α,β-unsaturated ester is the only one known in literature able to provide both spirocyclohexane- and spirocyclopentane- oxindoles.

[96] (a) Zhou B., Yang Y., Shi J., Luo Z., Li Y., *J. Org. Chem.* **2013**, 78, 2897-2907; (b) Jiang K., Jia Z., Yin X., Wu L., Chen Y., *Org. Lett.* **2010**, 12, 2766-2769; (c) Jiang K., Jia Z., Chen S., Wu L., Chen Y., *Chem. Eur. J.* **2010**, 16, 2852-2856.

[97] (a) Albertshofer K., Tan B., Barbas III C. F., *Org. Lett.* **2012**, 14, 1834-1837; (b) Li Y., Li X., Peng F., Li Z., Wu S., Sun Z., Zhang H., Shao Z., *Org. Lett.* **2011**, 13, 6200-6203; (c) Chandler B. D., Roland J. T., Li Y., Sorensen E. J., *Org. Lett.* **2010**, 12, 2746-2749.

[98] Noole A., Ilmarinen K., Järving I., Lopp M., Kanger T., *J. Org. Chem.* **2013**, 78, 8117-8122.

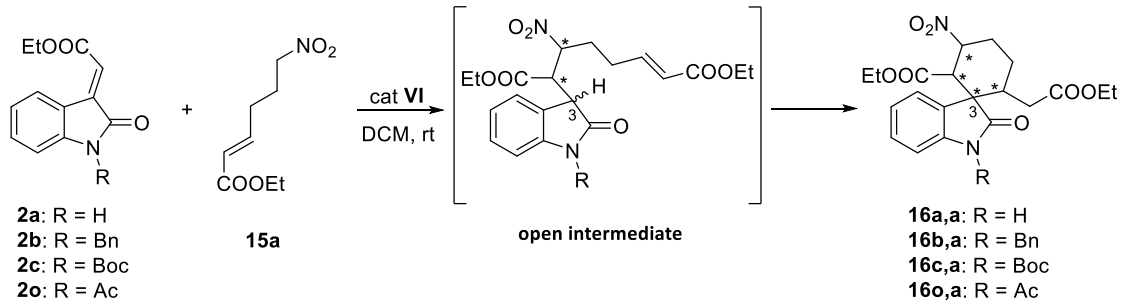
6. Asymmetric synthesis of spiro-oxindoles via bifunctional thiourea catalysed domino reaction

We first focused on the study of the bifunctional thiourea catalysed asymmetric synthesis of 3,3'-spirocyclohexane oxindoles using 3-ylidene oxindole and ε-nitro-α,β-unsaturated carboxyl compounds as reaction partners.

Protecting groups screening

We first carried out the *N*-protecting groups screening (Table 20) using Takemoto's catalyst (**VI**), since it was the catalyst of choice for the previously described addition of nitroalkanes to 3-ylidene oxindoles.

Table 20: *N*-protecting groups screening for the organocatalysed domino reaction between **15a** and 3-ylidene oxindoles (**2a-c,o**).[a] The stereochemistry of the product is not specified because it still has to be determined.



2a: R = H
2b: R = Bn
2c: R = Boc
2o: R = Ac

15a

open intermediate

16a,a: R = H
16b,a: R = Bn
16c,a: R = Boc
16o,a: R = Ac

Entry	Substrate	Time (d)	Conv. (%)[b]	*ee* (%)[c]
1	**2a**	4	traces[d]	-
2	**2b**	7	60	80
3	**2c**	3	90	97
4	**2o**	7	48	55

[a] Reaction conditions: **2** (0.1 mmol), **15a** (0.12 mmol), catalyst **VI** (10 mol%), dichloromethane (DCM, 0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Calculated with respect to the open intermediate. [c] Determined for the major diastereoisomer formed, by CSP-HPLC. [d] Only the first attack took place giving only traces of the spirocyclization product.

While for the addition of nitroalkanes to 3-ylidene-oxindoles the differences in reactivity and selectivity between the differently *N*-substituted oxindoles were really small, in this domino transformation the nature of the *N*-protecting group plays a crucial role. The unprotected substrate **2a** gave only traces of the desired product, while the insertion of a substituent on the nitrogen of the oxindole provided an increase of reactivity allowing the formation of the product as a single

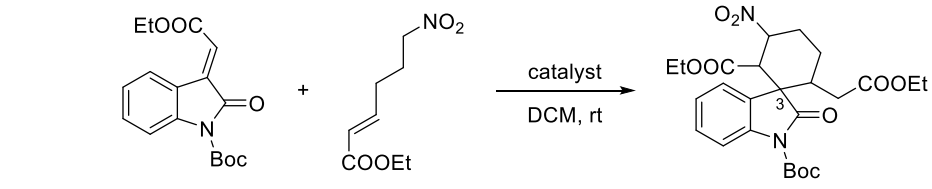
diastereoisomer. However, only Boc-protected oxindole **2c** gave excellent enantioselectivity and good reactivity, so we decided to carry out the study of the reaction using Boc-oxindole derivatives.

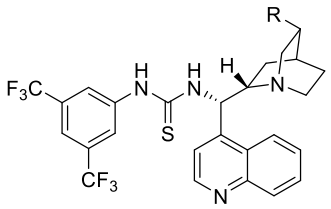
In this reaction, first the nitronate is formed and attacks the 3-ylidene-oxindole forming the first bond in few hours and generating two stereocenters with excellent enantiocontrol. Also the labile C-3 stereocenter is formed and exploited for the second bond formation that requires longer reaction time providing the stereodefinition of C-3 and the formation of another stereocenter. In this process only one diastereoisomer is observed in the ^{1}H NMR spectrum of the crude mixture and it is produced with high enantiomeric values.

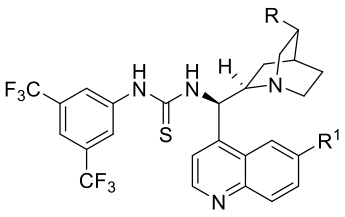
Catalysts screening

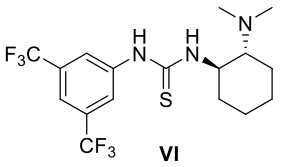
We tested other different bifunctional organocatalysts like Jacobsen's thiourea, *Cinchona* alkaloids and their thiourea derivatives (Table 21).

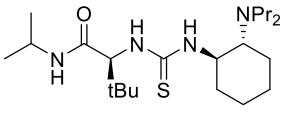
Table 21: Catalysts screening for the organocatalysed domino reaction between **15a** and **2c**.[a]

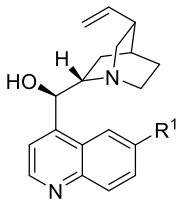


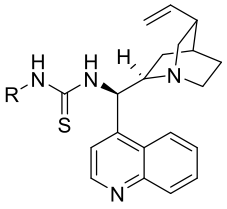


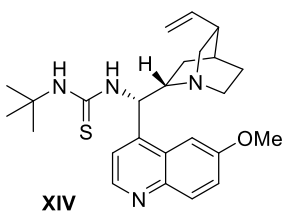












Entry	Catalyst	Time (d)	Conv. (%)[b]	*ee* (%)[c]
1	**I**	7	49	96
2	**II**	7	54	96[d]
3	**IV**	7	60	96[d]
4	**V**	7	54	97
5	**VI**	3	90	97
6	**VII**	7	60	63
7	**VIII**	7	59	73
8	**XII**	7	52	66
9	**XIII**	7	61	86
10	**XIV**	7	46	95[d]
11	**XV**	7	56	95
12	**XVI**	7	47	86

[a] Reaction conditions: **2c** (0.1 mmol), **15a** (0.12 mmol), catalyst (10 mol%), dichloromethane (DCM, 0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Calculated with respect to the open intermediate. [c] Determined for the major diastereoisomer formed, by CSP-HPLC. [d] Opposite enantiomers were formed.

Cinchonidine **VIII** and quinine **XII** (entries 7-8) were tested as bifunctional catalysts providing only modest enantioselectivity, probably because the hydroxyl group is not able to furnish an appropriate hydrogen-bonding with the substrate.

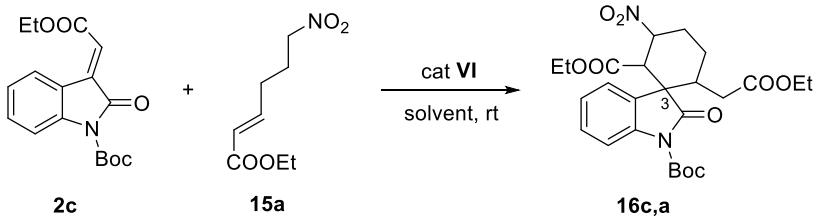
All the bifunctional thioureas tested gave very good results in terms of enantiocontrol (entries 1-5, 9-12) except of Jacobsen's catalyst **VII** (entry 6).

Catalyst **VI** was the one that gave the best reactivity, providing 90% of conversion in 3 days, together with excellent stereoselectivity (only one diastereoisomer formed with 97% *ee*).

Optimization of the reaction conditions

The reaction was performed in different solvents using catalyst **VI** checking in all cases the stereocontrol and the reactivity (Table 22).

Table 22: Solvents screening for the organocatalysed domino reaction between **15a** and **2c**.[a]



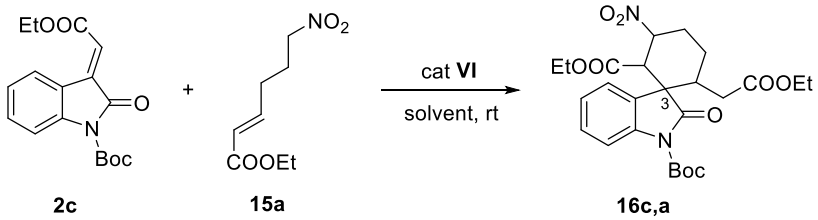
Entry	Solvent	Time (d)	Conv. (%)[b]	*ee* (%)[c]
1	DCM	3	90	97
2	Toluene	3	70	>99
3	CH_3CN	4	62	96
4	DMF	3	76	81
5	H_2O	2	72	94
6	THF	4	73	98
7	*n*-hexane	3	90	94
8	Et_2O	3	90	97

[a] Reaction conditions: **2c** (0.1 mmol), **15a** (0.12 mmol), catalyst **VI** (10 mol%), solvent (0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Calculated with respect to the open intermediate. [c] Determined for the major diastereoisomer formed, by CSP-HPLC.

The domino transformation showed excellent *ee* values in all the solvents except of dimethylformamide (DMF, entry 4) which probably partially compete with the substrate for the hydrogen-bonding to the catalyst. Even if toluene (entry 2) gave complete stereocontrol, the reaction rate was not so satisfying, so we chose DCM (entry 1) as the solvent for the reaction since, together with the more toxic diethyl ether (entry 8), provided the best trade-off between reactivity and selectivity. Noteworthy are also the reaction performances in water (entry 5).

Even if the reaction times were already pretty long, we tried the same to decrease the catalyst loading (Table 23) in order to improve the reaction conditions employed until now and already quite satisfactory: only 1.2 equivalents of nitrocompound, room temperature and 10 mol% of catalyst.

Table 23: Optimization of the reaction conditions for the organocatalysed domino reaction between **15a** and **2c**.[a]



Entry	Solvent	Catalyst **VI**	Time (d)	Conv. (%)[b]	*ee* (%)[c]
1	DCM	10 mol%	3	90	97
2	DCM	5 mol%	4	61	98
3	H_2O	10 mol%	2	72	94
4	H_2O	5 mol%	2	66	90

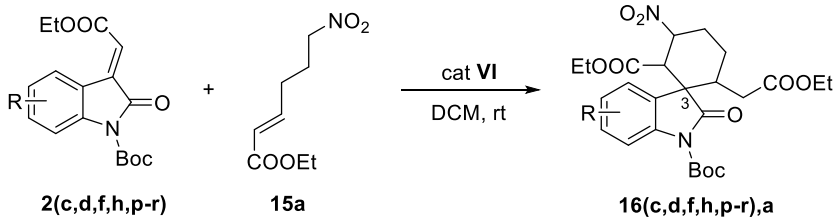
[a] Reaction conditions: **2c** (0.1 mmol), **15a** (0.12 mmol), catalyst **VI**, solvent (0.15 mL), rt. [b] Determined by ^{1}H NMR of the crude mixture. Calculated with respect to the open intermediate. [c] Determined for the major diastereoisomer formed, by CSP-HPLC.

We tried to decrease the catalyst loading to 5 mol% both in DCM and in water, but as expected, we had a clear increase of the reaction times; therefore we decided to study the scope of the reaction still using 10 mol% of TUC.

Scope of the reaction

We applied our protocol to different ethyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate Boc-protected (Table 24).

Table 24: Organocatalysed domino reaction between **15a** and **2(c,d,f,h,p-r)**.[a]



Entry	Substrate	R	Product	Time (d)	Y (%)[b]	*ee* (%)[c]
1	**2c**	H	**16c,a**	3	73	97
2	**2d**	5-Cl	**16d,a**	2	82	96
3	**2f**	6-Cl	**16f,a**	1	63	97
4	**2p**	7-Cl	**16p,a**	2	42	83
5	**2h**	5-OMe	**16h,a**	2	76	95
6	**2q**	5-Me	**16q,a**	5	77	97

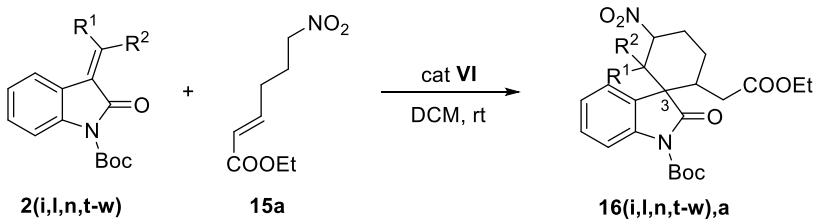
Entry	Substrate	R	Product	Time (d)	Y (%)[b]	*ee* (%)[c]
7	**2r**	5-OCF_3	**16r,a**	3	78	94

[a] Reaction conditions: **2** (0.1 mmol), **15a** (0.12 mmol), catalyst **VI** (10 mol%), dichloromethane (0.15 mL), rt. [b] Yield of the product after flash-chromatography. [c] Determined for the major diastereoisomer formed, by CSP-HPLC.

The model reaction (entry 1) provided only one diastereoisomer in good yield and excellent enantiocontrol. The substituents on the aromatic ring of the oxindole derivative tested were all tolerated by the process. Only the chloro in position 7 seemed to be problematic giving an enantiomeric excess of 83% and moderate yield (entry 4), while the chloro in 5 and 6 positions provided excellent stereocontrol and good yields (entries 2, 3). All the other substrates tested, holding electron donating groups, provided excellent enantioselectivities and good yields (entries 5-7). The reaction times varied from 1 to 5 days without a particular connection with the nature and the position of the substituents. The yields were not as high as the conversion values (entries 1 Table 23 and Table 24). The reason is that while the conversion in the product was calculated with respect to the open intermediate, the yield was obviously calculated with respect to the limiting starting material. During the reaction the oxindolic starting material or the intermediate probably partially decomposes giving the difference between conversion and yield. In fact from the ^{1}H NMR spectrum of the crude mixture we could see that an excess higher then 0.2 equivalents of nitrocompound remains unreacted. Despite of this probable decomposition we didn't observe any other byproduct, but studies are still in progress.

Also variations on the substituents of the exocyclic double bond were analysed (Table 25).

Table 25: Organocatalysed domino reaction between **15a** and **2(i,l,n,t-w)**.[a]



2(i,l,n,t-w) **15a** **16(i,l,n,t-w),a**

Entry	Substrate	R^1	R^2	Product	Time (d)	Y (%)[b]	*ee* (%)[c]
1	**2i**	COOBn	H	**16i,a**	1	74	97
2	**2t**	COPh	H	**16t,a**	1	19	90
3	**2l**	*p*-NO_2Ph	H	**16l,a**	2	83	56
4	**2u**	CN	H	**16u,a**	1	47	23
5	**2n**	COOEt	Me	**16n,a**	2	21	94
6[d]	**2v**	Me	COOEt	**16n,a**	2	38	94
7	**2w**	NHBoc	COOMe	**16w,a**	7	-	-

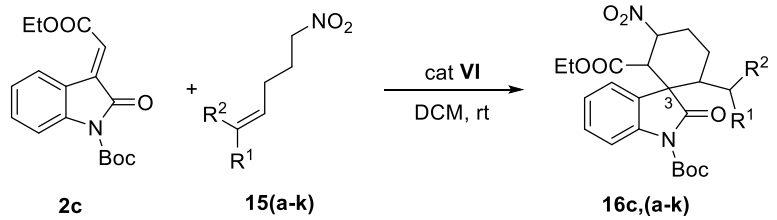
[a] Reaction conditions: **2** (0.1 mmol), **15a** (0.12 mmol), catalyst **VI** (10 mol%), dichloromethane (0.15 mL), rt. [b] Yield of product after flash-chromatography. [c] Determined for the major diastereoisomer formed, by CSP-HPLC. [d] **15a** (2 eq.), catalyst **VI** (20 mol%).

As in the addition of nitroalkanes to 3-ylidene oxindoles, also in this asymmetric organocatalytic domino spirocyclization the presence of an ester on the exocyclic double bond revealed to be essential. In fact when the ethyl ester was replaced with a benzyl ester (entry 1) the reaction preserved its efficiency with good yield and excellent *ee*; but when a ketone, an aromatic ring or a cyano group were present instead of the ester moiety the process was no more effective (entries 2-4). The ketone functional group seemed not to be tolerated giving low yield caused by the formation of a number of byproducts, but it still preserved high enantioselectivity in the formation of the desired 3,3'-spirocyclohexane oxindole. Conversely the presence of the *p*-NO_2-phenyl ring or of the cyano group provided poor enantiocontrol.

The geometry of the exocyclic double bond of 3-ylidene oxindole didn't seem to affect the product formation providing in both cases the same diastereoisomer with high enantiocontrol (entries 5, 6); to this purpose mechanistic investigations are still in progress. When also a methyl was present on the exocyclic double bond the reaction was less efficient; replacing the methyl with a much more hindered and electron donating substituent like NHBoc (entry 7) not even the first attack took place.

The scope of the nitrocompounds was explored and it is shown in Table 26.

Table 26: Organocatalysed domino reaction between **15(a-k)** and **2c**.[a]



2c **15(a-k)** **16c,(a-k)**

Entry	Substrate	R^1	R^2	Product	Time (d)	Y (%)[b]	*ee* (%)[c]
1	**15a**	COOEt	H	**16c,a**	3	73	97
2[d]	**15b**	H	COOEt	**16c,b**	1	79	97
3	**15c**	COOEt	Me	**16c,c**	4	19	98
4[e]	**15c**	COOEt	Me	**16c,c**	4	40	96
5[f]	**15c**	COOEt	Me	**16c,c**	7	18	98
6[e]	**15d**	Me	COOEt	**16c,c**	13	32	96
7	**15e**	COPh	H	**16c,e**	16h	Mixture of products	
8	**15f**	COOBn	H	**16c,f**	1	59	>99
9[d]	**15g**	H	COOBn	**16c,g**	1	75	98
10	**15h**	CN	H	**16c,h**	2	90[g]	99:91:>99:75
11	**15i**	H	CN	**16c,i**	2	83	95
12	**15j**	COOEt	F	**16c,j**	3	-[h]	-
13	**15k**	F	COOEt	**16c,k**	6	-[h]	-

[a] Reaction conditions: **2c** (0.1 mmol), **15a-k** (0.12 mmol), catalyst **VI** (10 mol%), dichloromethane (0.15 mL), rt. [b] Yield of product after flash-chromatography. [c] Determined for the major diastereoisomer formed, by CSP-HPLC. [d] A different diastereoisomer is obtained. [e] Catalyst **VI** (20 mol%). [f] **15c** (0.2 mmol). [g] 4 diastereoisomers formed in 22:35:27:16 ratio. [h] Only the first attack took place without giving spirocyclization.

Changing the geometry of the double bond in the ε-nitro-α,β-unsaturated ester we obtained a different diastereoisomeric product. With both the geometry only one diastereoisomer was formed with excellent enantiomeric excess and good yield (entries 1-2, 8-9).

The ketone was not tolerated also when it was installed on the nitro compound providing a complicated mixture of different products (entry 7).

When the double bond is trisubstituted, adding a methyl, the reaction became much slower (entry 3), so we tried to speed it up increasing both the catalyst loading (entry 4) and the excess of nitrocompound (entry 5). With 20 mol% of catalyst we obtained 40% yield in 4 days; in these conditions we tested also the *Z* isomer of the

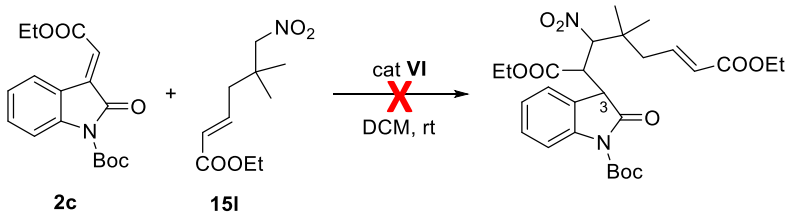
nitro compound which slowly provided the same major diastereoisomer produced using the *E* isomer with high *ee* (entry 6).

Conversely to the result presented in entry 4 Table 25 the cyano group can replace the ester moiety in this reaction partner (entries 10, 11). Using the *Z* isomer the reaction provided good yield and excellent enantioselectivity for the only diastereoisomer formed, while the *E* isomer provided 4 diastereoisomers in 22:35:27:16 ratio, being the minor isomer the only one provided by the reaction of the corresponding *Z* nitrocompound. The enantiomeric excesses of these diasteroisomers were very high except for the minor one that had only a moderate 75% *ee*.

We tested also *E* and *Z* isomers of the trisubstituted double bond with a fluoro in the α position, but in both cases the reaction provided only the first attack and not the spirocyclization (entries 12, 13).

In order to clarify the role of the double bond geometry of the nitrocompound further mechanistic studies are expected.

We performed the reaction also using compound **15l**, but only the first conjugate addition took place (Scheme 27).



Scheme 27

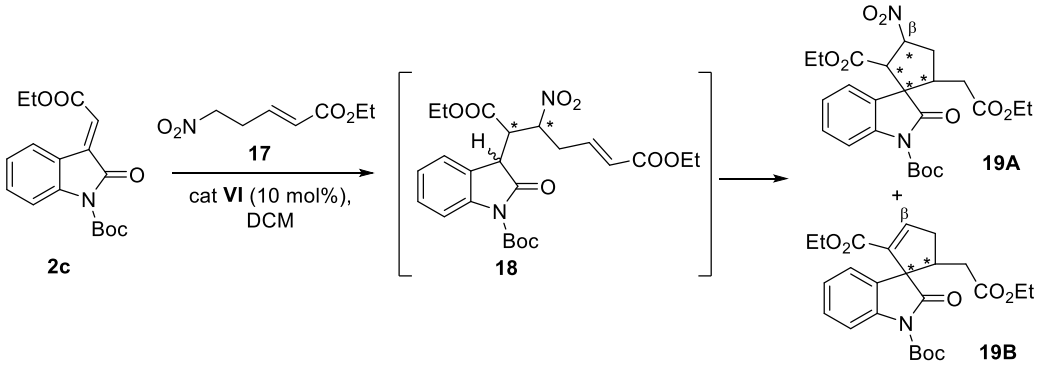
Preliminary studies on the bifunctional thiourea catalysed asymmetric synthesis of 3,3'-spirocyclopentane oxindoles

Encouraged by the results obtained for the synthesis of 3,3'-spirocyclohexane oxindoles, we expanded our study to the formation of 3,3'-spirocyclopentane oxindoles.

First, we performed the reaction with 10 mol% of catalyst **VI** (entry 1, Table 27) and we observed the complete conversion of the oxindolic starting material in only 5 hours into two products **19A** and **19B**. The reaction that produced the 5-membered ring was much faster than the one producing the 6-membered one. In the case of

spirocyclopentane we studied the reaction at different times via ^{1}H NMR and the intermediates (**18**) were never visible in the crude, since they react very fast.

Table 27: Preliminary study on the synthesis of 3,3'-spirocyclopentane-oxindoles.[a] The stereochemistry of the product is not specified because it still has to be determined.



Entry	Cat (%)	*T*(°C)	Time	Y (%)[b]	**19** (A:B)[c]	*ee* A (%)[d]	*ee* B (%)[d]
1[e]	**VI** (10%)	rt	5h	66	60:40	>99	92
2	**VI** (5%)	rt	3d	82	60:40	>99	96
3	**VI** (10%)	-10	2d	49	65:35	>99	>99

[a] Reaction conditions: **2c** (0.1 mmol), **17** (0.12 mmol), catalyst, DCM (0.15 mL). [b] Yield of product after flash-chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by CSP-HPLC. [e] **17** (0.2 mmol).

In order to exclude a possible epimerizarion of the C-β stereocenter due to the catalyst acting as a base, thus changing the relative configuration between C-α and C-β and enabling the elimination, we performed the reaction decreasing the catalyst loading. This should slower the elimination rate and change the ratio between **19A** and **19B**, but also with 5 mol% of catalyst the ratio between the two products remained unchanged (entry 2). We could infer that **19B** probably was not formed from **19A**; this was confirmed by isolating **19A** and reacting it with the catalyst; after 21 hours the formation of **19B** was not observed. Probably the reaction produced two different diastereoisomers and one of them was able to give elimination providing the unsaturated **19B**.

We also performed the reaction lowering the temperature to -10°C (entry 3). In these conditions we were able to observe the diastereoisomer from wich **19B** derives. Unfortunately, also at this temperature the final ratio between **19A** and **19B** didn't improve and further studies on the reaction are still in progress.

7. Conclusions

Even though asymmetric processes applied to indoles, oxindoles and isatins seem to represent a mature field in organocatalysis, we demonstrated that still a number of useful reactions and applications can be disclosed.

In the first part of this study, we developed a new asymmetric organocatalytic protocol for the conjugate addition of nitroalkanes to 3-ylidene oxindoles, which efficiently provided substituted β-nitro indolin-2-ones with good yields and excellent enantioselectivities. Indeed, up to three stereocenters were generated one-pot, two of them, C-α and C-β, with high stereocontrol. In our reaction conditions we had no chance to stereodefine the C-3 position, but, when the generated intermediate enolate was trapped with a second Michael acceptor, an all carbon quaternary stereocenter was formed in a perfectly defined configuration.

Furthermore, the conversion of the β-nitro oxindole adduct into the corresponding β-amino derivative disclosed intriguing and synthetically useful transformations, such as stereoconvergent processes and stereoselective base-promoted isomerizations.

In the second part we focused on the asymmetric domino spirocyclization catalysed by Takemoto's bifunctional thiourea. Spirocyclohexane oxindoles were generated as a single diastereoisomer owning up to five stereocenters with excellent enantiocontrol. In the same conditions also spirocyclopentane oxindoles could be generated with complete enantiocontrol and further studies are ongoing in the research group. To the best of our knowledge our reaction conditions are the only ones present in literature able to provide both 3,3'-spirocyclohexane oxindoles and 3,3'-spirocyclopentane oxindoles with high enantioselectivity and good yields.

At last we remark the usefulness of the asymmetric organocatalytic processes reported here in the synthesis of enantioenriched oxindole and indoline derivatives, potentially useful in drug discovery.

8. Experimental section

Materials. All of the chemicals were used as received. Catalysts **I-V** were known and prepared according to the literature procedures.[68] Compounds **2a**,[99] **2b-c**,[100] **2d-f,h**,[101]

[99] Malhotra S., Balwani S., Dhawan A., Singh B. K., Kumar S., Thimmulappa R., Biswal S., Olsen C. E., Van der Eycken E., Prasad A. K., Ghosh B., Parmar V. S., *Med. Chem. Commun.* **2011**, 2, 743-751.

[100] Cao S., Zhang X., Wei Y., Shi M., *Eur. J. Org. Chem.* **2011**, 2668-2672.

2i,[102] **2j-k**,[103] **2l**,[104] **2o**,[105] **2t,u**,[106] **1e**,[107] **15a,c,k**[108] were known and prepared according to the literature procedures.

Characterization of compounds. ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 400 NMR instrument with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals, chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hz. HPLC-MS analysis was performed using an HPLC system coupled with a single-quadrupole mass spectrometer. A ZOBRAX-Eclipse XDB-C8 column was employed for the chromatographic separation; mobile phase: H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 25 min, 0.4 mL min^{-1}. Mass spectrometric detection was performed in full-scan mode from *m/z* 50 to *m/z* 2600, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow 11.5 mL min^{-1}, fragmentor voltage 20 V. CSP-HPLC analyses were performed using hexane/2-propanol mixtures. Flash-chromatography was carried out using Merck silica gel 60 (230-400 mesh particle size). Thin-layer chromatography was performed on Merck 60 F254. The $[\alpha]_D^{25}$ values and the *major* enantiomers in the following characterization have been defined with respect to the products obtained with catalyst **VI**.

Synthesis of (*E*)-*tert*-butyl 7-bromo-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (2g). Ethyl 2-(triphenylphosphoranylidene)acetate (1.2 mmol) was added to a solution of 7-bromoindoline-2,3-dione (1 mmol, 226 mg) in DCM (4 mL). The reaction was stirred at rt overnight. After the reaction was complete, the solvent was removed under reduced pressure. The crude mixture was dissolved in THF (5 mL), DMAP (4-dimethylaminopyridine, 5 mol%) was added to the solution and, finally, Boc_2O (di-*tert*-butyl dicarbonate, 1.1 mmol) was added. The reaction was stirred at rt for 1 h. Then the solvent was removed under reduced pressure and the product was

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[101] Sun W., Zhu G., Wu C., Hong L., Wang R., *Chem. Eur. J.* **2012**, 18, 6737-6741.

[102] Tan B., Hernández-Torres G., Barbas III C. F., *J. Am. Chem. Soc.* **2011**, 133, 12354-12357.

[103] (a) Jia Z., Jiang H., Li J., Gschwend B., Li Q.-Z., Yin X., Grouleff J., Chen Y., Jørgensen K. A., *J. Am. Chem. Soc.* **2011**, 133, 5053-5061; (b) Tan B., Candeias N. R., Barbas III C. F., *J. Am. Chem. Soc.* **2011**, 133, 4672-4675.

[104] Liu Y., Nappi M., Arceo E., Vera S., Melchiorre P., *J. Am. Chem. Soc.* **2011**, 133, 15212-15218.

[105] Tan B., Zeng X., Leong W. W. Y., Shi Z., Barbas III C. F., Zhong G., *Chem. Eur. J.* **2012**, 18, 63-67.

[106] Halskov K. S., Johansen T. K., Davis R. L., Steurer M., Jensen F., Jørgensen K. A., *J. Am. Chem. Soc.* **2012**, 134, 12943-12946.

[107] Kodukulla R. P. K., Trivedi G. K., Vora J. D., Mathur H. H., *Synth. Commun.* **1994**, 24, 819-832.

[108] Rajkumar S., Shankland K., Brown G. D., Cobb A. J. A., *Chem. Sci.* **2012**, 3, 584-588.

purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 95% yield (376 mg), crystalline solid (mp = 73-77°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.66 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.66 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 27.7, 61.5, 85.8, 106.7, 123.4, 124.6, 125.6, 127.5, 136.2, 137.1, 140.8, 147.6, 164.9, 166.3. HPLC-MS (ESI): t_r = 12.7 min. $[M+Na]^+$ = 418.2 m/z, $[2M+Na]^+$ = 813.2 m/z, 817.2 m/z. Anal. Calcd for $C_{17}H_{18}BrNO_5$ (395.04): C, 51.53; H, 4.58; N, 3.53. Found: C, 51.37; H, 4.56; N, 3.54.

Synthesis of (*E*)-*tert*-butyl 3-(2,2-dimethylpropylidene)-2-oxoindoline-1-carboxylate (2m). Pivalaldehyde (1.2 mmol) was added to a solution of indolin-2-one (1 mmol, 133 mg) in EtOH (5 mL), finally piperidine (10 mol%) was added. The reaction was refluxed for 1.5 h, then it was cooled to room temperature and the solvent was removed under reduced pressure. The product was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 8/2). (*E*)-3-(2,2-dimethylpropylidene)indolin-2-one was dissolved in THF (5 mL), then DMAP (5 mol%) was added and finally Boc_2O (1.1 mmol). The reaction was stirred at room temperature for 1 h. After the reaction was complete, the solvent was removed under reduced pressure and the product was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 97% yield (292 mg), crystalline solid (mp = 82-86°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.36 – 7.29 (m, 1H), 7.25 (s, 1H), 7.17 (td, *J* = 7.7, 1.2 Hz, 1H), 1.65 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.1, 29.1, 32.7, 84.0, 115.0, 120.9, 123.5, 125.5, 126.0, 128.9, 140.0, 149.3, 154.3, 167.0. HPLC-MS (ESI): t_r = 13.4 min; $[2M+Na]^+$ = 625.4 m/z. Anal. Calcd for $C_{18}H_{23}NO_3$ (301.17): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.61; H, 7.71; N, 4.65.

Synthesis of (*E*)-*tert*-butyl 3-(1-ethoxy-1-oxopropan-2-ylidene)-2-oxoindoline-1-carboxylate (2n). DMAP (5 mol%) was added to a solution of indoline-2,3-dione (1 mmol, 147 mg) in THF (5 mL), finally Boc_2O (1.1 mmol) was added. The reaction was stirred at room temperature for 1 h. After the reaction was complete, the solvent was removed under reduced pressure. The crude mixture was dissolved in DCM (4 mL) and ethyl 2-(triphenylphosphoranylidene)propanoate (1.2 mmol) was added. The reaction was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the product was purified by flash-chromatography on silica gel

(cyclohexane/ethyl acetate 9/1). 50% yield (166 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.09 (t, *J* = 7.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 1.66 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 17.1, 28.1, 30.9, 62.0, 84.4, 114.9, 120.7, 122.0, 123.4, 123.9, 129.9, 138.8, 141.8, 149.2, 165.7, 169.2. HPLC-MS (ESI): t_r = 11.7 min; $[M+Na]^+$ = 354.2 m/z, $[2M+Na]^+$ = 685.5 m/z. Anal. Calcd for $C_{18}H_{21}NO_5$ (331.14): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.22; H, 6.37; N, 4.22.

Synthesis of (*E*)-*tert*-butyl 7-chloro-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (2p).

Same procedure used for **2n**. Yield = 12%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.65 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.0, 149.1, 147.6, 136.1, 134.0, 133.8, 127.1, 126.9, 123.0, 118.9, 85.8, 61.6, 27.7, 14.0. HPLC-MS (ESI) t_r = 13.1 min; $[M+Na]^+$ = 374.0 *m/z,* $[2M+Na]^+$ = 725.2 *m/z.*

Synthesis of (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-5-methyl-2-oxoindoline-1-carboxylate (2q).

Same procedure used for **2n**. Yield = 71%.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.75 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.63 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 165.3, 148.7, 139.6, 136.5, 134.1, 133.2, 128.6, 122.6, 120.0, 114.6, 84.4, 61.2, 28.0, 21.0, 14.1. HPLC-MS (ESI) t_r = 13.5 min; $[M+Na]^+$ = 354.2 *m/z,* $[2M+Na]^+$ = 685.2 *m/z.*

Synthesis of (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxo-5-(trifluoromethoxy)indoline-1-carboxylate (2r).

Same procedure used for **2n**. Yield = 96%.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 9.6 Hz, 1H), 6.97 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.65 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 165.1, 148.7, 145.7, 140.3, 135.5, 125.3, 125.1, 121.5, 121.2, 120.5 (q, *J* = 256 Hz), 116.0, 85.1, 61.6, 27.8, 13.9. HPLC-MS (ESI) t_r = 14.9 min; $[M+Na]^+$ = 424.0 *m/z,* $[2M+Na]^+$ = 825.2 *m/z.*

Synthesis of (*Z*)-*tert*-butyl 3-(1-ethoxy-1-oxopropan-2-ylidene)-2-oxoindoline-1-carboxylate (2v).

Compound **3c** (58 mg, 0.18 mmol) was dissolved in 1 mL of DCM and DBU (0.031 mL, 0.2 mmol) was added. The reaction was stirred for 6 h at room temperature, then quenched with a saturated solution of NH_4Cl and extracted 3 times with DCM. The organic phases were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The purification by column chromatography on silica gel (diethyl ether/cyclohexane 5:95) provided the desired product in 19% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.64 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). HPLC-MS (ESI) t_r = 11.1 min; $[M+Na]^+$ = 354.2 *m/z,* $[2M+Na]^+$ = 685.2 *m/z.*

Synthesis of *tert*-butyl (*E*)-3-(1-((tert-butoxycarbonyl)amino)-2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (2w).

DMAP (5 mol%) was added to a solution of indoline-2,3-dione (1 mmol, 147 mg) in THF (5 mL), finally Boc_2O (1.1 mmol) was added. The reaction was stirred at room temperature for 1 h. After the reaction was complete, the solvent was removed under reduced pressure.

A solution of (±)-trimethyl-Boc-α-phosphonoglycinate (1.2 mmol) in anhydrous THF (6 mL) was added dropwise to a suspension of NaH (60%, 1.2 mmol, 48 mg) in anhydrous THF (6 mL) at 0° C, then the reaction was stirred at this temperature for 15 min. Now, the crude of Boc-isatin (1 mmol) in 4 ml of THF was added slowly into the reaction mixture at 0°C, then the reaction was stirred at room temperature overnight. It was then quenched with a saturated solution of NH_4Cl and the aqueous phase was extracted 3 times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 9:1) afforded the title compound (362.1 mg, 87%, 0.87 mmol).

^{1}H NMR (400 MHz, CDCl3) δ 10.90 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.20 – 7.06 (m, 2H), 4.06 (s, 3H), 1.68 (s, 9H), 1.51 (s, 9H).

Synthesis of ethyl (*Z*)-6-nitrohex-2-enoate (15b).

Obtained as the minor isomer from the synthesis of **15a**.[108] Yield = 13%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 – 6.12 (m, 1H), 5.88 (d, *J* = 11.6 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.78 (q, *J* = 7.7 Hz, 2H), 2.19 (p, *J* = 7.3 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 146.3, 121.9, 74.7, 60.1, 26.4, 25.4, 14.1. HPLC-MS (ESI) t_r = 7.5 min; $[M+H]^+$ = 188.0 *m/z,* $[M+Na]^+$ = 210.0 *m/z.*

Synthesis of ethyl (*Z*)-2-methyl-6-nitrohex-2-enoate (15d).

KHMDS (2 mmol, 4 mL, 0.5 M in toluene) was added dropwise to a solution of triethyl 2-phosphonopropionate (2 mmol, 0.438 mL) and 18-crown-6 (3.6 mmol, 950 mg) in anhydrous THF (18 mL) at -78°C and the reaction was stirred for 20 min at this temperature. Then a solution of 4-bromobutanal[108] (2 mmol, 302 mg) in anhydrous THF (4.5 mL) was added dropwise and the reaction was stirred 1 h at -78°C, then 1 h at room temperature. The reaction was quenched with a saturated solution of NH_4Cl and extracted 3 times with diethyl ether. The organic phases were collected, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. Both *E* and *Z* isomer 1:3.3 of the product were produced and purification by column chromatography on silica gel (ethyl acetate/cyclohexane 1:9) afforded the title compound (322 mg, 69%, 1.37 mmol). The obtained ethyl 6-bromo-2-methylhex-2-enoate was dissolved in anhydrous DMF (13 mL) and $NaNO_2$ (2.06 mmol, 141.7 mg) was added. The reaction was stirred overnight at room temperature. Cold water was added to the reaction and the water phase was extracted 3 times with diethy ether. The organic phases were collected, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (diethyl ether/cyclohexane 5:95) allowed the separation of *E* and *Z* isomers affording the products as colorless oils. A 35% yield of *Z* product (95.7 mg, 0.48 mmol) and 58% total yield (161 mg, 0.8 mmol) were obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (t, *J* = 7.5 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.3 Hz, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 2.14 (p, *J* = 7.1 Hz, 2H), 1.91 (s, 3H), 1.29 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.9, 129.7, 74.8, 60.3, 26.8, 26.0, 20.6, 14.3. HPLC-MS (ESI) t_r = 8.6 min; $[M+Na]^+$ = 224.0 *m/z.*

Synthesis of (*E*)-6-nitro-1-phenylhex-2-en-1-one (15e).

Same procedure used for **15c**. Yield = 39%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.63 – 7.54 (m, 1H), 7.54 – 7.38 (m, 2H), 6.94 (d, *J* = 11.6 Hz, 1H), 6.31 (td, *J* = 11.6, 7.7 Hz, 1H), 4.46 (t, *J* = 7.2 Hz, 2H), 2.75 (q, *J* = 7.3 Hz, 2H), 2.26 (p, *J* = 7.3 Hz, 2H).

Synthesis of benzyl (*E*)-6-nitrohex-2-enoate (15f).

Same procedure used for **15c**. Yield = 74%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 6.95 (td, *J* = 15.6, 6.9 Hz, 1H), 5.95 (td, *J* = 15.7, 1.6 Hz, 1H), 5.20 (s, 2H), 4.41 (t, *J* = 6.8 Hz, 2H), 2.42 – 2.29 (m, 2H), 2.26 – 2.13 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7, 146.0, 135.8, 128.5, 128.14, 128.11, 122.8, 74.3, 66.1, 28.5, 25.4. HPLC-MS (ESI) t_r = 9.4 min; $[M+Na]^+$ = 272.0 *m/z.*

Synthesis of benzyl (*Z*)-6-nitrohex-2-enoate (15g).

Obtained as the minor isomer from the synthesis of **15f**. Yield = 8.8%.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 – 7.22 (m, 5H), 6.36 – 6.09 (m, 1H), 5.93 (d, *J* = 11.2 Hz, 1H), 5.17 (s, 2H), 4.39 (t, *J* = 7.1 Hz, 2H), 2.79 (q, *J* = 7.8 Hz, 2H), 2.19 (p, *J* = 7.1 Hz, 2H). HPLC-MS (ESI) t_r = 9.7 min; $[M+Na]^+$ = 272.0 *m/z.*

Synthesis of 6-nitrohex-2-enenitrileate (15h,i).

To a solution of (cyanomethyl)triphenylphosphonium chloride (2.4 mmol, 853.4 mg) in THF (10 mL) at 0° C was added NaH (2.4 mmol, 96 mg) and stirred at this temperature for 15 min. At this temperature 4-bromobutanal (302 mg, 2 mmol) in 10 mL of THF was added slowly into the reaction mixture. Then, the reaction was left stirring at room temperature overnight. It was then quenched with a saturated solution of NH_4Cl and the aqueous phase was extracted 3 times with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The reaction afforded both *E* and *Z* isomer (2:1) of the product. The mixture was purified by column chromatography on silica gel (diethyl ether/ cyclohexane 1:9) providing a colorless oil in quantitative yield. The two isomers were not separated and were dissolved in 20 mL of anhydrous DMF. Then, $NaNO_2$ (3 mmol, 207 mg) was added and the reaction was stirred at room temperature for 22 h. Cold water was added to the reaction and the water phase was extracted 3 times with diethy ether. The organic phases were collected, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (diethyl ether/cyclohexane from 1:9 to 3:7) allowed the separation of *E* and *Z* isomers and afforded the title compounds as colorless oils (89.1 mg, 32%, 0.64 mmol).

15h: Yield = 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.52 (m, 1H), 5.44 (d, *J* = 16.4 Hz, 1H), 4.42 (t, *J* = 6.7 Hz, 2H), 2.38 (q, *J* = 7.2 Hz, 2H), 2.29 – 2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 116.7, 102.0, 74.1, 29.8, 25.2. HPLC-MS (ESI) t_r = 4.7 min; $[M+H]^+$ = 141.0 *m/z,* $[M+Na]^+$ = 163.0 *m/z.*

15i: Yield = 6.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 – 6.38 (m, 1H), 5.45 (d, *J* = 10.8 Hz, 1H), 4.44 (t, *J* = 7.0 Hz, 2H), 2.57 (q, *J* = 7.7 Hz, 2H), 2.23 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.3, 115.2, 101.9, 74.3, 28.5, 25.7. HPLC-MS (ESI) t_r = 4.5 min; $[M+H]^+$ = 141.0 *m/z,* $[M+Na]^+$ = 163.0 *m/z.*

Synthesis of ethyl (*Z*)-2-fluoro-6-nitrohex-2-enoate (15j).

Obtained as the minor isomer from the synthesis of **15k**. Yield = 15%

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (td, *J* = 32.2, 7.8 Hz, 1H), 4.42 (t, *J* = 7.0 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.19 (p, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 6.7 Hz, 3H).

Synthesis of ethyl (*E*)-5,5-dimethyl-6-nitrohex-2-enoate (15l).

Nitromethane (6.25 mmol, 0.339 mL) and methyl 3-methylbut-2-enoate (2.5 mmol, 0.327 mL) were dissolved in acetonitrile (5 mL) and DBU (1.25 mmol, 0.185 mL) was added. The reaction was stirred overnight at room temperature, then the solvent was evaporated and the product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 9:1). The product was obtained as a colourless oil (0.47 mmol, 19%, 83.1 mg). The obtained methyl 3,3-dimethyl-4-nitrobutanoate was dissolved in anhydrous DCM (5 mL) and DIBAL-H (1M in DCM, 0.52 mmol, 0.52 mL) was added at -78°C. The reaction was stirred at this temperature for 1 h, then quenched with 1 mL of methanol and extracted with a saturated solution of potassium sodium tartrate. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The 3,3-dimethyl-4-nitrobutanal was directly used without further purifications. It was dissolved in DCM (1 mL) and ethyl (triphenylphosphoranylidene)acetate (0.56 mmol, 185.8 mg) was added. The reaction was stirred at room temperature for 6 h, then the solvent was evaporated and the product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 95:5). The product was obtained as a colourless oil (0.45 mmol, 95%, 95.9 mg).

^{1}H NMR (400 MHz, CDCl3) δ 6.94 (dt, *J* = 16.1, 8.0 Hz, 1H), 5.94 (d, *J* = 15.5 Hz, 1H), 4.30 – 4.15 (m, 4H), 2.31 (d, *J* = 8.0 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.12 (s, 6H).

Synthesis of ethyl (*E*)-5-nitropent-2-enoate (17).

Synthesised from 3-nitropropanal (produced according to literature procedure[109] and not purified) using the same procedure of **15c**. Yield = 37%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (td, *J* = 15.6, 6.9 Hz, 1H), 5.95 (td, *J* = 15.7, 1.5 Hz, 1H), 4.52 (t, *J* = 6.9 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.92 (q, *J* = 6.9 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 140.9, 125.0, 73.3, 60.6, 29.4, 14.2. HPLC-MS (ESI) t_r = 6.0 min; $[M+H]^+$ = 174.0 *m/z.*

General procedure for the organocatalysed Michael addition of nitroalkanes (1) to 3-ylidene oxindoles (2). The 3-ylidene oxindole (0.1 mmol) was added to a solution of catalyst (5 or 10 mol%) in DCM (0.15 mL), then nitroalkane (0.5 mmol) was added at room temperature or at 0°C. The mixture was stirred at the same temperature and the conversion was monitored by TLC and ^{1}H-NMR. The crude mixture of the reactions performed at room temperature was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15). The crude mixture of the reactions performed at 0°C was quenched at the same temperature with 2 mL of HCl (1N) and extracted with DCM (3 X 2 mL). The organic phases were collected, dried over Na_2SO_4, the solvent was evaporated under reduced pressure without heating and the product was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 85/15). Before CSP-HPLC analysis, the purified product (0.04 mmol) (and, when necessary, the crude reaction mixture) was deprotected using 18 equivalents of trifluoroacetic acid (TFA) in 0.4 mL of DCM. After 45 minutes the reaction was quenched with 2 mL of a 0.1 M solution of phosphate buffer (pH = 7) and the aqueous phase was extracted with DCM (2 X 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the corresponding *N*-deprotected β-nitro oxindole was obtained pure and directly injected into CSP-HPLC.

3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline (3a): mixture of two diastereoisomers. 85% yield (24 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (bs, 2H), 7.34 – 7.20 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 2H), 4.99 (dd, *J* = 14.5, 9.4 Hz, 1H), 4.78 (dd, *J* = 14.8, 8.9 Hz, 1H), 4.46 (m, 2H), 4.29 – 4.14 (m, 4H), 4.14 – 4.07 (m, 1H), 4.04 (m, 1H), 3.99 – 3.91 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 13.9, 43.0, 43.3, 45.0, 45.1,

[109] Griesser H., Öhrlein R., Schwab W., Ehrler R., Jäger V., *Org. Synth.* **2000**, 77, 236.

62.1, 62.2, 72.0, 72.3, 110.3, 122.9, 123.0, 124.3, 124.4, 124.8, 125.0, 129.2, 129.3, 141.3, 141.6, 169.1, 169.8, 176.5, 176.8. HPLC-MS (ESI): t_r = 6.4 min, 6.8 min; $[M+H]^+$ = 279.2 m/z, $[M+Na]^+$ = 301.2 m/z. Anal. Calcd for $C_{13}H_{14}N_2O_5$ (278.09): C, 56.11; H, 5.07; N, 10.07. Found: C, 55.91; H, 5.09; N, 10.04. CSP-HPLC: OJ 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 20 min, 80:20 up to 60 min; flow rate = 0.5 mL/min at 40°C. λ=214 nm. t_r(isomer A) = 38.5 min (major), 44.8 min (minor); t_r(isomer B) = 42.7 min (major), 53.8 min (minor).

(2*R*)-Ethyl 2-(1-benzyl-2-oxoindolin-3-yl)-3-nitropropanoate (3b): mixture of two diastereoisomers. 86% yield (32 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.16 (m, 14H), 7.10 – 7.01 (m, 2H), 6.84 – 6.72 (m, 2H), 5.03 – 4.88 (m, 5H), 4.80 (dd, *J* = 14.8, 8.9 Hz, 1H), 4.52 – 4.37 (m, 2H), 4.24 – 4.04 (m, 6H), 4.01 (d, *J* = 3.7 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.7, 13.8, 43.2, 43.4, 44.09, 44.11, 44.5, 44.6, 62.0, 62.1, 72.10, 72.41, 109.5, 122.9, 123.0, 124.0, 124.1, 124.3, 124.5, 127.4, 127.5, 127.88, 127.91, 128.86, 128.87, 129.0, 129.2, 135.40, 135.42, 143.4, 143.6, 169.2, 169.7, 174.4, 174.6. HPLC-MS (ESI): t_r = 9.5 min, 9.8 min; $[M+H]^+$ = 369.2 m/z, $[M+Na]^+$ = 391.2 m/z. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.14): C, 65.21; H, 5.47; N, 7.60. Found: C, 65.06; H, 5.47; N, 7.61. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 85:15 in 5 min, 85:15 up to 80 min; flow rate = 0.5 mL/min at rt. λ=254 nm. t_r(isomer A) = 56.1 min (major), 71.0 min (minor); t_r(isomer B) = 61.2 min (major), 73.6 min (minor).

***Tert*-butyl 3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3c)**: mixture of two diastereoisomers. 80% yield (30 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (dd, *J* = 8.4, 2.8 Hz, 2H), 7.41 – 7.33 (m, 2H), 7.29 – 7.14 (m, 4H), 5.01 (dd, *J* = 14.4, 9.3 Hz, 1H), 4.84 (dd, *J* = 14.9, 8.1 Hz, 1H), 4.64 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.40 (dd, *J* = 14.4, 5.0 Hz, 1H), 4.23 – 4.06 (m, 6H), 4.04 (d, *J* = 3.8 Hz, 1H), 3.99 (d, *J* = 3.1 Hz, 1H), 1.65 (s, 18H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 13.8, 28.0, 43.7, 43.9, 45.0, 45.4, 62.2, 62.3, 72.3, 72.4, 84.9, 85.0, 115.3, 115.4, 123.2, 123.5, 123.6, 123.7, 124.7, 124.8, 129.2, 129.5, 140.3, 140.6, 148.77, 148.76, 168.7, 169.2, 172.7, 173.4. HPLC-MS (ESI): t_r = 9.9 min, 10.0 min; $[M+Na]^+$ = 401.3 m/z. Anal. Calcd for $C_{18}H_{22}N_2O_7$ (378.14): C, 57.14; H, 5.86; N, 7.40. Found: C, 57.02; H, 5.85; N, 7.39.

3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers. CSP-HPLC: OJ 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 20 min, 80:20 up to 70 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 43.2 min (major), 51.8 min (minor); t_r(isomer B) = 49.5 min (major), 63.9 min (minor).

***Tert*-butyl 5-chloro-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3d)**: mixture of two diastereoisomers. 83% yield (34 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 5.1 Hz, 1H), 7.83 (d, *J* = 5.2 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.24 – 7.20 (m, 2H), 5.00 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.91 (dd, *J* = 14.8, 7.3 Hz, 1H), 4.78 (dd, *J* = 14.8, 6.6 Hz, 1H), 4.46 (dd, *J* = 14.4, 5.2 Hz, 1H), 4.22 – 4.03 (m, 6H), 4.00 (d, *J* = 4.3 Hz, 1H), 3.93 (d, *J* = 3.0 Hz, 1H), 1.64 (s, 18H), 1.22 – 1.09 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.68, 13.73, 28.0, 43.7, 44.0, 44.7, 45.2, 62.4, 62.5, 72.2, 72.6, 85.2, 85.3, 116.6, 116.7, 123.7, 123.9, 125.1, 125.8, 129.2, 129.5, 130.2, 130.3, 138.9, 139.1, 148.6, 168.4, 168.6, 171.9, 172.8. HPLC-MS (ESI): t_r = 10.7 min; $[M+Na]^+$ = 435.2, 437.3 m/z, $[M+K]^+$ = 451.2 m/z, $[2M+Na]^+$ = 847.4 m/z. Anal. Calcd for $C_{18}H_{21}ClN_2O_7$ (412.10): C, 52.37; H, 5.13; N, 6.79. Found: C, 52.21; H, 5.14; N, 6.78.

5-chloro-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (bs, 2H), 7.52 – 7.48 (m, 1H), 7.33 – 7.16 (m, 3H), 6.92 – 6.76 (m, 2H), 4.99 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.84 (dd, *J* = 14.7, 8.2 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.52 (dd, *J* = 14.5, 4.9 Hz, 1H), 4.40 (m, 1H), 4.27 – 4.16 (m, 3H), 4.12 – 4.05 (m, 2H), 4.02 – 3.87 (m, 2H), 1.31 – 1.15 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 13.9, 43.1, 43.3, 44.8, 44.9, 62.3, 62.4, 72.1, 72.2, 111.0, 111.1, 124.5, 124.7, 124.9, 124.9, 126.8, 128.0, 128.4, 129.1, 129.3, 129.5, 139.7, 139.9, 168.9, 169.3, 176.0. HPLC-MS (ESI): t_r= 7.5 min, 7.6 min; $[M+H]^+$= 313.1 m/z, $[M+Na]^+$= 335.1 m/z. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$ (312.05): C, 49.93; H, 4.19; N, 8.96. Found: C, 49.89; H, 4.20; N, 8.94. CSP-HPLC: IC 90:10 *n*-Hex/IPA up to 50 min; flow rate = 0.6 mL/min at rt. λ=214 nm. t_r(isomer A) = 31.4 min (major), 39.7 min (minor); t_r(isomer B) = 44.2 min (minor), 45.9 min (major).

***Tert*-butyl 5-bromo-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3e)**: mixture of two diastereoisomers. 72% yield (33 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.76 (m, 2H), 7.53 – 7.45 (m, 2H), 7.40 – 7.32 (m, 2H), 5.00 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.91 (dd, *J* = 14.8, 7.3 Hz, 1H), 4.80 (dd, *J* = 14.8, 6.6 Hz, 1H), 4.46 (dd, *J* = 14.5, 5.1 Hz, 1H), 4.24 – 4.02 (m, 6H), 4.00 (d, *J* = 4.3 Hz, 1H), 3.93 (d, *J* = 3.0 Hz,

1H), 1.64 (s, 18H), 1.22 – 1.09 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.7, 13.7, 28.0, 43.8, 44.1, 44.7, 45.1, 62.4, 62.5, 72.2, 72.6, 85.2, 85.4, 117.0, 117.0, 117.6, 117.7, 125.5, 126.2, 126.5, 126.7, 132.1, 132.5, 139.4, 139.6, 148.6, 168.4, 168.6, 171.8, 172.7. HPLC-MS (ESI): t_r= 10.9 min; $[M+Na]^+$= 479.2, 481.1 m/z. Anal. Calcd for $C_{18}H_{21}BrN_2O_7$ (456.05): C, 47.28; H, 4.63; N, 6.13. Found: C, 47.13; H, 4.61; N, 6.11.

5-bromo-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (bs, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.29 (m, 2H), 6.84 – 6.76 (m, 2H), 4.99 (dd, *J* = 14.5, 8.8 Hz, 1H), 4.84 (dd, *J* = 14.8, 8.1 Hz, 1H), 4.62 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.52 (dd, *J* = 14.5, 4.8 Hz, 1H), 4.26 – 4.18 (m, 4H), 4.12 – 4.04 (m, 1H), 4.00 – 3.89 (m, 3H), 1.31 – 1.14 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 13.9, 43.2, 43.3, 44.7, 44.8, 62.3, 62.4, 72.17, 72.23, 111.4, 111.5, 115.5, 127.2, 127.3, 127.6, 127.7, 132.0, 132.2, 140.2, 140.4, 168.9, 169.2, 175.2, 175.7. HPLC-MS (ESI): t_r= 7.7 min; $[M+H]^+$= 357.1, 359.1 m/z, $[M+Na]^+$= 379.1, 381.0 m/z. Anal. Calcd for $C_{13}H_{13}BrN_2O_5$ (356.00): C, 43.72; H, 3.67; N, 7.84. Found: C, 43.69; H, 3.68; N, 7.83. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 75:25 in 15 min, 75:25 up to 40 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 27.7 min (major), 31.3 min (minor); t_r(isomer B) = 32.4 min (major), 33.0 min (minor).

***Tert*-butyl 6-chloro-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3f)**: mixture of two diastereoisomers. 92% yield (38 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.92 (m, 2H), 7.22 – 7.12 (m, 4H), 5.00 (dd, *J* = 14.3, 9.0 Hz, 1H), 4.87 (dd, *J* = 14.8, 7.5 Hz, 1H), 4.74 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.44 (dd, *J* = 14.4, 5.3 Hz, 1H), 4.21 – 4.04 (m, 6H), 3.98 (d, *J* = 3.9 Hz, 1H), 3.92 (d, *J* = 2.7 Hz, 1H), 1.65 (s, 18H), 1.22 – 1.11 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.7, 13.8, 28.0, 43.8, 44.0, 44.6, 45.0, 62.3, 62.4, 72.3, 72.5, 85.4, 85.5, 116.16, 116.23, 121.7, 122.3, 124.3, 124.5, 124.7, 124.8, 135.1, 135.4, 141.3, 141.5, 148.5, 168.4, 168.8, 172.2, 173.0. HPLC-MS (ESI): t_r= 10.9 min; $[M+Na]^+$= 435.2 m/z, $[2M+Na]^+$= 847.4 m/z. Anal. Calcd for $C_{18}H_{21}ClN_2O_7$ (412.10): C, 52.37; H, 5.13; N, 6.79. Found: C, 52.16; H, 5.13; N, 6.78.

6-chloro-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (bs, 2H), 7.19 – 7.02 (m, 4H), 6.95 (s, 2H), 4.99 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.81 (dd, *J* = 14.7, 8.3 Hz, 1H), 4.57 (dd, *J* = 14.7, 5.5 Hz, 1H), 4.49 (dd, *J* = 14.4, 5.1 Hz, 1H), 4.26 – 4.11 (m, 4H), 4.08 (ddd, *J* = 8.6,

5.5, 3.4 Hz, 1H), 4.01 (m, 1H), 3.93 – 3.87 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.8, 13.9, 43.1, 43.3, 44.5, 44.6, 62.26, 62.34, 72.1, 72.3, 110.9, 122.9, 123.0, 123.37, 123.42, 125.28, 125.32, 135.0, 135.2, 142.4, 168.9, 169.5, 176.4, 176.7. HPLC-MS (ESI): t_r= 7.3 min, 7.7 min; $[M+Na]^+$= 335.1 m/z. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$ (312.05): C, 49.93; H, 4.19; N, 8.96. Found: C, 49.77; H, 4.18; N, 8.93. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 35 min, then up to 80:20 in 15 min, 80:20 for 10 min, then up to 70:30 in 5 min, 70:30 for 5 min, then up to 1:1 in 2 min, 1:1 up to 73 min; flow rate = 0.6 mL/min at rt. λ=254 nm. t_r(isomer A) = 33.4 min (major), 52.7 min (minor); t_r(isomer B) = 44.1 min (minor), 68.4 min (major).

***Tert*-butyl 7-bromo-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3g)**: mixture of two diastereoisomers. 82% yield (37 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.47 (m, 2H), 7.22 – 7.16 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 2H), 5.01 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.88 (dd, *J* = 14.9, 7.5 Hz, 1H), 4.74 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.44 (dd, *J* = 14.4, 5.1 Hz, 1H), 4.20 – 4.05 (m, 6H), 4.04 (d, *J* = 3.9 Hz, 1H), 3.99 (d, *J* = 3.2 Hz, 1H), 1.66 (s, 9H), 1.65 (s, 9H), 1.15 (t, *J* = 7.6 Hz, 3H), 1.12 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.6, 13.7, 27.7, 43.7, 44.0, 45.2, 45.6, 62.5, 72.3, 72.4, 86.0, 86.1, 106.5, 106.6, 122.6, 122.8, 125.49, 125.54, 127.0, 127.6, 134.0, 134.3, 139.3, 139.5, 147.5, 168.4, 168.6, 173.0, 173.7. HPLC-MS (ESI): t_r= 10.5 min; $[M+Na]^+$= 479.1, 481.2 m/z. Anal. Calcd for $C_{18}H_{21}BrN_2O_7$ (456.05): C, 47.28; H, 4.63; N, 6.13. Found: C, 47.13; H, 4.64; N, 6.14.

7-bromo-3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (bs, 2H), 7.43 (d, *J* = 3.7 Hz, 1H), 7.41 (d, *J* = 3.7 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.93 (m, 2H), 5.01 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.81 (dd, *J* = 14.8, 8.4 Hz, 1H), 4.60 (dd, *J* = 14.8, 5.5 Hz, 1H), 4.49 (dd, *J* = 14.5, 4.6 Hz, 1H), 4.26 – 3.99 (m, 8H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.7, 13.8, 43.2, 43.3, 46.0, 46.2, 62.2, 62.3, 72.1, 72.4, 103.2, 103.3, 123.1, 124.1, 126.30, 126.34, 131.8, 132.0, 140.8, 141.04, 168.8, 169.3, 174.8, 175.2. HPLC-MS (ESI): t_r= 7.3 min, 7.6 min; $[M+H]^+$= 357.2, 359.1 m/z, $[M+Na]^+$= 379.1, 381.0 m/z. Anal. Calcd for $C_{13}H_{13}BrN_2O_5$ (356.00): C, 43.72; H, 3.67; N, 7.84. Found: C, 43.71; H, 3.68; N, 7.81. CSP-HPLC: IC 85:15 *n*-Hex/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 10 min, then up to 70:30 in 10 min, 70:30 up

to 70 min; flow rate = 0.5 mL/min at 14°C. λ=214 nm. t_r(isomer A) = 48.4 min (major), 50.7 min (minor); t_r(isomer B) = 57.4 min (major), 66.1 min (minor).

***Tert*-butyl 3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-5-methoxy-2-oxoindoline-1-carboxylate (3h)**: mixture of two diastereoisomers. 89% yield (36 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 2.9 Hz, 1H), 7.77 (d, *J* = 2.9 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.80 (dd, *J* = 2.6, 1.1 Hz, 1H), 6.77 (dd, *J* = 2.6, 1.2 Hz, 1H), 4.97 (dd, *J* = 14.5, 9.1 Hz, 1H), 4.84 (dd, *J* = 14.8, 8.1 Hz, 1H), 4.64 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.35 (dd, *J* = 14.5, 4.6 Hz, 1H), 4.25 – 4.01 (m, 7H), 3.96 (d, *J* = 2.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 1.64 (s, 18H), 1.22 –1.13 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.7, 13.8, 28.1, 43.7, 43.9, 45.3, 45.7, 55.6, 55.7, 62.2, 62.3, 72.1, 72.5, 84.66, 84.74, 110.0, 110.2, 113.8, 113.9, 116.3, 116.4, 124.5, 125.0, 133.6, 133.8, 148.8, 156.97, 157.01, 168.7, 169.1, 172.6, 173.4. HPLC-MS (ESI): t_r= 9.9 min, 10.2 min; $[M+Na]^+$= 431.3 m/z, $[2M+Na]^+$ = 839.6 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.15): C, 55.88; H, 5.92; N, 6.86. Found: C, 55.77; H, 5.93; N, 6.87.

3-((*R*)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-5-methoxy-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.45 (bs, 2H), 6.90 – 6.73 (m, 6H), 4.96 (dd, *J* = 14.5, 9.3 Hz, 1H), 4.76 (dd, *J* = 14.8, 8.9 Hz, 1H), 4.49 – 4.35 (m, 2H), 4.29 – 4.15 (m, 4H), 4.10 (ddd, *J* = 8.6, 4.8, 3.3 Hz, 1H), 4.04 – 3.92 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.8, 13.9, 43.0, 43.3, 45.5, 45.6, 55.78, 55.84, 62.1, 62.2, 72.0, 72.1, 110.8, 111.6, 111.7, 113.7, 113.8, 126.1, 126.4, 134.6, 134.8, 156.09, 156.14, 169.1, 169.8, 176.5, 176.8. HPLC-MS (ESI): t_r= 5.9 min, 6.2 min; $[M+H]^+$= 309.2 m/z, $[M+Na]^+$= 331.2, $[2M+Na]^+$= 639.3 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_6$ (308.10): C, 54.54; H, 5.23; N, 9.09. Found: C, 54.42; H, 5.24; N, 9.12. CSP-HPLC: OD-H 85:15 *n*-Hex/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 10 min, then up to 70:30 in 10 min, 70:30 up to 41 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 24.9 min (major), 33.4 min (minor); t_r(isomer B) = 31.3 min (minor), 36.3 min (major).

***Tert*-butyl 3-((*R*)-1-(benzyloxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3i):** mixture of two diastereoisomers. 72% yield (32 mg), oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.2 Hz, 2H), 7.41 – 6.95 (m, 16H), 5.15 (s, 2H), 5.10 (s, 2H), 5.02 (dd, *J* = 14.4, 9.3 Hz, 1H), 4.81 (dd, *J* = 14.8, 8.3 Hz, 1H), 4.58 (dd, *J* = 14.9, 5.5 Hz, 1H), 4.39 (dd, *J* = 14.5, 4.6 Hz, 1H), 4.27 – 3.93 (m, 4H), 1.64 (s, 9H), 1.63 (s, 9H). ^{13}C

NMR (50 MHz, $CDCl_3$) δ = 28.0, 43.6, 43.7, 45.0, 45.4, 67.97, 68.02, 72.2, 84.9, 115.4, 115.5, 123.1, 123.3, 123.5, 124.6, 124.7, 128.4, 128.5, 128.6, 128.7, 129.2, 129.4, 134.4, 134.5, 140.2, 140.5, 148.6, 168.7, 169.1, 172.5, 173.2. HPLC-MS (ESI): t_r= 11.0 min, 11.2 min; $[M+Na]^+$= 463.3 m/z, $[2M+Na]^+$= 903.5 m/z. Anal. Calcd for $C_{23}H_{24}N_2O_7$ (440.16): C, 62.72; H, 5.49; N, 6.36. Found: C, 62.71; H, 5.48; N, 6.35.

3-((*R*)-1-(benzyloxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.42 (bs, 2H), 7.39 – 7.30 (m, 6H), 7.30 – 7.20 (m, 7H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.08 – 6.91 (m, 3H), 6.85 (t, *J* = 8.4 Hz, 1H), 5.26 – 5.08 (m, 4H), 5.01 (dd, *J* = 14.6, 9.5 Hz, 1H), 4.76 (dd, *J* = 14.8, 9.0 Hz, 1H), 4.51 – 4.38 (m, 2H), 4.16 (m, 1H), 4.10 (m, 1H), 3.98 – 3.91 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 43.0, 43.3, 44.98, 45.03, 67.8, 67.9, 71.9, 72.3, 110.3, 110.4, 122.96, 122.99, 124.3, 124.4, 124.6, 124.8, 128.4, 128.51, 128.54, 128.6, 128.7, 129.1, 129.3, 134.6, 134.7, 141.2, 141.5, 169.1, 169.7, 176.3, 176.5. HPLC-MS (ESI): t_r= 8.4 min, 8.7 min; $[M+H]^+$= 341.1 m/z, $[M+Na]^+$ = 363.2 m/z. Anal. Calcd for $C_{18}H_{16}N_2O_5$ (340.11): C, 63.52; H, 4.74; N, 8.23. Found: C, 63.42; H, 4.73; N, 8.22. CSP-HPLC: OJ 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 20 min, 80:20 up to 105 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 77.1 min (minor), 90.9 min (major); t_r(isomer B) = 84.8 min (major), 100.9 min (minor).

***Tert*-butyl 3-((*R*)-1-(*tert*-butoxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3j):** mixture of two diastereoisomers. 99% yield (40 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.28 – 7.14 (m, 4H), 5.06 (dd, *J* = 14.2, 9.0 Hz, 1H), 4.88 (dd, *J* = 14.7, 8.1 Hz, 1H), 4.69 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.49 (dd, *J* = 14.1, 5.6 Hz, 1H), 4.15 (ddd, *J* = 8.9, 5.7, 2.9 Hz, 1H), 4.00 (ddd, *J* = 8.1, 6.0, 3.3 Hz, 1H), 3.93 (d, *J* = 3.2 Hz, 1H), 3.82 (d, *J* = 2.8 Hz, 1H), 1.65 (s, 9H), 1.64 (s, 9H), 1.30 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 27.3, 27.5, 28.1, 44.5, 44.9, 45.1, 45.5, 72.9, 73.3, 83.5, 84.8, 115.2, 115.3, 123.5, 123.6, 123.7, 124.3, 124.6, 129.0, 129.3, 140.3, 140.7, 148.9, 167.4, 167.9, 172.8, 173.4. HPLC-MS (ESI): t_r= 10.8 min, 11.1 min; $[M+Na]^+$= 429.4 m/z, $[2M+Na]^+$ = 835.5 m/z. Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 58.95; H, 6.44; N, 6.91.

3-((*R*)-1-(*tert*-butoxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (bs, 2H), 7.32 – 7.25 (m,

2H), 7.25 – 7.19 (m, 2H), 7.11 – 7.03 (m, 2H), 6.95 – 6.88 (m, 2H), 5.00 (dd, *J* = 14.2, 9.3 Hz, 1H), 4.80 (dd, *J* = 14.7, 9.1 Hz, 1H), 4.46 (ddd, *J* = 14.2, 12.1, 5.0 Hz, 2H), 4.08 – 3.96 (m, 2H), 3.91 (d, *J* = 3.5 Hz, 1H), 3.81 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 43.9, 44.0, 45.00, 45.2, 72.3, 73.1, 109.9, 110.0, 122.9, 122.8, 124.4, 124.5, 125.2, 125.4, 129.0, 129.2, 141.1, 141.6, 167.8, 168.7, 176.2, 176.3. HPLC-MS (ESI): t_r= 7.3 min, 7.9 min; $[M+H]^+$= 251.1 m/z. Anal. Calcd for $C_{11}H_{10}N_2O_5$ (250.06): C, 52.80; H, 4.03; N, 11.20. Found: C, 52.74; H, 4.01; N, 11.23. CSP-HPLC: OJ 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 20 min, 80:20 up to 56 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 27.6 min (major), 38.4 min (minor); t_r(isomer B) = 33.0 min (major), 52.2 min (minor).

***Tert*-butyl 3-((*S*)-2-nitro-1-phenylethyl)-2-oxoindoline-1-carboxylate (3k):** mixture of two diastereoisomers. 52% yield (20 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.08 (m, 10H), 7.08 – 6.95 (m, 5H), 6.63 (d, *J* = 7.5 Hz, 1H), 5.43 – 5.29 (m, 2H), 5.12 (dd, *J* = 13.9, 7.9 Hz, 1H), 4.92 (dd, *J* = 13.1, 9.0 Hz, 1H), 4.25 (td, *J* = 7.6, 3.8 Hz, 1H), 4.03 (m, 1H), 3.92 (d, *J* = 3.7 Hz, 1H), 3.80 (d, *J* = 7.8 Hz, 1H), 1.65 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.99, 28.01, 45.5, 46.0, 48.2, 48.7, 75.7, 77.1, 84.5, 84.6, 114.9, 115.0, 123.9, 124.1, 124.3, 124.4, 124.6, 124.8, 128.0, 128.2, 128.4, 128.48, 128.53, 128.7, 128.8, 129.0, 134.1, 135.2, 140.2, 140.4, 148.5, 148.6, 173.5, 173.9. HPLC-MS (ESI): t_r= 10.6 min; $[M+Na]^+$= 405.2 m/z. Anal. Calcd for $C_{21}H_{22}N_2O_5$ (382.15): C, 65.96; H, 5.80; N, 7.33. Found: C, 65.87; H, 5.81; N, 7.32.

3-((*S*)-2-nitro-1-phenylethyl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.00 (m, 14H), 6.93 – 6.85 (m, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 5.48 (dd, *J* = 13.1, 6.7 Hz, 1H), 5.35 (dd, *J* = 13.7, 7.3 Hz, 1H), 5.14 (dd, *J* = 13.7, 8.0 Hz, 1H), 4.92 (dd, *J* = 13.1, 9.1 Hz, 1H), 4.29 (dt, *J* = 7.7, 4.0 Hz, 1H), 4.01 (m, 1H), 3.84 (d, *J* = 3.9 Hz, 1H), 3.73 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 44.5, 45.3, 47.9, 48.6, 75.8, 77.5, 109.8, 110.0, 122.4, 122.5, 124.4, 125.4, 126.26, 126.32, 128.0, 128.1, 128.40, 128.45, 128.50, 128.53, 128.8, 134.9, 136.0, 141.2, 141.5, 177.4, 177.5. HPLC-MS (ESI): t_r= 7.6 min; $[M+H]^+$= 283.3 m/z, $[M+Na]^+$= 305.3 m/z. Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.10): C, 68.07; H, 5.00; N, 9.92. Found: C, 67.94; H, 5.00; N, 9.96. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 for 15 min, then up to 70:30 in 5 min,

70:30 up to 36 min; flow rate = 0.5 mL/min at rt. λ=230 nm. t_r(isomer A) = 25.0 min (minor), 26.8 min (major); t_r(isomer B) = 29.7 min (major), 31.7 min (minor).

***Tert*-butyl 3-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-2-oxoindoline-1-carboxylate (3l):** mixture of two diastereoisomers. 98% yield (42 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.30 – 7.17 (m, 6H), 7.16 – 7.07 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.42 – 5.22 (m, 3H), 4.97 (dd, *J* = 13.4, 9.5 Hz, 1H), 4.37 (ddd, *J* = 8.5, 6.8, 3.9 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.98 (d, *J* = 3.8 Hz, 1H), 3.88 (d, *J* = 6.7 Hz, 1H), 1.58 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 27.97, 28.00, 45.1, 45.5, 48.1, 48.5, 75.4, 85.1, 115.2, 115.4, 123.3, 123.6, 123.7, 123.8, 124.4, 124.5, 124.7, 129.2, 129.3, 129.5, 129.6, 140.0, 140.5, 141.5, 142.4, 147.7, 147.9, 148.2, 148.3, 172.8, 173.4. HPLC-MS (ESI): t_r= 10.7 min; $[M+Na]^+$= 450.2 m/z, $[2M+Na]^+$= 877.7 m/z. Anal. Calcd for $C_{21}H_{21}N_3O_7$ (427.14): C, 59.01; H, 4.95; N, 9.83. Found: C, 58.85; H, 4.94; N, 9.81.

3-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.9 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.91 (bs, 1H), 7.38 – 7.23 (m, 6H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.87 – 6.80 (m, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.41 – 5.26 (m, 3H), 4.97 (dd, *J* = 13.3, 9.4 Hz, 1H), 4.41 (ddd, *J* = 8.3, 6.9, 4.0 Hz, 1H), 4.27 (dt, *J* = 9.4, 6.7 Hz, 1H), 3.90 (d, *J* = 3.9 Hz, 1H), 3.81 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 44.3, 44.9, 47.8, 48.3, 75.4, 76.6, 110.2, 110.4, 122.9, 123.0, 123.6, 123.9, 124.3, 125.0, 125.4, 129.1, 129.2, 129.4, 129.5, 140.8, 141.3, 142.1, 142.9, 147.6, 147.9, 176.4, 176.7. HPLC-MS (ESI): t_r= 7.5 min, 7.6 min; $[M+H]^+$= 328.3 m/z, $[M+Na]^+$= 350.1 m/z. Anal. Calcd for $C_{16}H_{13}N_3O_5$ (327.09): C, 58.72; H, 4.00; N, 12.84. Found: C, 58.52; H, 4.01; N, 12.85. CSP-HPLC: IC 85:15 *n*-Hex/IPA for 20 min, then up to 80:20 in 20 min, 80:20 up to 52 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 39.0 min (minor), 46.8 min (major); t_r(isomer B) = 43.0 min (major), 45.5 min (minor).

***Tert*-butyl 3-((*S*)-3,3-dimethyl-1-nitrobutan-2-yl)-2-oxoindoline-1-carboxylate (3m):** mixture of two diastereoisomers. 62% yield (22 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.11 (m, 6H), 4.71 – 4.47 (m, 4H), 3.82 (s, 1H), 3.74 (s, 1H), 3.05 (ddd, *J* = 10.4, 4.7, 1.7 Hz, 1H), 2.86 (m, 1H), 1.65 (s, 18H), 1.13 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.1, 28.3, 28.6, 33.7, 34.1, 45.3, 45.4, 48.0, 49.7, 73.7, 74.1, 84.4, 84.5, 115.0, 115.6, 123.3, 124.0, 124.4, 124.5, 127.4, 128.4,

128.8, 139.8, 140.8, 149.0, 149.1, 174.0, 175.7. HPLC-MS (ESI): t_r= 10.8 min, 11.2 min; $[M+Na]^+$= 385.2 m/z, $[2M+Na]^+$= 747.7 m/z. Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.95; H, 7.24; N, 7.74.

3-((*S*)-3,3-dimethyl-1-nitrobutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (bs, 1H), 8.22 (bs, 1H), 7.31 – 7.16 (m, 4H), 7.13 – 6.98 (m, 2H), 6.95 – 6.81 (m, 2H), 4.74 – 4.47 (m, 4H), 3.72 (s, 1H), 3.66 (s, 1H), 3.06 (ddd, *J* = 9.9, 4.9, 1.7 Hz, 1H), 2.90 (ddd, *J* = 8.6, 5.1, 1.8 Hz, 1H), 1.14 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.4, 28.5, 33.7, 34.1, 45.4, 47.1, 48.8, 74.2, 74.6, 109.8, 110.3, 122.3, 122.7, 123.9, 125.1, 126.1, 128.3, 128.6, 129.1, 140.8, 141.8, 177.6, 179.5. HPLC-MS (ESI): t_r= 7.8 min, 8.4 min; $[M+H]^+$= 263.1 m/z, $[M+Na]^+$= 285.2 m/z, $[2M+H]^+$= 525.3 m/z. Anal. Calcd for $C_{14}H_{18}N_2O_3$ (262.13): C, 64.10; H, 6.92; N, 10.68. Found: C, 63.88; H, 6.94; N, 10.70. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 10 min, then up to 70:30 in 5 min, 70:30 for 5 min, then up to 1:1 in 1 min, 1:1 up to 53 min; flow rate = 0.5 mL/min at rt. λ=254 nm. t_r(isomer A) = 31.5 min (major), 39.2 min (minor); t_r(isomer B) = 45.9 min (major), 47.7 min (minor).

***Tert*-butyl 3-((*R*)-1-ethoxy-2-methyl-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (3n):** mixture of two diastereoisomers. 57% yield (22 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 – 7.78 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.22 – 7.12 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.38 (d, *J* = 13.2 Hz, 1H), 5.15 (d, *J* = 13.2 Hz, 2H), 4.97 (d, *J* = 12.4 Hz, 1H), 4.46 – 4.33 (m, 4H), 3.95 (s, 1H), 3.94 (s, 1H), 1.65 (s, 9H), 1.64 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 6.8 Hz, 3H), 1.13 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer) δ = 13.9, 14.6, 28.1, 49.1, 49.9, 62.2, 80.0, 85.1, 115.0, 122.6, 124.6, 125.1, 129.4, 140.8, 148.6, 171.6, 172.8. HPLC-MS (ESI): t_r = 10.8 min; $[M+Na]^+$ = 415.4 m/z, $[2M+Na]^+$ = 807.5 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 58.08; H, 6.18; N, 7.15.

3-((*R*)-1-ethoxy-2-methyl-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (bs, 1H), 7.57 (bs, 1H), 7.40 – 7.19 (m, 3H), 7.09 – 6.94 (m, 3H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.46 (d, *J* = 13.2 Hz, 1H), 5.17 (d, *J* = 12.8 Hz, 1H), 5.15 (d, *J* = 13.2 Hz, 1H), 4.93 (d, *J* = 12.8 Hz, 1H), 4.48 – 4.34 (m, 4H), 3.85 (s, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ = 14.1, 14.3, 48.4, 49.5, 62.2,

79.8, 109.8, 122.9, 124.3, 125.2, 129.2, 141.4, 171.9, 175.7. HPLC-MS (ESI): t_r = 6.7 min, 7.4 min; $[M+H]^+$= 293.3 m/z, $[M+Na]^+$ = 315.2 m/z, $[2M+Na]^+$ = 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.51; H, 5.54; N, 9.56. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 for 15 min, then up to 70:30 in 15 min, 70:30 up to 47 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 23.2 min (major), 29.0 min (minor); t_r(isomer B) = 35.3 min (minor), 41.6 min (major).

***Tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (*anti*-4b):** mixture of two diastereoisomers. 71% yield (28 mg), gum. ^{1}H NMR (400 MHz, CDCl3) δ = 7.84 (t, *J* = 8.6 Hz, 2H), 7.39 – 7.29 (m, 4H), 7.17 (t, *J* = 7.7 Hz, 2H), 5.67 (dq, *J* = 9.9, 6.8 Hz, 1H), 5.30 (dq, *J* = 9.2, 6.3 Hz, 1H), 3.99 – 3.91 (m, 4H), 3.91 – 3.84 (m, 1H), 3.80 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.74 (d, *J* = 4.3 Hz, 1H), 3.62 (d, *J* = 4.0 Hz, 1H), 1.78 (d, *J* = 6.5 Hz, 3H), 1.64 (m, 21H), 0.99 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.5, 13.6, 18.1, 18.9, 28.0, 28.1, 44.1, 45.3, 50.6, 51.5, 61.8, 61.8, 79.5, 81.8, 84.5, 84.7, 115.1, 115.2, 123.4, 123.7, 124.0, 124.4, 124.5, 124.6, 129.1, 129.3, 140.4, 140.5, 148.9, 149.1, 167.9, 168.1, 172.8, 172.9. HPLC-MS (ESI): t_r= 10.3 min, 10.4 min; $[M+Na]^+$= 415.3 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 57.98; H, 6.18; N, 7.14.

3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (bs, 1H), 8.01 (bs, 1H), 7.34 – 7.19 (m, 4H), 7.12 – 7.01 (m, 2H), 6.94 – 6.83 (m, 2H), 5.62 (dq, *J* = 9.6, 6.9 Hz, 1H), 5.36 (dq, *J* = 8.6, 6.6 Hz, 1H), 4.08 – 3.96 (m, 4H), 3.90 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.77 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.70 (d, *J* = 4.4 Hz, 1H), 3.60 (d, *J* = 5.2 Hz, 1H), 1.77 (d, *J* = 6.6 Hz, 3H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.02, (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.67, 13.72, 17.4, 18.7, 44.0, 44.8, 49.8, 50.4, 61.68, 61.73, 79.5, 81.6, 109.8, 109.9, 122.5, 122.8, 124.6, 125.2, 125.3, 125.4, 128.9, 129.0, 141.2, 141.4, 168.3, 168.7, 176.3. HPLC-MS (ESI): t_r= 6.9 min, 7.0 min; $[M+H]^+$= 293.3 m/z, $[M+Na]^+$= 315.2 m/z, $[2M+Na]^+$= 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.39; H, 5.51; N, 9.55. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 for 20 min, then up to 75:25 in 15 min, 75:25 up to 53 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 24.4 min (major), 31.5 min (minor); t_r(isomer B) = 39.8 min (minor), 47.0 min (major).

***Tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxopentan-2-yl)-2-oxoindoline-1-carboxylate (*anti*-4c):** mixture of two diastereoisomers. 76% yield (31 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.22 (m, 4H), 7.20 – 7.12 (m, 2H), 5.62 (ddd, *J* = 10.8, 7.3, 5.8 Hz, 1H), 5.16 (ddd, *J* = 10.3, 8.3, 5.0 Hz, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.89 – 3.81 (m, 3H), 3.77 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.62 (d, *J* = 4.3 Hz, 1H), 3.54 – 3.47 (m, 1H), 2.19 – 2.05 (m, 2H), 2.00 – 1.89 (m, 2H), 1.65 (s, 18H), 1.08 (t, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.6, 10.5, 13.4, 13.5, 26.3, 26.6, 28.0, 28.1, 44.0, 45.6, 49.9, 50.8, 61.76, 61.78, 84.5, 84.6, 85.4, 88.9, 115.0, 115.1, 123.1, 123.6, 123.9, 124.4, 124.6, 124.7, 129.1, 129.2, 140.4, 140.5, 148.9, 149.1, 167.9, 168.1, 172.6, 172.9. HPLC-MS (ESI): t_r= 10.9 min, 11.0 min; $[M+Na]^+$= 429.2 m/z. Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.43; N, 6.92.

3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxopentan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (bs, 2H), 7.39 – 7.17 (m, 4H), 7.14 – 6.98 (m, 2H), 6.95 – 6.81 (m, 2H), 5.60 (ddd, *J* = 10.6, 8.4, 4.7 Hz, 1H), 5.25 – 5.12 (m, 1H), 4.00 – 3.80 (m, 5H), 3.73 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.56 (d, *J* = 4.4 Hz, 1H), 3.45 (d, *J* = 3.7 Hz, 1H), 2.24 – 2.05 (m, 2H), 2.05 – 1.87 (m, 2H), 1.11 – 1.05 (m, 3H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.99 – 0.91 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 9.7, 10.5, 13.5, 13.6, 26.2, 26.3, 44.1, 45.4, 49.3, 49.7, 61.6, 61.7, 85.5, 88.9, 109.9, 110.0, 122.5, 122.7, 124.4, 124.9, 125.3, 125.4, 128.9, 129.0, 141.6, 141.7, 168.2, 168.7, 176.7, 177.0. HPLC-MS (ESI): t_r= 7.8 min, 7.9 min; $[M+H]^+$= 307.3 m/z, $[M+Na]^+$= 329.1 m/z, $[2M+Na]^+$= 635.5 m/z. Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.12): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.65; H, 5.91; N, 9.17. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 for 20 min, then up to 75:25 in 15 min, 75:25 up to 58 min; flow rate = 0.5 mL/min at rt. λ=230 nm. t_r(isomer A) = 21.9 min (major), 27.9 min (minor); t_r(isomer B) = 32.6 min (minor), 51.0 min (major).

(2*R*,3*S*)-1-ethyl 6-methyl 2-(1-(*tert*-butoxycarbonyl)-2-oxoindolin-3-yl)-3-nitrohexanedioate (*anti*-4d): mixture of two diastereoisomers. 83% yield (39 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.79 (m, 2H), 7.40 – 7.28 (m, 4H), 7.22 – 7.13 (m, 2H), 5.70 - 5.60 (m, 1H), 5.41 – 5.26 (m, 1H), 4.06 – 3.92 (m, 3H), 3.92 - 3.77 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.65 (d, *J* = 4.0 Hz, 1H), 3.53 (d, *J* = 2.4 Hz, 1H), 2.60 – 2.19 (m, 8H), 1.65 (s, 18H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ = 13.4, 13.5, 27.8, 27.9, 28.0, 28.1, 29.8, 30.3, 44.0, 45.4, 49.9, 50.7, 51.9, 61.9, 62.0, 83.5, 84.5, 84.7, 86.3, 115.1, 115.2, 123.6, 123.7, 124.4, 124.5, 124.6, 124.7, 129.1, 129.3, 140.4, 140.5, 148.9, 149.0, 167.7, 167.8, 171.8, 172.5, 172.8. HPLC-MS (ESI): t_r= 11.2 min; $[M+Na]^+$= 487.3 m/z. Anal. Calcd for $C_{22}H_{28}N_2O_9$ (464.18): C, 56.86; H, 6.08; N, 6.03. Found: C, 56.69; H, 6.08; N, 6.05.

(2*R*,3*S*)-1-ethyl 6-methyl 3-nitro-2-(2-oxoindolin-3-yl)hexanedioate: mixture of two diastereoisomers, gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 – 7.50 (bs, 2H), 7.34 – 7.20 (m, 4H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.90 – 6.81 (m, 2H), 5.68 - 5.59 (m, 1H), 5.41 – 5.29 (m, 1H), 4.05 – 3.92 (m, 4H), 3.86 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.74 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.59 (d, *J* = 4.4 Hz, 1H), 3.51 (d, *J* = 4.4 Hz, 1H), 2.54 – 2.39 (m, 6H), 2.28 – 2.20 (m, 2H), 1.03 – 0.94 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 13.7, 27.4, 27.7, 29.9, 30.4, 43.9, 44.9, 49.4, 49.7, 51.9, 61.8, 61.9, 83.5, 86.1, 109.6, 109.7, 122.6, 122.9, 124.5, 124.9, 125.2, 125.3, 129.0, 129.1, 141.2, 141.4, 168.0, 168.4, 171.9, 171.9, 175.7, 175.9. HPLC-MS (ESI): t_r= 7.3 min; $[M+H]^+$= 365.3 m/z, $[M+Na]^+$= 387.2 m/z, $[2M+Na]^+$= 751.5 m/z. Anal. Calcd for $C_{17}H_{20}N_2O_7$ (364.13): C, 56.04; H, 5.53; N, 7.69. Found: C, 55.83; H, 5.53; N, 7.68. CSP-HPLC: IC 80:20 *n*-Hex/IPA for 10 min, then up to 75:25 in 5 min, 75:25 for 25 min, then up to 65:35 in 15 min, 65:35 up to 67 min; flow rate = 0.5 mL/min at rt. λ=254 nm. t_r(isomer A) = 26.8 min (major), 33.3 min (minor); t_r(isomer B) = 34.5 min (minor), 63.1 min (major).

***Tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (*anti*-4e):** mixture of two diastereoisomers. 72% yield (34 mg), amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 – 7.78 (m, 2H), 7.39 – 7.24 (m, 12H), 7.22 – 7.13 (m, 4H), 5.86 (ddd, *J* = 4.4, 8.4, 10.4 Hz, 1H), 5.46 (dt, *J* = 2.8, 10.4 Hz, 1H), 3.98 – 3.84 (m, 6H), 3.67 (d, *J* = 4.0 Hz, 1H), 3.53 (d, *J* = 2.8 Hz, 1H), 3.45 (dd, *J* = 2.8, 14.4 Hz, 1H), 3.32 (dd, *J* = 10.8, 14.4 Hz, 1H), 3.28 – 3.16 (m, 2H), 1.66 (s, 9H), 1.65 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.4, 13.5, 28.0, 28.1, 39.0, 39.1, 44.2, 45.6, 49.8, 50.7, 61.9, 62.0, 84.6, 84.7, 85.7, 89.2, 115.1, 115.2, 123.0, 123.7, 123.8, 124.4, 124.6, 124.7, 127.7, 127.8, 128.8, 128.8, 128.9, 128.9, 129.0, 129.1, 129.3, 134.1, 135.1, 140.4, 140.5, 148.9, 168.0, 168.0, 172.4, 172.9. HPLC-MS (ESI): t_r= 12.1 min, 12.4 min; $[M+Na]^+$= 491.3 m/z, $[2M+Na]^+$= 959.6 m/z. Anal. Calcd for $C_{25}H_{28}N_2O_7$ (468.19): C, 64.09; H, 6.02; N, 5.98. Found: C, 64.02; H, 6.00; N, 6.00.

3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxo-4-phenylbutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 – 7.89 (bs, 2H), 7.40 – 7.21 (m, 13H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.13 – 7.00 (m, 2H), 6.96 – 6.82 (m, 2H), 5.88 – 5.79 (m, 1H), 5.53 (dt, *J* = 2.8, 10.0 Hz, 1H), 4.08 – 3.92 (m, 4H), 3.90 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.82 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.63 (d, *J* = 4.0 Hz, 1H), 3.52 (d, *J* = 4.0 Hz, 1H), 3.43 (dd, *J* = 3.6, 14.8 Hz, 1H), 3.35 (dd, *J* = 10.0, 14.4 Hz, 1H), 3.27 – 3.10 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 13.7, 38.5, 39.0, 44.3, 45.3, 49.3, 49.7, 61.8, 61.9, 85.8, 89.1, 110.0, 110.2, 122.6, 122.9, 124.5, 124.7, 124.8, 125.3, 127.6, 127.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.1, 134.4, 135.3, 141.4, 141.6, 168.3, 168.6, 176.3, 176.6. HPLC-MS (ESI): t_r= 9.1 min, 9.2 min; $[M+H]^+$= 369.4 m/z, $[M+Na]^+$= 391.2 m/z, $[2M+Na]^+$= 759.5 m/z. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.14): C, 65.21; H, 5.47; N, 7.60. Found: C, 65.15; H, 5.48; N, 7.59. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min, 70:30 for 5 min, then up to 1:1 in 5 min, 1:1 up to 76 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(isomer A) = 27.2 min (major), 45.7 min (minor); t_r(isomer B) = 39.8 min (minor), 70.0 min (major).

***Tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-2-methyl-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (5):** major diastereoisomer. 72% yield (29 mg), syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.0 (d, *J* = 6.8 Hz, 1H), 5.50 (q, *J* = 6.8 Hz, 1H), 4.41 – 4.30 (m, 2H), 4.23 (s, 1H), 1.96 (d, *J* = 7.2 Hz, 3H), 1.65 (s, 9H), 1.36 (t, *J* = 6.8 Hz, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.9, 15.8, 15.8, 28.1, 48.9, 51.4, 62.2, 85.1, 88.5, 115.0, 124.1, 124.7, 129.2, 129.7, 140.7, 148.7, 170.6, 172.7. HPLC-MS (ESI): t_r= 11.6 min; $[M+Na]^+$= 429.4 m/z. $[\alpha]_D^{25}$ = 19 (c = 0.48, CH_2Cl_2). Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.45; N, 6.91.

3-((2*R*,3*S*)-1-ethoxy-2-methyl-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: major diastereoisomer, syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (bs, 1H), 7.05 – 6.97 (m, 2H), 6.90 – 6.84 (m, 2H), 5.59 (q, *J* = 6.4 Hz, 1H), 4.40 – 4.31 (m, 2H), 4.12 (s, 1H), 1.95 (d, *J* = 6.4 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.9, 15.7, 15.8, 48.6, 50.7, 62.0, 88.2, 109.7, 123.0, 124.8, 129.0, 129.1, 141.3, 175.6, 178.5. HPLC-MS (ESI): t_r= 8.2 min; $[M+H]^+$= 307.3 m/z, $[M+Na]^+$= 329.1 m/z. $[\alpha]_D^{25}$ = 13 (c = 0.13, CH_2Cl_2). Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.12): C, 58.82; H, 5.92; N, 9.15. Found:

C, 58.58; H, 5.92; N, 9.16. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 up to 25 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(major isomer) = 14.5 min (major), 17.8 min (minor).

Synthesis of (*S*)-*tert*-butyl 3-((*R*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (6): (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **2c** (0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), then nitroethane **1b** (0.5 mmol) was added at 0°C. The mixture was stirred at the same temperature till complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), DCM (0.3 mL) was added and *N*-phenylmaleimide (0.2 mmol) was lastly added at 0°C. The conversion was monitored by TLC and ^{1}H-NMR till full conversion (1.5 h). The crude reaction mixture was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 81% yield (46 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.37 (m, 4H), 7.27 – 7.25 (m, 1H), 7.20 – 7.13 (m, 3H), 5.95 – 5.85 (m, 1H), 4.89 (d, *J* = 4.8 Hz, 1H), 3.87 – 3.81 (m, 3H), 2.92 (dd, *J* = 9.2, 18.0 Hz, 1H), 2.11 (dd, *J* = 5.2, 18.0 Hz, 1H), 1.69 (s, 9H), 1.64 (d, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 18.6, 28.1, 30.7, 42.0, 52.0, 52.8, 61.6, 79.0, 85.4, 115.7, 123.8, 124.4, 125.1, 126.4, 129.0, 129.2, 130.7, 131.1, 140.7, 144.6, 148.4, 168.2, 173.1, 174.4, 174.7. HPLC-MS (ESI): t_r= 10.9 min; $[M\text{-Boc}+H]^+$= 466.4 m/z, $[M+H_2O]^+$= 583.4 m/z. $[\alpha]_D^{25}$ = 107 (c = 0.71, CH_2Cl_2). Anal. Calcd for $C_{29}H_{31}N_3O_9$ (565.21): C, 61.59; H, 5.52; N, 7.43. Found: C, 61.49; H, 5.54; N, 7.40. The absolute configuration of the stereocenters generated in the addition of *N*-phenylmaleimide was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[20]

Synthesis of (*R*)-*tert*-butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (7): (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **2c** (0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), then nitroethane **1b** (0.5 mmol) was added at 0°C. The mixture was stirred at the same temperature till complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), toluene (0.6 mL) was added and 1,1-bis(benzenesulfonyl)-ethylene

(0.2 mmol) was lastly added at -10°C. The conversion was monitored by TLC and ^{1}H-NMR till full conversion (overnight). The reaction was quenched with 2 mL of HCl (1N) at 0°C and extracted with ethyl acetate (3 X 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 8/2). 68% yield (48 mg), syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 – 7.93(m, 3H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.73 – 7.66 (m, 2H), 7.61 – 7.50 (m, 5H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.24 (m, 1H), 5.16 – 5.09 (m, 1H), 4.41 (dd, *J* = 3.2, 6.0 Hz, 1H), 4.13 (d, *J* = 5.2 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.94 (dd, *J* = 5.6, 16.0 Hz, 1H), 2.85 (dd, *J* = 2.8, 16.0 Hz, 1H), 1.64 (s, 9H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 17.4, 28.1, 29.6, 50.9, 55.9, 61.8, 79.2, 79.4, 84.8, 116.0, 124.7, 125.6, 126.2, 128.9, 129.0, 129.7, 130.1, 131.0, 134.5, 134.9, 135.6, 137.7, 140.7, 148.8, 168.0, 174.3. HPLC-MS (ESI): t_r= 11.9 min; $[M\text{-}Boc+H]^+$= 601.3 m/z, $[M+H_2O]^+$= 718.4 m/z. $[\alpha]_D^{25}$ = 8 (c = 0.54, CH_2Cl_2). Anal. Calcd for $C_{33}H_{36}N_2O_{11}S_2$ (700.18): C, 56.56; H, 5.18; N, 4.00. Found: C, 56.38; H, 5.17; N, 4.01. The absolute configuration of the stereocenter generated in the addition of 1,1-bis(benzenesulfonyl)-ethylene was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[21b]

Synthesis of (*R*)-*tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-3-((*S*)-2-nitro-1-phenylethyl)-2-oxoindoline-1-carboxylate (8): (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **2c** (0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), then nitroethane **1b** (0.5 mmol) was added at 0°C. The mixture was stirred at the same temperature till complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), DCM (0.3 mL) was added and *trans*-β-nitrostyrene (0.2 mmol) was lastly added at -40°C. The conversion was monitored by TLC and ^{1}H-NMR (90% of conversion after 24 hours). The reaction was quenched with 2 mL of HCl (1N) and extracted with ethyl acetate (3 X 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by flash-chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 76% yield (41 mg), syrup. Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 – 7.82 (m, 1H), 7.65 – 7.41 (m, 3H), 7.23 – 7.15 (m, 2H), 7.10 – 6.97 (m, 2H), 6.86 (d, *J* = 7.6

Hz, 1H), 5.37 – 5.23 (m, 2H), 4.52 – 4.36 (m, 3H), 4.17 (dd, *J* = 3.2, 10.4 Hz, 1H), 4.13 (d, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.63 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 17.8, 28.0, 50.0, 51.9, 55.8, 62.9, 75.1, 81.6, 85.1, 114.8, 115.2, 123.7, 124.4, 124.6, 126.3, 127.9, 128.4, 129.1, 129.8, 132.8, 139.8, 147.8, 168.9, 174.2. HPLC-MS (ESI): t_r= 12.1 min; $[M+Na]^+$= 564.3 m/z, $[2M+Na]^+$= 1105.7 m/z. $[\alpha]_D^{25}$ = 16 (c = 0.91, CH_2Cl_2). Anal. Calcd for $C_{27}H_{31}N_3O_9$ (541.21): C, 59.88; H, 5.77; N, 7.76. Found: C, 59.65; H, 5.77; N, 7.77. The absolute configuration of the stereocenters generated in the addition of *trans*-β-nitrostyrene was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[22b]

Synthesis of (*S*)-*tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxo-3-((*R*)-3-oxocyclohexyl)indoline-1-carboxylate (9): (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **2c** (0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), then nitroethane **1b** (0.5 mmol) was added at 0°C. The mixture was stirred at the same temperature till complete conversion (about 4.5 hours). The reaction was quenched with 2 mL of HCl (1N) at 0°C and extracted with DCM (3 X 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure (without heating) and the crude mixture was directly used in the next transformation. Catalyst **X**·3HCl (10 mol %), triethylamine (30 mol %) and benzoic acid (20 mol %) were dissolved in toluene (0.3 mL). After stirring at room temperature for 10 min, 2-cyclohexen-1-one (0.12 mmol) was added followed by the addition of crude **4b** dissolved in toluene (0.3 mL). The mixture was stirred at room temperature for 48 hours. The crude reaction was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15). 65% yield (32 mg), gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 6.4 Hz, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 5.46 – 5.39 (m, 1H), 4.16 (d, *J* = 5.2 Hz, 1H), 3.95 – 3.87 (m, 2H), 2.45 – 2.33 (m, 3H), 2.10 – 2.03 (m, 2H), 1.90 – 1.78 (m, 2H), 1.66 (s, 9H), 1.58 – 1.46 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 18.2, 24.0, 25.6, 28.1, 40.7, 42.3, 43.1, 52.7, 54.8, 61.7, 79.4, 85.0, 115.1, 124.4, 124.8, 126.1, 129.6, 140.7, 148.6, 168.2, 175.1, 208.7. HPLC-MS (ESI): t_r= 10.7 min; $[M\text{-}Boc+H]^+$= 389.3 m/z, $[M+H_2O]^+$= 506.5 m/z, $[2M+Na]^+$= 999.8 m/z. $[\alpha]_D^{25}$ = -13 (c = 1.02, CH_2Cl_2). Anal. Calcd for $C_{25}H_{32}N_2O_8$ (488.22): C, 61.46;

H, 6.60; N, 5.73. Found: C, 61.35; H, 6.59; N, 5.75. The absolute configuration of the stereocenters generated in the addition of 2-cyclohexen-1-one was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[10p]

Synthesis of (*S*)-*tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxo-3-((*R*)-4-oxobutan-2-yl)indoline-1-carboxylate (10): To a solution of catalyst **XI** (20 mol %) and crude product **4b** (0.1 mmol, prepared as described for product **9**) in DCM (1 mL) at -40°C, benzoic acid (20 mol %) and then crotonaldehyde (0.15 mmol) were added. After stirring at the same temperature for 24 h, the reaction was quenched with 2 mL of HCl (1N) at 0°C and extracted with DCM (3 X 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 71% yield (33 mg), gum. Mixture of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.62 (d, *J* = 2.0 Hz, 1H), 9.61 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.32 (m, 4H), 7.20 (t, *J* = 7.6 Hz, 2H), 5.50 – 5.43 (m, 1H), 5.30 – 5.23 (m, 1H), 4.13 (d, *J* = 5.6 Hz, 1H), 4.12 (d, *J* = 5.6 Hz, 1H), 3.99 – 3.88 (m, 4H), 2.86 – 2.77 (m, 2H), 2.65 (d, *J* = 16.4 Hz, 1H), 2.53 (d, *J* = 17.6 Hz, 1H), 2.23 (ddd, *J* = 2.8, 10.8, 14.0 Hz, 1H), 2.08 (ddd, *J* = 2.4, 10.4, 12.4 Hz, 1H), 1.66 (s, 18H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.6, 13.7, 15.0, 18.1, 28.1, 32.6, 33.2, 45.4, 45.7, 53.0, 53.0, 54.7, 61.7, 61.8, 79.3, 79.9, 84.8, 84.9, 115.0, 115.1, 124.3, 124.4, 124.5, 124.7, 126.3, 126.3, 129.5, 140.3, 140.6, 148.6, 148.7, 168.1, 168.3, 175.5, 175.7, 199.5, 200.0. HPLC-MS (ESI): t_r= 10.7 min; $[M\text{-}Boc+H]^+$= 363.4 m/z, $[M+H_2O]^+$= 480.4 m/z, $[M+Na]^+$= 485.3 m/z, $[2M+Na]^+$= 947.8 m/z. Anal. Calcd for $C_{23}H_{30}N_2O_8$ (462.20): C, 59.73; H, 6.54; N, 6.06. Found: C, 59.68; H, 6.52; N, 6.08. The absolute configuration of the stereocenters generated in the addition of crotonaldehyde was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[8c]

Synthesis of *tert*-butyl 3-((2*R*,3*S*)-3-amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (11a + 11b): Compound **4b** (0.38 mmol, 149 mg) was dissolved in EtOH (5.5 mL), Raney Nickel (6 drops of the commercially available suspension in water) was

added and the reaction mixture was stirred at rt under H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure and the diastereomeric mixture of **11a** and **11b** (dr = 54:46) was obtained pure. 95% yield (131 mg), oil. Mixture of two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 2H), 7.31 – 7.22 (m, 4H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.14 – 7.09 (m, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.43 (bs, 2H), 4.29 (d, *J* = 10.8 Hz, 2H), 4.24 – 4.16 (m, 2H), 3.98 – 3.84 (m, 2H), 3.28 (dd, *J* = 8.8, 10.0 Hz, 1H), 3.09 (dd, *J* = 8.8, 10.0 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.6, 14.1, 21.3, 21.6, 28.4, 45.2, 47.4, 50.4, 51.0, 52.6, 54.4, 61.3, 61.8, 80.1, 80.3, 124.5, 124.7, 125.0, 126.7, 127.7, 128.1, 128.2, 137.1, 137.2, 151.0, 153.8, 169.5, 170.0, 171.8, 175.2. HPLC-MS (ESI): t_r= 7.4 min, 8.0 min; $[M\text{-}Boc+H]^+$= 263.3 m/z, $[M+H]^+$= 363.4 m/z, $[2M+Na]^+$= 747.7 m/z. Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.84; H, 7.22; N, 7.72.

Procedure for the stereoconvergent epimerization to (*R*)-*tert*-butyl 3-((2*R*,3*S*)-3-amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (11a): The diastereomeric mixture of **11a** and **11b** (dr = 54:46) (0.1 mmol, 36.2 mg) was dissolved in acetone (0.6 mL) and K_2CO_3 (0.2 mmol) was added. The reaction mixture was stirred at 50°C for 24 h and the conversion was monitored by ^{1}H-NMR. After completion, the solvent was removed, the residue was dissolved in water (3 mL) and extracted with DCM (3 X 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and compound **11a** was obtained pure. 95% yield, 34 mg, oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (bs, 1H), 7.31 – 7.27 (m, 2H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.22 (bs, 1H), 4.28 (d, *J* = 10.4 Hz, 1H), 4.24 – 4.16 (m, 2H), 3.97 – 3.90 (m, 1H), 3.09 (dd, *J* = 10.8, 8.0 Hz, 1H), 1.52 (s, 9H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 21.6, 28.4, 47.4, 51.0, 54.3, 61.8, 80.1, 124.6, 125.0, 127.6, 128.2, 128.4, 137.2, 153.7, 171.8, 175.2. HPLC-MS (ESI): t_r= 8.0 min; $[M\text{-}Boc+H]^+$= 263.1 m/z, $[M+H]^+$= 363.2 m/z, $[2M+Na]^+$= 747.2 m/z. $[\alpha]_D^{25}$ = 34 (c = 0.99, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.77; H, 7.24; N, 7.76.

Synthesis of 12a + 12b: Compound **4b** (0.2 mmol, 78.5 mg) was dissolved in MeOH (3.5 mL) and Pd on C (20 % w/w) was added. The reaction mixture was stirred at rt under

H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1/1). 90% yield, 68 mg, oil.

(*R*)-*tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-(hydroxyamino)-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (12a): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (bs, 1H), 7.28 – 7.23 (m, 1H), 7.15 – 7.06 (m, 1H), 7.02 – 6.97 (m, 2H), 4.44 – 4.37 (m, 1H), 4.27 (d, *J* = 9.6 Hz, 1H), 3.94 – 3.76 (m, 2H), 3.20 (dd, *J* = 10.0, 8.4 Hz, 1H), 1.54 (s, 9H), 1.44 (d, *J* = 5.6 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 13.5, 18.3, 28.4, 42.2, 48.8, 55.7, 61.5, 80.5, 118.9, 125.0, 127.3, 128.5, 129.7, 136.9, 153.4, 168.3, 169.4. HPLC-MS (ESI): t_r= 7.0 min; $[M\text{-}Boc+H]^+$= 279.4 m/z, $[2M+Na]^+$= 779.6 m/z. $[\alpha]_D^{25}$ = -5 (c = 0.67, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_6$ (378.18): C, 60.30; H, 6.93; N, 7.40. Found: C, 60.28; H, 6.91; N, 7.39.

(*S*)-*tert*-butyl 3-((2*R*,3*S*)-1-ethoxy-3-(hydroxyamino)-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (12b): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (bs, 1H), 7.32 – 7.27 (m, 1H), 7.18 – 6.99 (m, 3H), 4.31 – 4.18 (m, 3H), 3.97 – 3.91 (m, 1H), 2.87 (t, *J* = 8.4 Hz, 1H), 1.53 (s, 9H), 1.47 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 19.0, 28.4, 50.5, 51.3, 56.6, 62.1, 80.3, 118.6, 124.6, 128.2, 128.4, 129.7, 137.2, 153.7, 169.3, 171.4. HPLC-MS (ESI): t_r= 7.6 min; $[M\text{-}Boc+H]^+$= 279.2 m/z, $[2M+Na]^+$= 779.6 m/z. $[\alpha]_D^{25}$ = 8 (c = 0.93, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_6$ (378.18): C, 60.30; H, 6.93; N, 7.40. Found: C, 60.10; H, 6.94; N, 7.39.

Procedure for the stereoconvergent epimerization to 12a: The diastereomeric mixture of **12a** and **12b** (dr = 60:40) (0.1 mmol, 37.8 mg) was dissolved in EtOH (0.7 mL) and $NaHCO_3$ (10 drops of a saturated solution) was added. The reaction mixture was stirred at rt for 48 h and the conversion was monitored by ^{1}H-NMR. After completion, water (3 mL) was added to the mixture and it was extracted with ethyl acetate (3 X 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and compound **12a** was obtained pure (90% yield, 34 mg, oil).

Synthesis of ((2*S*,3*R*,3a*R*)-2,8-dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3-yl)methanol (13): Compound *anti*-**4b** (0.2 mmol, 78.5 mg) was dissolved in EtOH (3 mL), Raney Nickel (4 drops of the commercially available suspension in water) was

added and the reaction mixture was stirred at rt under H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure and the diastereomeric mixture of **11a** and **11b** (dr = 54:46) was obtained pure. The crude mixture was dissolved in acetone (1.5 mL) and K_2CO_3 (0.4 mmol) was added. The reaction mixture was stirred at 50°C for 24 h and the conversion was monitored by ^{1}H-NMR. After completion, the solvent was removed, the residue was dissolved in water (5 mL) and extracted with DCM (3 X 6 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product **11a** was dissolved in THF (5 mL). $LiAlH_4$ (2 mmol) was added and the mixture was heated at 75°C for 2 h. It was cooled to room temperature, quenched with ethyl acetate (6 mL) and then H_2O (1.2 mL). The resulting mixture was filtered through celite and washed with ethyl acetate and MeOH. The filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (DCM/MeOH 20/1) providing compound **13**. 72% yield over 3 steps, 31 mg, amorphous solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.14 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.70 – 6.66 (m, 2H), 3.72 (d, *J* = 8.0 Hz, 1H), 3.64 (dd, *J* = 12.0, 4.0 Hz, 1H) 3.60 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.59 – 3.53 (m, 1H), 2.80 (s, 3H), 2.10 – 2.04 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ = 21.8, 30.8, 47.2, 52.6, 54.6, 62.4, 111.7, 118.1, 125.3, 128.8, 129.2, 149.3, 179.7. HPLC-MS (ESI): t_r= 2.2 min; $[M+H]^+$= 217.1 m/z, $[M+H_2O+H]^+$= 235.3 m/z, $[M+Na]^+$= 239.1 m/z. $[\alpha]_D^{25}$ = -14 (c = 0.45, MeOH). Anal. Calcd for $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.43; N, 12.99.

Synthesis of *tert*-butyl 3-((2*R*,3*R*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (*syn*-4b): Compound *anti*-**4b** (0.1 mmol, 39 mg) was dissolved in DCM (0.4 mL) and DBU (1,5-diazabiciclo[5.4.0]undec-5-ene, 30 mol %) was added. The reaction mixture was stirred at rt for 24 h and the conversion was monitored by ^{1}H-NMR. The solvent was evaporated under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1). 70% yield, 27.5 mg, gum. Mixture of two diastereoisomers (dr = 70:30). ^{1}H NMR (400 MHz, CDCl3) δ = 7.89 – 7.82 (m, 2H), 7.38 – 7.27 (m, 3H), 7.21 – 7.12 (m, 3H), 5.33 – 5.23 (m, 2H), 4.13 (dd, *J* = 2.4, 10.0 Hz, 1H), 4.05 (q, *J* = 6.8 Hz, 2H), 3.96 – 3.85 (m, 4H), 3.81 (s, 1H), 1.75 (d, *J* = 7.2 Hz, 3H), 1.67 – 1.64 (m, 21H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.91 (t,

J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.4, 13.6, 17.9, 18.4, 28.1, 44.4, 44.6, 49.1, 49.4, 61.8, 62.0, 80.9, 81.6, 84.8, 84.9, 115.3, 115.4, 123.5, 123.6, 123.7, 124.6, 124.6, 129.2, 129.4, 140.2, 140.5, 148.9, 168.6, 169.6, 173.0, 173.2. HPLC-MS (ESI): t_r= 10.3 min, 10.4 min; $[M\text{-}Boc+H]^+$= 293.3 m/z, $[M+H_2O]^+$= 410.3 m/z, $[M+Na]^+$= 415.3 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 58.06; H, 6.18; N, 7.15. To check the optical purity of compound *syn*-**4b**, it was deprotected as previously described and injected in CSP-HPLC.

3-((2*R*,3*R*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: amorphous solid, mixture of two diastereoisomers (dr = 76:24), the signals of the major one have been described. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (bs, 1H), 7.30 – 7.25 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.25 – 5.17 (m, 1H), 4.11 (q, *J* = 6.8 Hz, 2H), 3.91 (dd, *J* = 2.8, 10.0 Hz, 1H), 3.87 (d, *J* = 2.8 Hz, 1H), 1.59 (d, *J* = 6.4 Hz, 3H), 1.13, (t, *J* = 7.2 Hz, 3H).). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 17.8, 44.3, 48.4, 61.9, 81.5, 110.0, 122.9, 124.7, 124.9, 129.1, 140.9, 170.3, 176.0. HPLC-MS (ESI): t_r= 7.0 min; $[M+H]^+$= 293.3 m/z, $[M+Na]^+$= 315.2 m/z, $[2M+Na]^+$= 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.35; H, 5.51; N, 9.62. CSP-HPLC: IC 90:10 *n*-Hex/IPA for 10 min, then up to 80:20 in 5 min, 80:20 for 20 min, then up to 75:25 in 15 min, 75:25 up to 47 min; flow rate = 0.5 mL/min at rt. λ=214 nm. t_r(major isomer) = 25.4 min (minor), 34.0 min (major); t_r(minor isomer) = 28.6 min (major), 42.7 min (minor).

Synthesis of ((2*R*,3*R*,3a*S*)-2,8-dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3-yl)methanol (14): Compound *syn*-**4b** (0.1 mmol, 39 mg) was dissolved in EtOH (2 mL), Raney Nickel (3 drops of the commercially available suspension in water) was added and the reaction mixture was stirred at rt under H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure and the β-amino oxindole **14a** was obtained pure as an oil. The crude **14a** was dissolved in THF (3 mL), $LiAlH_4$ (1 mmol) was added and the mixture was heated at 75°C for 2 h. It was cooled to room temperature, quenched with ethyl acetate (4 mL) and then H_2O (0.8 mL). The resulting mixture was filtered through celite and washed with ethyl acetate and MeOH. The filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel

(DCM/MeOH 20/1) providing compound **14.** 76% yield over 2 steps, 16.5 mg, amorphous solid.

(*S*)-*Tert*-butyl 3-((2*R*,3*R*)-3-amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (14a): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 1H), 7.32 – 7.23 (m, 2H), 7.15 – 7.08 (m, 2H), 5.88 (bs, 1H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.28 – 4.13 (m, 3H), 3.64 (dd, *J* = 8.8, 9.2 Hz, 1H), 1.54 (s, 9H), 1.30 – 1.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 18.0, 28.4, 43.5, 49.0, 51.7, 61.6, 80.0, 124.6, 127.6, 128.0, 128.1, 128.5, 137.4, 153.7, 171.2, 176.2. HPLC-MS (ESI): t_r= 7.7 min; $[M\text{-Boc}+H]^+$= 263.3 m/z, $[M+H]^+$= 363.4 m/z. $[\alpha]_D^{25}$ = 19 (c = 1.69, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.77; H, 7.21; N, 7.72.

((2*R*,3*R*,3a*S*)-2,8-dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3-yl)methanol (14): ^{1}H NMR (400 MHz, CD_3OD) δ = 7.14 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.72 – 6.65 (m, 2H), 3.95 – 3.88 (m, 1H), 3.75 (dd, *J* = 7.6, 10.8 Hz, 1H) 3.66 (d, *J* = 6.4 Hz, 1H), 3.56 (dd, *J* = 7.6, 10.4 Hz, 1H), 2.81 (s, 3H), 2.54 – 2.47 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (50 MHz, CD_3OD) δ = 16.0, 30.8, 47.0, 51.3, 60.8, 111.6, 117.9, 124.0, 128.0, 129.2, 149.3, 180.1. HPLC-MS (ESI): t_r= 2.1 min; $[M+H_2O+H]^+$= 235.3 m/z, $[2M+Na]^+$= 455.5 m/z. $[\alpha]_D^{25}$ = 15 (c = 0.15, MeOH). Anal. Calcd for $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.45; N, 13.00.

General procedure for the organocatalysed spirocyclization.

The 3-ylidene oxindole (0.1 mmol) was added to a solution of catalyst (10 or 20 mol%) in DCM (0.15 mL), then the nitrocompound (0.12 or 0.2 mmol) was added at room temperature. The mixture was stirred at the same temperature and the conversion was monitored by TLC and ^{1}H NMR. The crude mixture was directly purified by flash chromatography on silica gel (cyclohexane/diethyl ether 9:1).

Ethyl 1'-benzyl-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-2-carboxylate (16b,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.39 (m, 2H), 7.38 – 7.21 (m, 5H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 5.26 (dt, *J* = 12.2, 4.7 Hz, 1H), 5.09 (d, *J* = 15.3 Hz, 1H), 4.79 (d, *J* = 15.0 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.94 (d, *J* = 11.7 Hz, 1H), 3.67 (q, *J* = 7.1 Hz, 2H), 2.79 – 2.59 (m, 2H), 2.25 – 2.02 (m, 2H), 1.87 (dd, *J* = 16.0, 2.8 Hz, 1H), 1.80 – 1.63 (m, 1H), 1.55 – 1.45 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.67 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 171.0, 168.3, 143.4, 135.6, 129.4, 128.8, 128.1, 127.9, 125.9, 125.2, 122.6, 109.6, 82.3, 61.4, 60.7, 53.9, 49.9, 44.7, 40.1,

34.7, 30.7, 25.8, 14.1, 13.4. HPLC-MS (ESI) t_r = 10.7 min; $[M+H]^+$ = 495.4 *m/z*, $[2M+Na]^+$ = 1011.7 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 20 min; flow rate 0.7 mL/min at 40°C; λ 210 nm; t_r = 63.3 min (minor), t_r = 65.2 min (major).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.8, 1H), 7.25 (d, *J* = 6.3 Hz, 1H), 7.18 (t, *J* = 7.5, 1H), 5.23 (dt, *J* = 12.3, 4.7 Hz, 1H), 4.13 – 3.99 (m, 2H), 3.95 (d, *J* = 11.7 Hz, 1H), 3.76 (q, *J* = 7.2, 2H), 2.78 – 2.66 (m, 1H), 2.67 – 2.57 (m, 1H), 2.23 – 2.02 (m, 2H), 1.97 (dd, *J* = 16.1, 3.0 Hz, 1H), 1.68 (s, 9H), 1.56 – 1.46 (m, 2H), 1.20 (t, *J* = 7.1, 3H), 0.87 (t, *J* =7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.5, 170.7, 168.2, 148.8, 140.1, 129.7, 125.0, 124.61, 124.58, 115.6, 85.0, 81.9, 61.7, 60.8, 54.4, 50.3, 40.6, 35.1, 30.6, 28.1, 25.3, 14.1, 13.3. HPLC-MS (ESI) t_r = 11.0 min; $[M+Na]^+$ = 527.5 *m/z*, $[2M+Na]^+$ = 1031.8 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 57.5 min (minor), t_r = 78.7 min (major).

Ethyl 1'-acetyl-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-2-carboxylate (16o,a): ^{1}H NMR (400 MHz, CDCl3) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.34 (m, 1H), 7.34 – 7.15 (m, 2H), 5.24 (dt, J = 12.3, 4.7 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.82 – 3.67 (m, 2H), 2.77 (s, 3H), 2.74 – 2.58 (m, 2H), 2.26 – 2.07 (m, 2H), 1.86 (dd, *J* = 16.0, 3.2 Hz, 1H), 1.63 – 1.50 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 214 nm; t_r = 31.2 min (major), t_r = 41.5 min (minor).

1'-(*tert*-butyl) 2-ethyl 5'-chloro-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16d,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 1H), 7.37 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 5.23 – 5.10 (m, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.94 (d, *J* = 11.8 Hz, 1H), 3.87 – 3.72 (m, 2H), 2.80 – 2.68 (m, 1H), 2.69 – 2.56 (m, 1H), 2.24 – 2.01 (m, 2H), 1.95 (dd, *J* = 16.1, 3.1 Hz, 1H), 1.67 (s, 9H), 1.61 – 1.48 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 170.4, 168.0, 148.6, 138.7, 130.1, 129.8, 126.9, 124.7, 116.8, 85.5, 81.6, 61.9, 60.9, 54.4, 50.1, 40.6, 35.0, 30.5, 28.1, 25.3, 14.1, 13.3.

HPLC-MS (ESI) t_r = 11.5 min; $[M+Na]^+$ = 561.0 *m/z*, $[2M+Na]^+$ = 1099.2 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min; flow rate 0.5 mL/min at 40°C; λ 210 nm; t_r = 47.5 min (minor), t_r = 50.2 min (major).

1'-(*tert*-butyl) 2-ethyl 6'-chloro-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16f,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 1H), 7.22 – 7.13 (m, 2H), 5.23 – 5.10 (m, 1H), 4.13 – 4.01 (m, 2H), 3.93 (d, *J* = 11.6 Hz, 1H), 3.80 (q, *J* = 7.3 Hz, 2H), 2.77 – 2.66 (m, 1H), 2.67 – 2.56 (m, 1H), 2.22 – 2.00 (m, 2H), 1.94 (dd, *J* = 15.9, 2.4 Hz, 1H), 1.68 (s, 9H), 1.63 – 1.47 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 170.5, 168.1, 148.5, 141.1, 135.8, 125.4, 124.6, 123.4, 116.4, 85.6, 81.7, 61.9, 60.9, 54.2, 50.2, 40.6, 35.0, 30.5, 28.0, 25.3, 14.1, 13.4. HPLC-MS (ESI) t_r = 12.1 min; $[M+Na]^+$ = 561.2 *m/z*, $[2M+Na]^+$ = 1099.7 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 41.5 min (minor), t_r = 57.2 min (major).

1'-(*tert*-butyl) 2-ethyl 7'-chloro-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16p,a): ^{1}H NMR (400 MHz, CDCl3) δ 7.38 (d, *J* = 7.0 Hz, 1H), 7.23 – 7.04 (m, 2H), 5.20 (dt, *J* = 12.3, 4.7 Hz, 1H), 4.15 – 3.99 (m, 2H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 2.78 – 2.66 (m, 1H), 2.66 – 2.55 (m, 1H), 2.39 – 2.25 (m, 1H), 2.17 – 1.96 (m, 2H), 1.66 (s, 9H), 1.61 – 1.42 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 40.0 min (major), t_r = 42.8 min (minor).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-5'-methoxy-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16h,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 5.19 (dt, *J* = 12.3, 4.7 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.94 (d, *J* = 11.7 Hz, 1H), 3.86 – 3.74 (m, 5H), 2.75 – 2.65 (m, 1H), 2.66 – 2.57 (m, 1H), 2.20 – 2.01 (m, 2H), 1.96 (dd, *J* = 16.1, 3.0 Hz, 1H), 1.67 (s, 9H), 1.61 – 1.49 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 170.7, 168.2, 156.5, 148.8, 133.3, 126.3, 116.3, 112.9, 112.3, 84.8, 81.8, 61.7, 60.8, 55.7, 54.5, 50.1, 40.5, 35.0, 30.5, 28.1, 25.2,

14.1, 13.3. HPLC-MS (ESI) t_r = 10.9 min; $[M\text{-}Boc]^+$ = 435.4 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 210 nm; t_r = 48.0 min (minor), t_r = 77.0 min (major). $[\alpha]_D^{20}$ = +24.3° (*c* = 0.55, $CHCl_3$).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-5'-methyl-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16q,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 5.23 (dt, *J* = 12.3, 4.7 Hz, 1H), 4.15 – 4.00 (m, 2H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 2.78 – 2.66 (m, 1H), 2.67 – 2.55 (m, 1H), 2.37 (s, 3H), 2.20 – 2.01 (m, 2H), 1.96 (dd, *J* = 16.1, 3.0 Hz, 1H), 1.67 (s, 9H), 1.59 – 1.46 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 170.8, 168.3, 148.8, 137.7, 134.3, 130.2, 125.1, 125.0, 115.3, 84.8, 81.9, 61.7, 60.8, 54.4, 50.2, 40.6, 35.1, 30.6, 28.1, 25.3, 21.3, 14.1, 13.3. HPLC-MS (ESI) t_r = 11.5 min; $[M+Na]^+$ = 541.4 *m/z*, $[2M+Na]^+$ = 1059.9 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 60.1 min (minor), t_r = 73.8 min (major). $[\alpha]_D^{20}$ = +19.8° (*c* = 1.08, $CHCl_3$).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxo-5'-(trifluoromethoxy)spiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16r,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 1H), 7.33 – 7.16 (m, 1H), 7.13 – 7.03 (m, 1H), 5.14 (dt, *J* = 12.5, 4.8 Hz, 1H), 4.18 – 3.99 (m, 2H), 3.96 (d, *J* = 11.8 Hz, 1H), 3.79 (q, *J* = 7.1 Hz, 2H), 2.79 – 2.70 (m, 1H), 2.70 – 2.57 (m, 1H), 2.26 – 2.01 (m, 2H), 1.95 (dd, *J* = 16.1, 3.1 Hz, 1H), 1.67 (s, 9H), 1.63 – 1.47 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 170.4, 167.9, 148.6, 145.5, 138.8, 126.8, 122.3, 120.4 (q, *J* = 256 Hz), 118.1, 116.7, 85.6, 81.6, 61.9, 61.0, 54.5, 50.2, 40.5, 35.0, 30.5, 28.1, 25.4, 14.1, 13.3. HPLC-MS (ESI) t_r = 12.0 min; $[M+Na]^+$ = 611.3 *m/z*, $[2M+Na]^+$ = 1199.7 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 25.9 min (minor), t_r = 48.8 min (major). $[\alpha]_D^{20}$ = +15.5° (*c* = 0.88, $CHCl_3$).

2-benzyl 1'-(*tert*-butyl) 6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16i,a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.16 (m, 6H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.97 – 6.90 (m, 1H), 5.25 (dt, *J* = 12.4, 4.8 Hz, 1H), 4.84 – 4.67 (m, 2H), 4.16 – 3.93 (m, 3H), 2.79 – 2.66 (m, 1H), 2.66 – 2.54

(m, 1H), 2.21 – 1.99 (m, 2H), 1.91 (dd, *J* = 16.1, 3.1 Hz, 1H), 1.73 – 1.44 (m, 11H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 170.7, 168.3, 148.5, 139.9, 134.3, 129.6, 128.5, 128.33, 128.30, 124.6, 124.38, 124.36, 115.7, 84.8, 81.9, 67.4, 60.8, 54.3, 50.1, 40.8, 34.9, 30.6, 28.1, 25.3, 14.1. HPLC-MS (ESI) t_r = 12.0 min; $[M+Na]^+$ = 589.4 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 210 nm; t_r = 42.0 min (minor), t_r = 69.6 min (major). $[\alpha]_D^{20}$ = +11.5° (*c* = 0.72, $CHCl_3$).

***tert*-butyl 2-benzoyl-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (16t,a):** ^{1}H NMR (400 MHz, CDCl3) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.18 (m, 8H), 5.51 (dt, *J* = 12.1, 4.4 Hz, 1H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.05 (q, *J* = 6.7 Hz, 2H), 2.93 – 2.82 (m, 1H), 2.83 – 2.71 (m, 1H), 2.39 – 2.12 (m, 2H), 1.89 – 1.77 (m, 1H), 1.63 – 1.50 (m, 11H), 1.19 (t, *J* = 7.1 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 41.3 min (major), t_r = 60.0 min (minor).

***tert*-butyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2-(4-nitrophenyl)-2'-oxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (16l,a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (bt, *J* = 6.8 Hz, 2H), 7.57 (t, *J* = 6.8 Hz, 2H), 7.43 – 7.26 (m, 2H), 6.88 (bs, 2H), 5.37 (dt, *J* = 12.2, 4.2 Hz, 1H), 4.15 – 4.03 (m, 2H), 4.00 (d, *J* = 12.2 Hz, 1H), 3.01 – 2.85 (m, 1H), 2.80 – 2.67 (m, 1H), 2.49 – 2.31 (m, 2H), 2.10 – 1.84 (m, 2H), 1.79 – 1.65 (m, 1H), 1.50 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.8, 170.7, 147.63, 147.55, 140.5, 140.1, 129.9, 124.8, 124.7, 124.6, 123.0, 122.9, 115.7, 85.2, 84.8, 60.8, 57.9, 53.5, 39.1, 36.3, 31.2, 27.9, 25.8, 14.1. HPLC-MS (ESI) t_r = 11.4 min; $[M+Na]^+$ = 576.3 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 40.4 min (minor), t_r = 42.1 min (major).

***tert*-butyl 2-cyano-6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (16u,a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.38 – 7.27 (m, 2H), 5.03 (dt, *J* = 12.2, 4.4 Hz, 1H), 4.15 – 3.98 (m, 2H), 3.88 (d, *J* = 11.9 Hz, 1H), 2.81 – 2.67 (m, 1H), 2.68 – 2.55 (m, 1H), 2.33 – 2.08 (m, 2H), 1.95 (dd, *J* = 16.2, 3.2 Hz, 1H), 1.89 – 1.72 (m, 1H), 1.72 – 1.56 (m, 10H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 170.2, 148.1, 140.4, 130.7, 125.1, 124.4, 123.7, 116.5, 114.3, 85.9, 82.1, 61.0, 54.7, 39.7, 38.8, 35.4, 30.3, 28.0, 25.0,

14.1. HPLC-MS (ESI) t_r = 10.1 min; $[M+Na]^+$ = 480.0 *m/z*, $[2M+Na]^+$ = 937.4 *m/z*. CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min, 80:20 in 8 min, then up to 1:1; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 31.0 min (minor), t_r = 36.3 min (major).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-2-methyl-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16n,a): ^{1}H NMR (400 MHz, CDCl3) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.93 (dd, *J* = 13.4, 4.9 Hz, 1H), 4.42 – 4.31 (m, 2H), 4.12 – 3.95 (m, 2H), 3.59 – 3.46 (m, 1H), 3.26 (dq, *J* = 13.3, 5.5 Hz, 1H), 2.54 – 2.39 (m, 1H), 1.93 – 1.72 (m, 2H), 1.64 (s, 9H), 1.56 – 1.43 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 22.1 min (major), t_r = 26.8 min (minor).

1'-(*tert*-butyl) 2-ethyl 6-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.20 (m, 3H), 5.63 (dt, *J* = 11.7, 6.0 Hz, 1H), 4.07 – 3.90 (m, 2H), 3.80 (q, *J* = 7.2 Hz, 2H), 3.45 (d, *J* = 11.4 Hz, 1H), 2.73 – 2.55 (m, 1H), 2.54 – 2.39 (m, 1H), 2.35 – 2.19 (m, 1H), 2.19 – 1.89 (m, 3H), 1.90 – 1.78 (m, 1H), 1.65 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 171.3, 168.3, 148.7, 140.0, 129.4, 127.5, 125.0, 122.6, 115.0, 84.8, 81.8, 61.6, 60.8, 53.8, 53.0, 41.2, 34.6, 30.6, 28.1, 24.3, 14.0, 13.4. HPLC-MS (ESI) t_r = min; $[M+]^+$ = *m/z*. CSP-HPLC: IC 90:10 *n*-hexane/IPA for 10 min, then up to 80:20 in 10 min, 80:20 for 10 min, then up to 70:30; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 29.1 min (minor), t_r = 30.5 min (major).

1'-(*tert*-butyl) 2-ethyl 6-(1-ethoxy-1-oxopropan-2-yl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 1H), 7.41 – 7.29 (m, 2H), 7.23 – 7.13 (m, 1H), 5.73 (dt, *J* = 11.9, 4.4 Hz, 1H), 4.28 – 4.10 (m, 2H), 3.75 (q, *J* = 7.1 Hz, 1H), 3.74 (q, *J* = 7.1 Hz, 1H), 3.42 (d, *J* = 11.5 Hz, 1H), 2.75 – 2.59 (m, 2H), 2.45 (dd, *J* = 12.5, 3.3 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.64 (s, 9H), 1.61 – 1.45 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 173.8, 167.9, 149.3, 140.1, 129.4, 128.3, 124.0, 123.9, 115.7, 84.1, 81.5, 62.4, 61.5, 55.6, 51.9, 51.0, 30.4, 28.2, 26.5, 21.8, 14.1, 13.4. CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15

min, then up to 70:30 in 10 min, 70:3 for 15 min, then up to 1: in 2 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 53.7 min (major), t_r = 86.4 min (minor). $[\alpha]_D^{20}$ = +15.8° (*c* = 0.74, $CHCl_3$).

1'-(*tert*-butyl) 2-ethyl 6-(2-(benzyloxy)-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,f): ^{1}H NMR (400 MHz, CDCl3) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.18 (m, 8H), 5.64 (dt, *J* = 11.7, 3.9 Hz, 1H), 5.00 (d, *J* = 13.3 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 3.80 (q, *J* = 8.0 Hz, 2H), 3.45 (d, *J* = 11.4 Hz, 1H), 2.68 – 2.56 (m, 1H), 2.56 – 2.42 (m, 1H), 2.42 – 1.76 (m, 5H), 1.64 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 210 nm; t_r = 52.4 min (minor), t_r = 59.6 min (major).

1'-(*tert*-butyl) 2-ethyl 6-(2-(benzyloxy)-2-oxoethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.20 (m, 8H), 5.63 (dt, *J* = 11.8, 4.3 Hz, 1H), 5.00 (d, *J* = 12.2 Hz, 1H), 4.94 (d, *J* = 12.2 Hz, 1H), 3.80 (q, *J* = 7.1 Hz, 2H), 3.45 (d, *J* = 11.5 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.55 – 2.42 (m, 1H), 2.34 – 2.18 (m, 1H), 2.16 – 2.01 (m, 2H), 1.99 – 1.84 (m, 2H), 1.64 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 171.2, 168.3, 148.7, 140.0, 135.3, 129.5, 128.6, 128.4, 128.2, 127.4, 125.0, 122.6, 115.1, 84.8, 81.8, 66.7, 61.6, 53.8, 52.9, 41.3, 34.6, 30.5, 28.1, 24.2, 13.4. HPLC-MS (ESI) t_r = 12.1 min; $[M+Na]^+$ = 589.0 *m/z*, $[2M+Na]^+$ = 1155.2 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 57.5 min (minor), t_r = 78.7 min (major).

1'-(*tert*-butyl) 2-ethyl 6-(cyanomethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,h): 4 diastereoisomers obtained.

Isomer A: ^{1}H NMR (400 MHz, CDCl3) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 7.1 Hz, 1H), 5.53 (dt, *J* = 12.8, 4.8 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.00 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.42 (d, *J* = 5.8 Hz, 1H), 3.13 – 2.99 (m, 1H), 2.97 – 2.80 (m, 1H), 2.63 – 2.50 (m, 1H), 2.38 – 2.25 (m, 1H), 1.97 – 1.87 (m, 1H), 1.66 (s, 9H), 1.63 – 1.48 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min, 73: 30 for 8 min, then up to 1:1 in 8 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 37.4 min (major), t_r = 42.6 min (minor).

Isomer B: ^{1}H NMR (400 MHz, CDCl3) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.32 – 7.18 (m, 2H), 5.24 (dt, *J* = 12.3, 4.8 Hz, 1H), 3.92 (d, *J* = 11.7 Hz, 1H), 3.87 – 3.67 (m, 2H), 2.88 – 2.75 (m, 1H), 2.57 – 2.44 (m, 1H), 2.35 – 2.23 (m, 1H), 2.19 – 2.00 (m, 2H), 1.84 (ddd, *J* = 27.1, 13.7, 3.4 Hz, 1H), 1.75 – 1.51 (m, 10H), 0.87 (t, *J* = 7.1 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min, 73: 30 for 8 min, then up to 1:1 in 8 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 56.8 min (major), t_r = 65.5 min (minor).

Isomer C: ^{1}H NMR (400 MHz, CDCl3) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.10 (m, 3H), 5.31 (dt, *J* = 11.8, 6.1 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 1H), 3.76 (q, *J* = 7.1 Hz, 2H), 2.83 (dd, *J* = 17.3, 4.8 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.34 – 2.02 (m, 3H), 1.74 – 1.61 (m, 11H), 0.83 (t, *J* = 7.1 Hz, 3H). CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min, 73: 30 for 8 min, then up to 1:1 in 8 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 69.4 min (major), t_r = 81.5 min (minor).

Isomer D: **16c,i**.

1'-(*tert*-butyl) 2-ethyl 6-(cyanomethyl)-3-nitro-2'-oxospiro[cyclohexane-1,3'-indoline]-1',2-dicarboxylate (16c,i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.35 – 7.27 (m, 2H), 5.64 (dt, *J* = 11.9, 4.4 Hz, 1H), 3.82 (q, *J* = 7.0 Hz, 2H), 3.44 (d, *J* = 11.5 Hz, 1H), 2.80 – 2.67 (m, 1H), 2.49 – 2.33 (m, 1H), 2.33 – 1.91 (m, 5H), 1.65 (s, 9H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 167.9, 148.4, 139.9, 130.1, 126.5, 125.4, 122.2, 117.0, 115.4, 85.3, 81.4, 61.9, 53.5, 52.6, 42.0, 30.1, 28.1, 24.0, 18.8, 13.4. HPLC-MS (ESI) t_r = 9.9 min; $[M+Na]^+$ = 480.0 *m/z*, $[2M+Na]^+$ = 937.2 *m/z*. CSP-HPLC: IC 90:10 *n*-hexane/IPA for 8 min, then up to 80:20 in 8 min, 80:20 for 8 min, then up to 70:30 in 8 min, 73: 30 for 8 min, then up to 1:1 in 8 min; flow rate 0.5 mL/min at 40°C; λ 230 nm; t_r = 50.7 min (minor), t_r = 53.1 min (major).

1'-(*tert*-butyl) 2-ethyl 5-(2-ethoxy-2-oxoethyl)-3-nitro-2'-oxospiro[cyclopentane-1,3'-indoline]-1',2-dicarboxylate (19A): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 5.68 (ddd, *J* = 10.8, 7.6, 3.0 Hz, 1H), 4.44 (d, *J* = 7.7 Hz, 1H), 4.10 – 3.95 (m, 2H), 3.87 – 3.65 (m, 2H), 3.37 – 3.20 (m, 1H), 3.03 – 2.92 (m, 1H), 2.54 – 2.42 (m, 1H), 2.01 (dd, *J* = 16.2, 5.5 Hz, 1H), 1.90 (dd, *J* = 16.2, 9.3 Hz, 1H), 1.67 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.6, 170.3, 167.7, 148.9, 140.3, 129.7, 124.61, 124.58, 123.4, 115.7, 84.9, 84.3, 61.6, 60.9, 60.4, 57.6, 44.4, 36.4, 34.6, 28.1, 14.0,

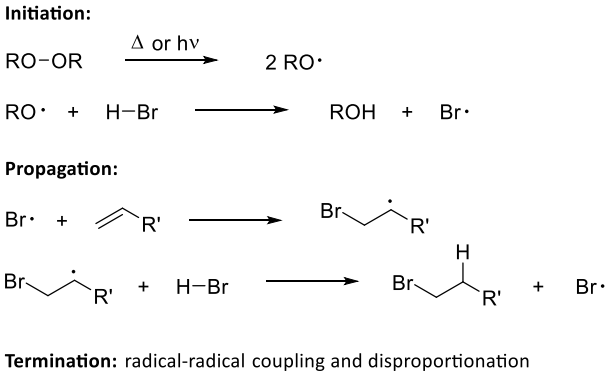
13.2. HPLC-MS (ESI) t_r = 10.7 min; $[2M+Na]^+$ = 1003.7 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 47.6 min (minor), t_r = 60.1 min (major).

1'-(*tert*-butyl) 2-ethyl 5-(2-ethoxy-2-oxoethyl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-1',2-dicarboxylate (19B): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.17 (bt, *J* = 2.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 4.11 – 3.82 (m, 4H), 3.53 – 3.38 (m, 1H), 3.05 (ddd, *J* = 18.7, 8.5, 3.0 Hz, 1H), 2.51 (ddd, *J* = 18.6, 9.5, 2.2 Hz, 1H), 2.25 (dd, *J* = 16.4, 8.5 Hz, 1H), 2.13 (dd, *J* = 16.4, 7.3 Hz, 1H), 1.67 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 171.1, 162.2, 149.3, 146.3, 140.0, 138.6, 128.9, 127.4, 124.0, 123.8, 115.4, 84.0, 62.6, 60.6, 60.5, 45.1, 38.4, 35.7, 28.1, 14.0, 13.6. HPLC-MS (ESI) t_r = 10.3 min; $[M+Na]^+$ = 466.4 *m/z*, $[2M+Na]^+$ = 909.7 *m/z.* CSP-HPLC: IC 90:10 *n*-hexane/IPA for 15 min, then up to 80:20 in 10 min, 80:20 for 15 min, then up to 70:30 in 10 min; flow rate 0.5 mL/min at 40°C; λ 254 nm; t_r = 67.2 min (major), t_r = 83.1 min (minor). $[\alpha]_D^{20}$ = -32.3° (*c* = 1.12, $CHCl_3$).

Photochemical Organocatalytic Atom Transfer Radical Addition to Alkenes

1. Introduction on atom transfer radical addition reactions

In 1937, during their investigations on the regioselectivity of the addition of HBr to unsymmetrical alkenes in the presence of peroxides, Kharasch and co-workers observed the formation of the *anti*-Markovnikov adduct.[110] They proposed that such products were formed by means of a free radical mechanism in which the peroxides acted as free-radical initiators. Subsequent works confirmed the ability of peroxides to act as free-radical initiators in this reaction, generating bromine radicals by homolytic cleavage of the HBr bond. The addition of a bromine radical to an alkene occurs at the least substituted carbon atom producing a more stable alkyl radical, which is irreversibly trapped by the hydrogen atom from HBr molecule, giving the *anti*-Markovnikov addition product (Scheme 28).

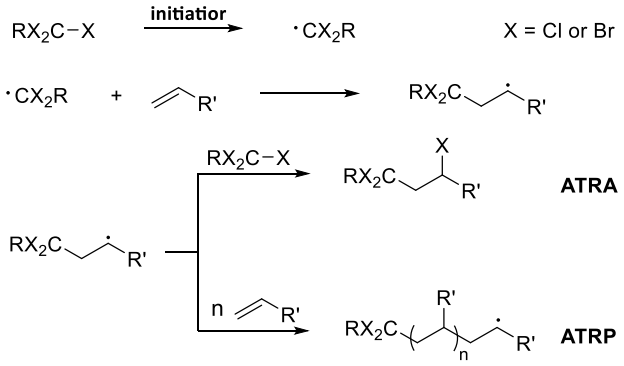


Scheme 28

After the discovery of the "peroxide effect" it was recognized that a variety of substrates could be used in the radical addition to alkenes. In particular, Kharasch

[110] Kharasch M. S., Engelmann H., Mayo F. R., *J. Org. Chem.* **1937**, 2, 288-302.

investigated the addition of polyhalogenated alkanes to alkenes in the presence of free-radical initiators or light.[111] This reaction is today known as the Kharasch addition or atom transfer radical addition (ATRA). Very high yields of the monoadduct were obtained in the case of simple 1-olefins, but were significantly decreased for more reactive alkenes (styrene, methyl acrylate and methyl methacrylate), that were highly active in free-radical polymerization. In this case the reaction was called atom transfer radical polymerization (ATRP) and was mostly the result of radical-radical termination reactions and multiple radical additions to alkene generating oligomers and polymers (Scheme 29). Since the ATRA reaction competes with radical mediated olefin polymerization, it found limited application in organic synthesis.



Scheme 29

In the middle of the past century, Minisci and co-workers noticed, during their studies of acrylonitrile polymerization in halogenated solvents (CCl_4 and $CHCl_3$), the formation of considerable amounts of the addition product of the halomethane to the olefin.[112] They realized that iron species, originated from corrosion in the reactor, were responsible for the catalytic process and they therefore proposed a mechanism in which iron chlorides increased the addition rate.[113] These seminal findings can be considered as the beginning of the transition-metal-catalysed (TMC) Kharasch reaction or TMC-ATRA.[114]

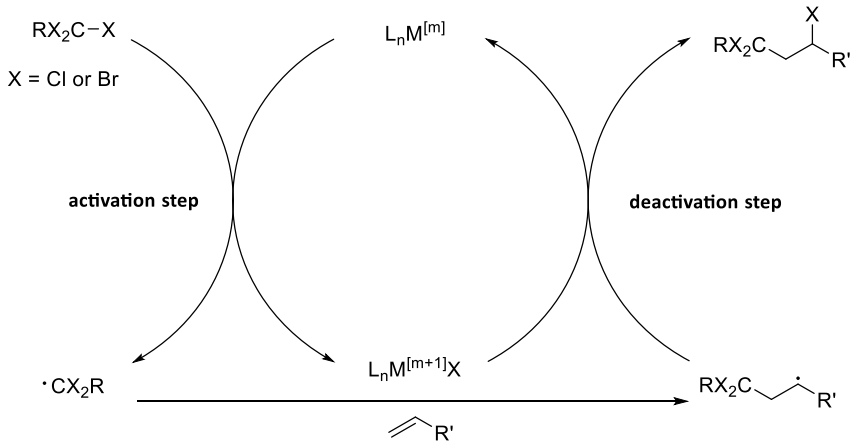
[111] (a) Kharasch M. S., Jensen E. V., Urry W. H., *Science* **1945**, 102, 128-128; (b) Kharasch M. S., Jensen E. V., Urry W. H., *J. Am. Chem. Soc.* **1945**, 67, 1626-1626.

[112] De Malde M., Minisci F., Pallini U., Volterra E., Quilico A., *Chim. Ind. (Milan, Italy)* **1956**, 38, 371-382.

[113] (a) Minisci F., *Gazz. Chim. Ital.* **1961**, 91, 386-389; (b) Minisci F., Pallini U., *Gazz. Chim. Ital.* **1961**, 91, 1030-1036; (c) Minisci F., Galli R., *Tetrahedron Lett.* **1962**, 3, 533-538; (d) Minisci F., Galli R., *Chim. Ind. (Milan, Italy)* **1963**, 45, 1400-1401; (e) Minisci F., Cecere M., Galli R., *Gazz. Chim. Ital.* **1963**, 93, 1288-1294.

[114] Muñoz-Molina J. M., Belderrain T. B., Pérez P. J., *Eur. J. Inorg. Chem.* **2011**, 3155-3164.

The TMC-ATRA reaction (Scheme 30) begins with the activation step in which the carbon–halogen (C-X) bond is homolytically dissociated by the metal catalyst (L_nM), yielding a carbon-centered radical and a metal halide. The former species interacts with the olefin affording another radical, which provides the halogen abstraction from the metal halide in the deactivation step. The metal is reduced to the initial oxidation state and the desired addition product is formed.



Scheme 30

The principal drawback of this synthetic method was the large amount of catalyst (typically 10-30 mol%) required to achieve high selectivity towards the desired compound, which causes serious problems for product separation and catalyst recycling. Additionally, these relatively large catalyst loadings make the process environmentally unfriendly and expensive. One of the main reasons for high catalyst loading was the accumulation of the metal complex in the higher oxidation state, as a result of radical termination reactions. Different methodologies were developed to overcome these drawbacks, like for example the design of solid supported catalysts, the use of biphasic systems such as fluorous solvents, or the use of highly active metal complexes based on ligand design.[115] Perhaps, the most significant solution to the problem of catalyst recycling and regeneration in ATRA relies on the use of reducing agents[116] such as radical initiator AIBN (azobisisobutyronitrile).[117] In this case the

[115] Clark A. J., *Chem. Soc. Rev.* **2002**, 31, 1-11.

[116] (a) Eckenhoff W. T., Pintauer T., *Catalysis Reviews: Science and Engineering* **2010**, 1-59; (b) Pintauer T., *Eur. J. Inorg. Chem.* **2010**, 2449-2460.

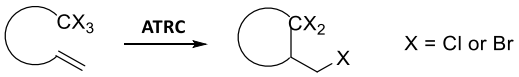
[117] (a) Eckenhoff W. T., Garrity S. T., Pintauer T., *Eur. J. Inorg. Chem.* **2008**, 563-571; (b) Eckenhoff W. T., Pintauer T., *Dalton Trans.* **2011**, 40, 4909-4917; (c) Quebatte L., Thommes K., Severin K., *J. Am. Chem. Soc.* **2006**, 128, 7440-7441.

decomposition of AIBN provides constant source of radicals which continuously reduce the transition metal complex in the higher oxidation state to the lower oxidation state. As a result, ATRA reactions can now be conducted using metal catalysts at ppm level. The recent developments in this area could have important industrial implications on the synthesis of small organic molecules, natural products and pharmaceutical drugs.

Great progress was made not only in controlling product selectivity, but also in utilizing a variety of halogenated compounds (alkyl and aryl halides, *N*-chloroamines, alkylsulfonyl halides and polyhalogenated compounds). Furthermore, it was also demonstrated that different alkenes such as styrene, alkyl acrylates and acrylonitrile could be used in the reaction. Therefore, TMC-ATRA became a broadly applicable synthetic tool.

Transition metal complexes of Ru, Fe, Ni and Cu are typically used as catalysts for atom transfer radical addition (ATRA) and cyclization (ATRC) providing the formation of carbon-carbon bonds.

The ATRC (Scheme 31) has found a number of synthetic applications constituting a useful tool for the synthesis of valuable cyclic compounds.



Scheme 31

The most successful catalysts for ATRC reactions are copper complexes[115] that induce the formation of an array of ring sizes from 4 to 18. Furthermore, the halide functionality in the resulting product can be very beneficial because it can be easily reduced, eliminated, displaced, converted to a Grignard reagent, or can serve as a further radical precursor. Recently, copper-catalysed ATRA and ATRC reactions were utilized in cascade or sequential additions[118] in the synthesis of natural products and pharmaceutical drugs.

In 1995, a new class of radical polymerization methods was reported independently by the groups of Matyjaszewski[119] and Sawamoto.[120] This new process named atom

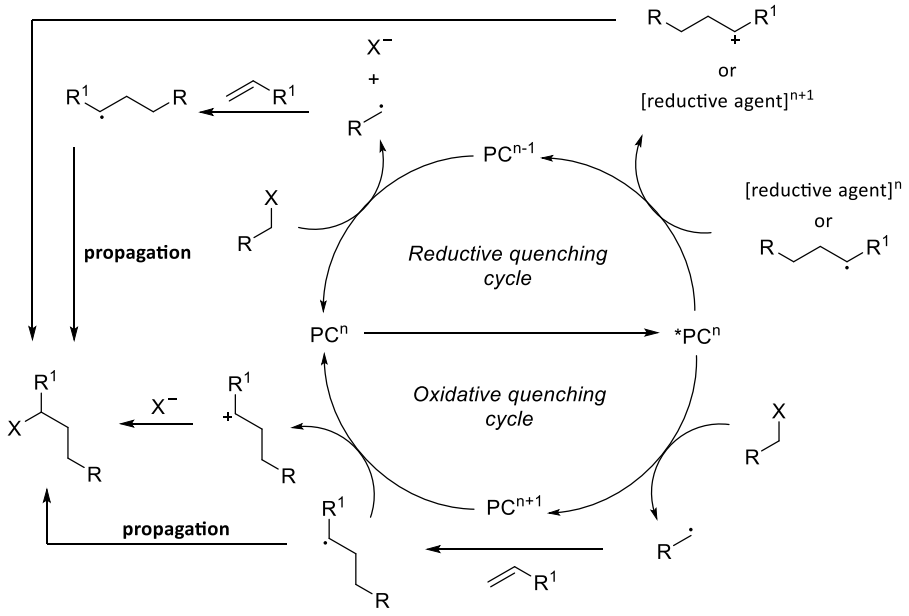
[118] Stevens C. V., Van Meenen E., Masschelein K. G. R., Eeckhout Y., Hooghe W., D'hondt B., Nemykinb V. N., Zhdankin V. V., *Tetrahedron Lett.* **2007**, 48, 7108-7111.

[119] Wang J., Matyjaszewski K., *J. Am. Chem. Soc.* **1995**, 117, 5614-5615.

[120] Kato M., Kamigaito M., Sawamoto M., Higashimura T., *Macromolecules* **1995**, 28, 1721-1723.

transfer radical polymerization (ATRP),[121] had a tremendous impact on the synthesis of macromolecules with well-defined compositions, architectures and functionalities. ATRP was successfully mediated by a variety of metals (Ti, Mo, Re, Fe, Ru, Os, Rh, Co, Ni, Pd and Cu), but copper complexes were found to be the most efficient catalysts.[122] ATRP is mechanistically similar to ATRA with the exception that more than one addition step occurs (Scheme 29). ATRP reactions became one of the most powerful synthetic methods to obtain polymers and copolymers because they were able to provide them with predetermined and narrow molecular weight distribution.

The use of photoredox catalysts, such as Ru-$(bpy)_3Cl_2$, to initiate organic transformations has recently gained a lot of interest.[123] Stephenson et al. realized the goal of performing ATRA between activated halides and alkenes utilizing visible light photocatalysis[124] (Scheme 32).



Scheme 32

Both reductive quenching, which can be achieved in the presence of an external electron donor, and oxidative quenching of photocatalysts can effectively be used for

[121] (a) Matyjaszewski K., Xia J., *Chem. Rev.* **2001**, 101, 2921-2990; (b) Patten T. E, Matyjaszewski K., *Acc. Chem. Res.* **1999**, 32,895-903; (c) Tsarevsky N. V, Matyjaszewski K., *Chem. Rev.* **2007**, 107, 2270-2299.

[122] Pintauer T., Matyjaszewski K., *Chem. Soc. Rev.* **2008**, 37, 1087-1097.

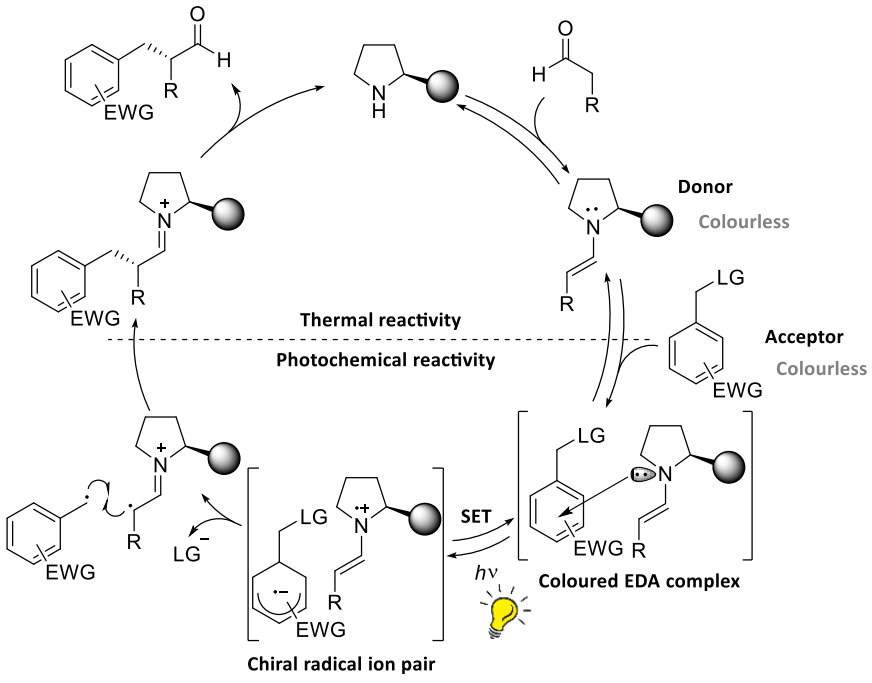
[123] (a) Prier C. K., Rankic D. A., MacMillan D. W. C., *Chem. Rev.* **2013**, 113, 5322-5363; (b) Xi Y., Yia H., Lei A., *Org. Biomol. Chem.* **2013**, 11, 2387-2403; (c) Narayanam J. M. R., Stephenson C. R. J., *Chem. Soc. Rev.* **2011**,40, 102-113; (d) Yoon T. P., Ischay M. A., Du J., *Nat. Chem.* **2010**, 2, 527-532.

[124] (a) Nguyen J. D., Tucker J. W., Konieczynska M. D., Stephenson C. R. J., *J. Am. Chem. Soc.* **2011**, 133, 4160-4163; (b) Wallentin C., Nguyen J. D., Finkbeiner P., Stephenson C. R. J., *J. Am. Chem. Soc.* **2012**, 134, 8875-8884.

ATRA transformations. This ATRA protocol provided high yields under mild reaction conditions, with a simple reaction setup, minimal side reactions, optimal catalytic efficiency and straightforward purification.

2. Origin of the project

Melchiorre and co-workers found out that the photochemical activity of a key donor–acceptor complex can drive a stereoselective catalytic α-alkylation of aldehydes[125] (Scheme 33). In this process the electron donor-acceptor (EDA) complex formed is able to absorb visible light and to give a single electron transfer (SET) from the enamine donor to the acceptor, as for example 2,4-dinitrobenzyl bromide, thus forming a chiral radical ion pair. Then the living group on the radical anion is released and the in cage radical coupling takes place providing the final α-alkylation of the aldehyde. The light source can be a 23 W compact fluorescent light (CFL) bulb or, even better, the sun.

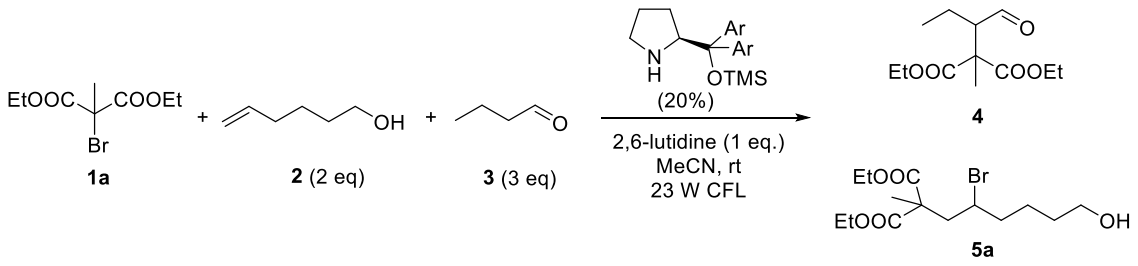


Scheme 33

Even if not via EDA complex, in these reaction conditions, also α-bromomalonates were able to provide the α-alkylation of aldehydes.

[125] Arceo E., Jurberg I. D., Álvarez-Fernández A., Melchiorre P., *Nat. Chem.* **2013**, 5, 750-756.

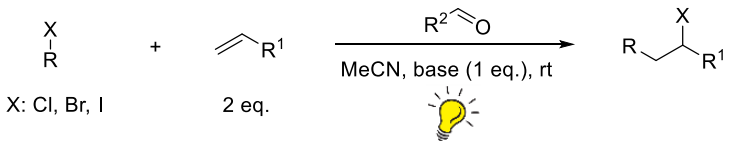
During the mechanistic study of the reaction, one of the attempts made to trap the radical intermediates was the addition of olefin **2** to the reaction mixture (Scheme 34). This brought to the formation of the expected product **4** and also of **5a** given by the trapping of the diethyl-methylmalonate radical by the olefin.



Scheme 34

In order to prove that the enamine formation was essential for the generation of the radical, the same reaction shown in Scheme 34 was carried out without the catalyst. In this case the enamine, which is a good electron donor, could not be formed, hence no electron transfer and radical generation were expected and an absence of reactivity was anticipated. However, while product **4** was not detected as expected, product **5a** was surprisingly still yielded. Since enols are also known to be good electron donors,[126] the reaction in the absence of the catalyst was also performed with a non enolizable aldehyde like pivalaldehyde, but again product **5a** was formed thus demonstrating that the possible formation of the enol was not responsible for the reaction.

The discovery that the ATRA reaction could be promoted by an aldehyde, in the presence of a base, performing the reaction in front of an house bulb (23 W CFL) as shown in Scheme 35, prompted us to deeply study this new process.



Scheme 35

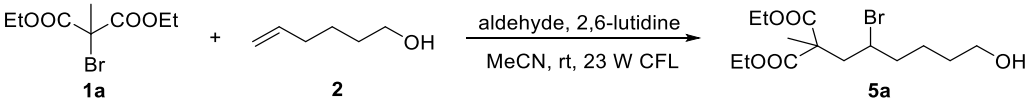
[126] (a) Russell G. A., Janzen E. G., Strom E. T., *J. Am. Chem. Soc.* **1964**, 86, 1807-1814; (b) Kornblum N., *Angew. Chem. Int. Ed.* **1975**, 14, 734-745; (c) Bunnett J. F., Singh P., *J. Org. Chem.* **1981**, 46, 5022-5025; (d) Russell G. A., Mudryk B., Jawdosiuk M., *J. Am. Chem. Soc.* **1981**, 103, 4611-4613; (e) Ashby E. C., Argyropoulos J. N., Richard Meyer G., Goel A. G., *J. Am. Chem. Soc.* **1982**, 104, 6788-6789; (f) Ashby E. C., Park W., *Tetrahedron Let.* **1983**, 24, 1667-1670; (g) Ashby E. C., Argyropoulos J. N., *J. Org. Chem.* **1985**, 50, 3274-3283; (h) Gassman P. G., Bottorff K. J., *J. Org. Chem.* **1988**, 53, 1097-1100.

3. Study of the reaction

The study of this photochemical organocatalytic atom transfer radical addition started from the observation that this reaction between an alkyl halide and an olefin could be mediated by an aldehyde when the reaction was irradiated with a normal 23 W CFL house bulb in the absence of oxygen.

The preliminary exploratory reactions set up in this study are shown in Table 28.

Table 28: Preliminary reactions for the photochemical organocatalysed ATRA between **1a** and **2**.[a]



Entry	Aldehyde	Time (h)	Conv. (%)[b]
1	Butanal (3 eq.)	18	16
		42	34
2	Pivalaldehyde (3 eq.)	18	28
		42	60
3	2,6-dichlorobenzaldehyde (3 eq.)	20	64
		44	84
		68	>99
4	2,6-dichlorobenzaldehyde (0.2 eq.)	21	23

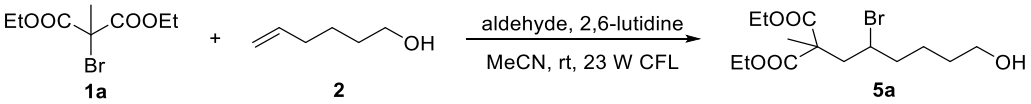
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), aldehyde, 2,6-lutidine (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

The first reaction was carried out in the same conditions used when the product was initially observed i.e. using 3 equivalents of butanal (entry 1); in these conditions the conversion of **1a** was only 34% after 42 hours. As previously described we performed the reaction also using pivalaldehyde (entry 2) in order to exclude the formation of an enol that might be able to act as electron donor like the enamine in electron transfer processes. Using pivalaldehyde the reactivity improved giving a 60% of conversion of the alkyl halide in the same reaction time. We decided also to test an aromatic aldehyde in this process and we chose 2,6-dichlorobenzaldehyde (entry 3) which provided 64% of conversion of the alkyl halide in only 20 hours and attained complete conversion in 68 hours. Encouraged by this result we tried to decrease the

amount of aldehyde from 3 equivalents to 20 mol% (entry 4) obtaining a 23% conversion of **1a** in 21 hours.

Since the aldehydic additives did not appear to be consumed in the reaction, and motivated by the interest of a catalytic version of this reaction, we soon after examined those additives in sub-stoichiometric amount. A large number of aldehydes were tested in catalytic amount in the reaction of olefin **2** and alkyl bromide **1a** under irradiation in CH_3CN (Table 29). The necessity of light irradiation was confirmed by performing the experiments under careful exclusion of light. In the absence of irradiation the functionalization of olefin **2** with **1a** in the presence of the aldehydes did not occur. The reaction was very sensitive to small amounts of oxygen, which implied the requirement of a process for degassing the reaction mixture prior to irradiation.

Table 29: Aldehydes screening for the photochemical organocatalysed ATRA between **1a** and **2**.[a]



Entry	Aldehyde	Time (h)	Conv. (%)[b]
1	2,6-Dichlorobenzaldehyde	21	23
2	4-Cyanobenzaldehyde	21	30
3	4-Bromobenzaldehyde	21	74
4	4-Anisaldehyde	19	>99
5	Butanal	19	8
6	Benzaldehyde	18	77
7	Salicylaldehyde	18	-
8	Ethyl Glyoxalate	18	-
9	Hydrocinnamaldehyde	18	-
10	Furfural	19	-
11	2-Bromobenzaldehyde	19	46
12	4-Methoxycinnamaldehyde	19	-
13	1-Naphthaldehyde	19	-
14	Pivalaldehyde	18	9
15	4-(dimethylamino)benzaldehyde	16	40

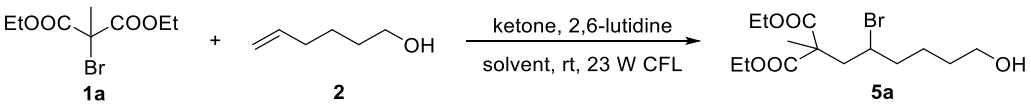
Entry	Aldehyde	Time (h)	Conv. (%)[b]
16	2,4,6-Trimethoxybenzaldehyde	16	>99
17	2,4-Dimethoxybenzaldehyde	15.5	71
18	2,3-Dimethoxybenzaldehyde	17	23
19	3,4,5-Trimethoxybenzaldehyde	18	17

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), aldehyde (20 mol%), 2,6-lutidine (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

We tested aliphatic, aromatic, heteroaromatic and α,β-unsaturated aldehydes as additives in the model reaction (entries 1-15) finding that 4-anisaldehyde (entry 4) was the one that provided the best result: complete conversion of **1a** was achieved in 19 hours. It was curious to observe such differences in reactivity for example between benzaldehyde (77% conversion in 18 hours) and salicylaldehyde (no reaction). All these results revealed to be very difficult to rationalize. However, one thing still common in all cases was that the aldehyde was not consumed in the process (considering the sensitivity of ^{1}H NMR analysis). Since *p*-anisaldehyde gave impressive results, we tested other aldehydes with more methoxy groups in order to see if increasing the number of electron-donating groups on the aromatic ring the reactivity improved, but again we obtained results difficult to rationalize and effects that differed depending on the position of the substituents in the aromatic ring (entries 16-19). While 2,4,6-trimethoxybenzaldehyde provided an improved reactivity, all the other methoxy polysubstituted aromatic aldehydes didn't equal the performance of *p*-anisaldehyde. Although 2,4,6-trimethoxybenzaldehyde was slightly more reactive we decided to use the inexpensive and easily available *p*-anisaldehyde for further studies and optimization.

Some attempts of using ketones instead of aldehydes as additives to promote this ATRA reaction were made, but these carbonyl compounds turned out to be much less efficient (Table 30). For example the reaction using acetone as solvent without aldehyde didn't give any product (entry 1), while the reaction using benzophenone (entry 4), acetophenone (entry 3) or butanone (entry 2) in stoichiometric or super-stoichiometric amounts provided much worse results compared to those obtained with a catalytic amount of *p*-anisaldehyde.

Table 30: Ketones screening for the photochemical organocatalysed ATRA between **1a** and **2**.[a]



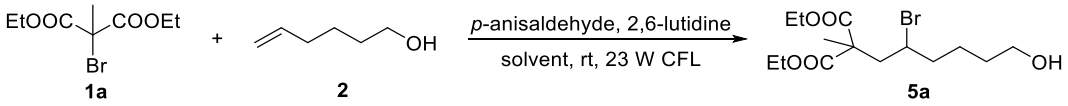
Entry	Ketone	Solvent	Time (h)	Conv. (%)[b]
1	-	Acetone	13	-
2	Butanone (3 eq.)	MeCN	42	23
3	Acetophenone (3 eq.)	MeCN	17	traces
4	Benzophenone (1 eq.)	MeCN	17	40

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), ketone, 2,6-lutidine (0.1 mmol), solvent (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

We carried out the reaction with benzophenone (Table 30, entry 4) also adding 1 equivalent of *p*-anisaldehyde and we obtained a conversion of **1a** of 83% after 18 hours, while the reaction with 1 equivalent of *p*-anisaldehyde and without benzophenone afforded complete conversion of the alkyl halide after the same time of reaction. This may suggest some kind of competition between benzophenone and *p*-anisaldehyde when they are both present in the reaction thus reducing the reactivity of the latter.

The model reaction was studied in different solvents, and the process showed a relative insensitivity to the nature of the solvent (Table 31). Polar aprotic solvents were in general effective (CH_3CN, DMF, CH_2Cl_2, DMSO, 1,4-dioxane, TCE), with acetonitrile providing the best reactivity (entry 1). However, acetone and $CHCl_3$ only afforded modest values of conversion at the same reaction time. Nevertheless, when using apolar solvents such as *n*-hexane, methyl *tert*-butyl ether and toluene, similar results as those found in polar solvents were obtained. Except of THF that gave traces of by-products (entry 3), in all the other solvents tested the selectivity of the reaction towards product **5a** is remarkable, the product mixtures containing neither dimers nor dehalogenated products.

Table 31: Solvents screening for the photochemical organocatalysed ATRA between **1a** and **2**.[a]

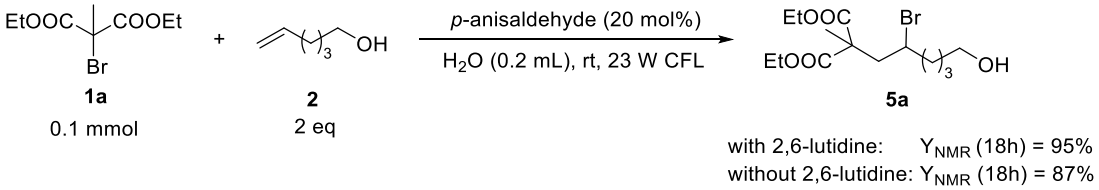


Entry	Solvent	Time (h)	Conv. (%)[b]
1	MeCN	19	>99
2	Toluene	19	62
3	THF	19	By-products
4	1,4-Dioxane	20	92
5	MTBE	19	84
6	*n*-Hexane	19	86
7	TCE	19	66
8	$CHCl_3$	19	47
9	DMF	19	95
10	DMSO	19	83
11	DCM	19	85
12	Acetone	15	54

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), *p*-anisaldehyde (20 mol%), 2,6-lutidine (0.1 mmol), solvent (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

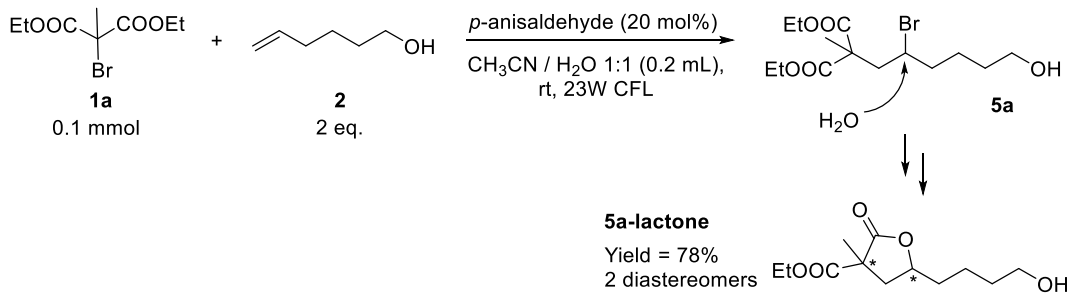
In the same conditions used for the solvent screening, the reaction carried out on-water gave 95% of NMR yield after 18 hours, while the same reaction on water performed without 2,6-lutidine provided 87% of NMR yield in the same reaction time (Scheme 36). In the case of the on-water reactions we didn't determine the conversion of the alkyl halide from the ^{1}H NMR of the aliquot taken from the reaction mixture, because on-water the reaction was heterogeneous. So we extracted the reaction with DCM, we added a known amount of 1,3,5-trimethoxybenzene as internal standard and we calculated the NMR yield from the relative amount of the internal standard and the product **5a**. The results obtained in the on-water conditions are noteworthy because the reaction in an organic solvent, like for example acetonitrile, needed the presence of 2,6-lutidine when 20 mol% of *p*-anisaldehyde was used as catalyst, otherwise the reaction didn't take place. Also in the case of the on-water reaction the light irradiation

and the exclusion of oxygen were strictly necessary. While a protocol on-water might be interesting to develop further in the future, our preliminary experiments in the reaction of **2** (2 eq.) and **1a** (0.1 mmol) in the presence of catalytic *p*-anisaldehyde and 0.2 mL of H_2O afforded good but non-reproducible results varying from 60 to 90% yield of **5a** isolated after 18 hours of irradiation. A plausible explanation for this variation might be due to the intrinsic heterogeneity of the mixture and therefore the difficulty in achieving consistent irradiation. A drawback of the on-water protocol is the inherent limitation to liquid and non-water sensitive reagents.



Scheme 36

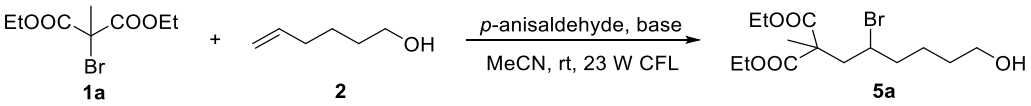
On the other hand, the reaction performed in a mixture of acetonitrile and water provided a simple method for the preparation of lactones from simple olefins and α-bromo esters. When we used a 1:1 mixture of acetonitrile and water as solvent, where two phases were still present, longer reaction times were required and while monitoring the reaction progress by NMR the disappearance of the ATRA product together with the formation of a new compound were observed. This was due to further polar reactions on the ATRA product involving first a nucleophilic substitution of the bromo by the water and then a lactonization (Scheme 37). This is an interesting possibility of one-pot synthesis of a different class of compounds. Using the 1:1 mixture of acetonitrile and water also solid olefins without hydroxyl group, like norbornene, could be used and the base was still not needed.



Scheme 37

The presence of 2,6-lutidine revealed to be necessary for the reaction to work in organic solvents and for obtaining synthetically useful yields. A standard control experiment showed that in the absence of aldehyde, 2,6-lutidine was not able to confer any reactivity. In order to have more information on the necessity of the base, we carried out the screening of several inorganic and organic bases in the reaction of olefin **2** with the alkyl halide **1a** catalyzed by *p*-anisaldehyde under irradiation in acetonitrile (Table 32).

Table 32: Bases screening for the photochemical organocatalysed ATRA between **1a** and **2**.[a]



Entry	Base	pKa[b]	Time (h)	Conv. (%)[c]
1	2,6-Lutidine	6.7	19	>99
2	NaOAc		20	8
3	Cs_2CO_3		20	Unselective, by-products
4	4-Methoxypyridine	6.6	20	12
5	1-Methylimidazole	6.9	20	-
6	Pyridine	5.2	18	traces
7	2,4,6-Collidine	7.5	18	76
8	2,6-Di-*tert*-butylpyridine	5.0	20	5
9	2,3-Lutidine	6.6	18	76
10	4-Phenylenediamine	6.1	18	25
11	*N,N*-diethylaniline	6.6	18	71

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), *p*-anisaldehyde (20 mol%), base (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Referred to the conjugate acids in water.[127] [c] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

The reactivity varied significantly depending on the base used and the tests confirmed that 2,6-lutidine was the best among the bases screened (entry 1). Inorganic bases seemed to be non suitable for this process (entries 2, 3), while the reactivity of the organic bases seemed to depend both on the pKa and on the steric hindrance. In fact not hindered bases like 4-methoxypyridine (entry 4), 1-methylimidazole (entry 5), pyridine (entry 6) and 4-phenylenediamine (entry 10) didn't provide good results,

[127] http://research.chem.psu.edu/brpgroup/pKa_compilation.pdf

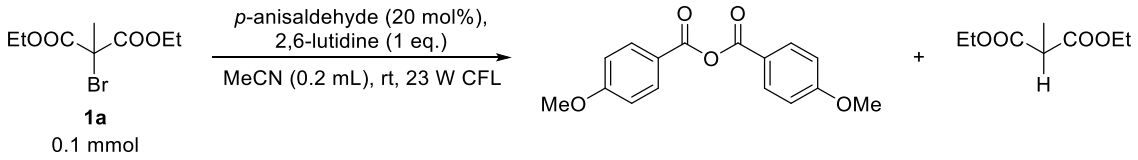
while better results were obtained when sterically hindered bases with a pKa similar to 2,6-lutidine were used. 2,4,6-collidine (entry 7), 2,3-lutidine (entry 9) and *N,N*-diethylaniline (entry 11) provided a reactivity comparable to the one obtained with 2,6-lutidine. In particular *N,N*-diethylaniline, that has a completely different structure respect to 2,6-lutidine, gave good results having comparable basicity and steric effects around the nitrogen. 2,6-Di-*tert*-butylpyridine (entry 8) was probably not basic enough to allow the reaction to take place. Hence the base had to be moderately strong and non-nucleophilic owning substituents which provide steric hindrance near the nitrogen avoiding the possibility of coordination or creation of adducts.

The role of the base in the reaction is still unclear; in fact apparently there is no obvious need for deprotonation or neutralization of acids generated during the reaction. Since the reaction on water, as mentioned above, worked well also in the absence of 2,6-lutidine, it suggests that the role of 2,6-lutidine should also be able to be played by water and that makes us think that the role might be that of simple acid removal.

Seeing that the on-water protocol provided the ATRA product efficiently even without the addition of base, we decided to perform some experiments and check the pH of the media after reaction. When the reaction was performed with the light irradiation on water or in acetonitrile, without 2,6-lutidine, at 16 hours of reaction the pH was acidic, while the experiment in acetonitrile but with 2,6-lutidine had a slightly basic pH after overnight reaction. When we irradiated only solutions of the aldehyde or the malonate in on-water conditions overnight the pH of the solution after that time was neutral, but when we irradiated a 1:1 mixture of aldehyde and malonate on water for the same time we had acidic pH with the formation of diethyl 2-methylmalonate and 4-methoxybenzoic anhydride in 2:1 ratio and with less than 10% conversion of the malonate. This was not observed when an equivalent mixture was stirred in similar conditions but not irradiated (performed in the dark): in this case the pH was neutral and both the reagents remained unreacted. So this indicates that these two species are probably the ones involved in the initiation step and that this process can involve the generation of an acid, but only when irradiated with light.

We observed the formation of diethyl 2-methylmalonate and 4-methoxybenzoic anhydride in 2:1 ratio (traces formed after 18 hours) also when the reaction was

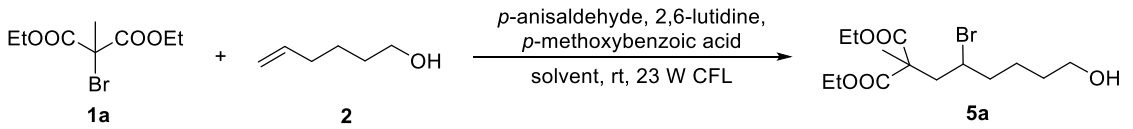
performed in the exact conditions as the model reaction but in the absence of the olefin (Scheme 38).



Scheme 38

Since 2,6-lutidine in the reaction performed in an organic solvent should play the same role as the water in the on-water protocol (assuming the same mechanism for both the reaction in organic solvent and on water) and the reaction in acetonitrile doesn't work without 2,6,-lutidine, probably the formation of a small amount of acid takes place at an early stage and this acid is somehow detrimental for the ATRA reaction. So we decided to set up some reactions adding *p*-methoxybenzoic acid to see if we were able to shut down the reactivity and have some evidence that this was the acid being generated in the reaction. The results are reported in Table 33.

Table 33: Effect of *p*-methoxybenzoic acid on the photochemical organocatalysed ATRA between **1a** and **2**.[a]



Entry	2,6-lutidine	*p*-methoxybenzoic acid	Solvent	Time (h)	Conv. (%)[b]
1	-	5 mol %	H_2O	14	74
2	1 eq.	5 mol %	MeCN	14	85
3	1 eq.	20 mol %	MeCN	14	64
4	1 eq.	1 eq.	MeCN	20	49

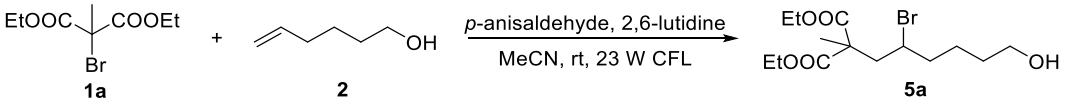
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), *p*-anisaldehyde (20 mol%), 2,6-lutidine, *p*-methoxybenzoic acid, solvent (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

As we can see in the table, when increasing the amount of acid the reaction rate decreased, but we were not able to completely shut down the reactivity even when using 1 equivalent of *p*-methoxybenzoic acid. This indicates that *p*-methoxybenzoic acid could not be the acid generated because it should derive from the *p*-anisaldehyde that was present in the reaction in catalytic amount (20 mol %).

Looking at the result reported in Scheme 38 we hypothesised that the acid formed could be hydrobromic acid produced together with diethyl 2-methylmalonate and 4-methoxybenzoic anhydride. Since the reaction is able to reach complete conversion of the alkyl halide and give a very high isolated yield of the ATRA product incorporating the bromo atom, obviously the amount of hydrobromic acid produced should be very low, although maybe enough to prevent the reaction from taking place in the absence of 2,6-lutidine. Unfortunately we still don't have reliable experimental data to prove, without any doubt, the formation of HBr and so to attribute with certainty the role of 2,6-lutidine; studies on the role of the base are still in progress.

In addition to studying the effects of different aldehydes on the reaction and the effect of solvents and bases of diverse nature, both alkene and halide amounts and concentrations were varied to determine the effects on the reaction time and conversion. A study varying the stoichiometry of the reactants in the reaction is presented in Table 34.

Table 34: Study of the stoichiometry of the photochemical organocatalysed ATRA between **1a** and **2**.[a]



Entry	**1a** (eq.)	**2** (eq.)	*p*-anisaldehyde (eq.)	2,6-lutidine (eq.)	MeCN [**1a**]^0	Time (h)	Conv. (%)[b]
1	1	2	0.2	1	0.5M	21	>99
2	1	1	0.2	1	0.5M	20 51	50 78
3	1	1	1	1	0.5M	21	62
4[c]	2	1	0.2	1	0.5M	20	40
5	1	2	0.1	1	0.5M	17	72
6	1	2	0.05	0.2	0.5M	63	70
7	1	2	0.05	0.05	0.5M	63	42
8[d]	1	2	0.2	1	0.1M	20	44
9[e]	1	2	0.2	1	2.5M	17	90
10[e]	1	2	0.2	-	2.5M	15d	20

[a] Reaction conditions: **1a** (0.1 mmol), **2**, *p*-anisaldehyde, 2,6-lutidine, acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**. [c] **1a** (0.2 mmol), **2** (0.1 mmol). [d] acetonitrile (1 mL). [e] **1a** (0.5 mmol).

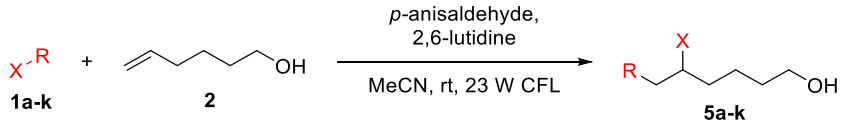
Comparing the results reported in entries 1 and 2 the importance of an excess of olefin is evident. Furthermore the use of 2 equivalents of olefin (entry 1) provided better results than the use of stoichiometric amount of *p*-anisaldehyde (entry 3) or of the use of an excess of alkyl bromide (entry 4).

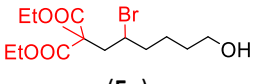
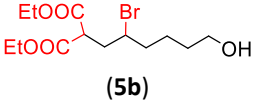
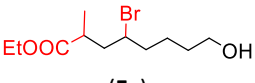
We tried to lower the amount of *p*-anisaldehyde (entry 5) to 10 mol% obtaining only a small decrease of reactivity, so we lowered both the amount of *p*-anisaldehyde and 2,6-lutidine (entries 6, 7) and we still observed reactivity with an increase of the reaction times.

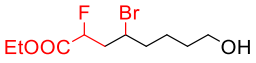
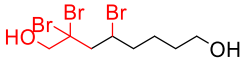
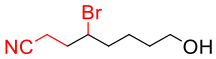
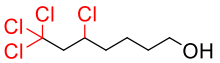
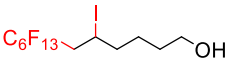
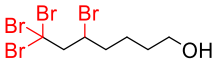
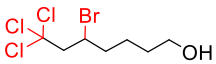
We examined also the dilution noting that a decrease in the concentration (entry 8) provided a slower reaction, while an increase in the concentration (entry 9) didn't improve the reactivity. The reaction with higher concentration was also performed without 2,6-lutidine (entry 10); this result together with the one reported in entry 9 implies that the efficiency of the reaction on water was not due to an effect of concentration.

Having optimized the reaction conditions for the model reaction, we studied the scope of the reaction in order to establish the viability and limitations of this method. First, we tested different alkyl halides as partners in the reaction with olefin **2**, as reported in Table 35.

Table 35: Scope of the alkyl halides for the photochemical organocatalysed ATRA.[a]



Entry	Product	Time (h)	Conv. (%)[b]	Yield (%)[c]
1	 (**5a**)	19	>99	88
2	 (**5b**)	15	>99	98
3	 (**5c**)	74	>99	78
4	 (**5d**)	40	>99	71

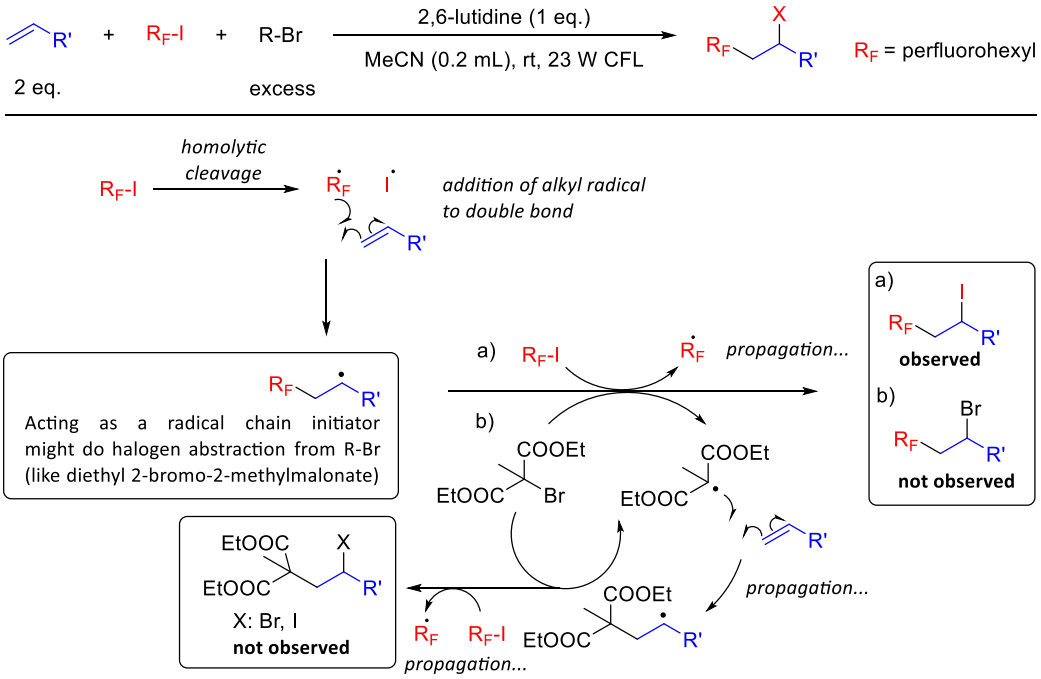
Entry	Product	Time (h)	Conv. (%)[b]	Yield (%)[c]
5	 (**5e**)	48	>99	60
6	 (**5f**)	20	>99	94
7[d]	 (**5g**)	20	95	85
8[e]	 (**5h**)	42	>99	79
9[f]	 (**5i**)	23	>99	94
10	 (**5j**)	40	92	65 (Y_{NMR}=92%)
11	 (**5k**)	20.5	>99	94

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), *p*-anisaldehyde (20 mol%), 2,6-lutidine (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1** (or **2**) and **5**. [c] Yield of isolated product after flash-chromatography. [d] Reaction set up on doubled scale. [e] **1h** (0.5 mmol), **2** (0.1 mmol). [f] Reaction conditions: **1i** (0.2 mmol), **2** (0.1 mmol), *p*-anisaldehyde (20 mol%), water (0.2 mL), rt, 23 W CFL, freeze-pump-thaw repeated three times.

The scope for the alkyl halide is quite broad. The diethyl bromomalonate was slightly more reactive than the methyl-substituted diethyl 2-bromo-2-methylmalonate (entries 1, 2), while the monoester ethyl 2-bromopropionate (entry 3) revealed to be less reactive. We tested also ethyl bromoacetate, but the reaction was very slow and never reached synthetically useful yields. In the cases with polybrominated compounds reported in entries 4 and 6 the reactions provided high yields of products **5d** and **5f** exclusively, without proceeding further to give a second ATRA reaction between the product and the excess of olefin. We performed the reaction also with ethyl 2-bromo-2-fluoroacetate (entry 5) affording the particularly valuable fluorinated compound **5e** in good yield, in which the bromo was the halogen atom transferred. The use of bromoacetonitrile in this simple protocol allowed the direct introduction of a nitrile group, reacting in 20 hours with almost complete conversion and affording

high yields (entry 7). Noteworthy is the result obtained with carbon tetrachloride (entry 8). In fact this substrate is very difficult to reduce, but slightly modifying the reaction conditions we were able to obtain complete conversion of olefin **2** in 42 hours and good yields of the corresponding polychlorinated product. Except for some specific examples, the isolation of the product in these reactions was relatively simple by column chromatography, due to the high selectivity of the reaction and subsequently the absence of byproducts. However visualization of the thin layer chromatography plates was not always easy using the common stain solutions. Moreover we carried out the reaction with perfluorohexyl iodide (entry 9) achieving excellent results also performing the reaction on water; in these reaction we used an excess of alkyl halide to avoid the difficult separation of the product from the olefin in this specific case. During the series of control experiments performed for all the substrates under study, for this particular substrate we recorded a background reaction. Indeed the ATRA took place also in the absence of aldehyde, because the perfluorohexyl iodide can suffer homolytic cleavage of the carbon-iodine bond under irradiation in our conditions. While without aldehyde the reaction gave a conversion of the perfluorinated iodo compound of less then 30% overnight, addition of 20 mol% of *p*-anisaldehyde to the reaction in acetonitrile resulted in complete conversion in the same reaction time; so even in the presence of a background reaction our protocol provided a major improvement of the reactivity. Background reactions were detected as well for carbon tertrabromide and bromotrichloromethane (entries 10, 11), but in these cases the background reactions afforded very high reaction rates, and no substantial improvement was observed in the presence of the aldehydic catalyst.

We tried to exploit the homolytic cleavage of perfluorohexyl iodide to initiate the ATRA reaction of other compounds, like for example diethyl 2-bromo-2-methylmalonate, in the absence of *p*-anisaldehyde, with the idea of providing a protocol in which this easily cleavable halide compound would serve as initiator of the ATRA reaction of a second alkyl halide. However, the reaction provided only the ATRA product of the perfluoroalkyl iodide even when the bromomalonate was used as the solvent (Scheme 39).

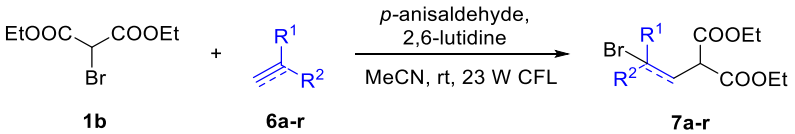


Scheme 39

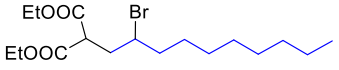
So we inferred that the aldehyde is strictly necessary for the reaction with diethyl 2-bromo-2-methylmalonate to take place. Furthermore, it was not possible to initiate the reaction of alkyl halides that didn't show reactivity using our protocol (for example the chloro-analogue diethyl chloromalonate) using a small amount of other halides able to work in this process (for example bromo diethyl malonate in catalytic amount or carbon tetrachloride as solvent). The reaction of diethyl chloromalonate was never initiated in those attempts.

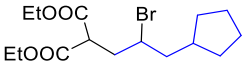
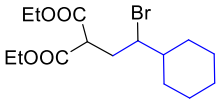
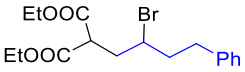
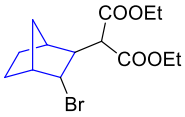
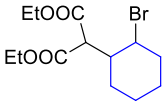
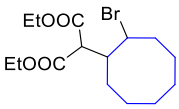
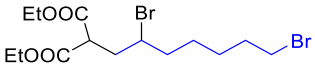
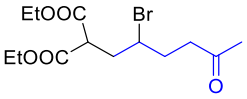
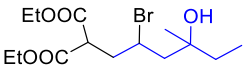
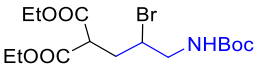
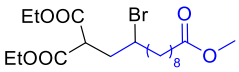
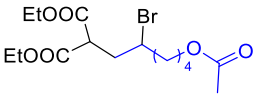
After our success in finding halide partners applicable to our ATRA protocol, we investigated the behaviour of different olefins under the optimized reaction condition (Table 36). Since diethyl bromomalonate was among the most reactive alkyl halides tested, we decided to use it for this study.

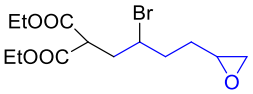
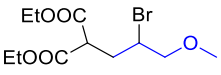
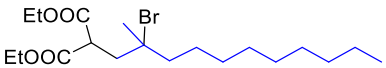
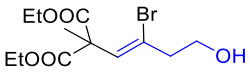
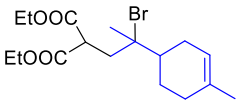
Table 36: Scope of the olefins for the photochemical organocatalysed ATRA.[a]



1b **6a-r** **7a-r**

Entry	Product	Time (h)	Conv. (%)[b]	Yield (%)[c]
1[d]	 (**7a**)	12	>99	86

Entry	Product	Time (h)	Conv. (%)[b]	Yield (%)[c]
2	 (**7b**)	16	96	92
3	 (**7c**)	15	>99	89
4	 (**7d**)	23	97	70
5	 (**7e**)	12	97	89
6	 (**7f**)	95	78	75
7[e]	 (**7g**)	14	>99	97
8	 (**7h**)	88	>99	92
9	 (**7i**)	16	>99	88
10	 (**7j**)	19	95	89
11	 (**7k**)	111	84	78
12	 (**7l**)	16	94	78
13	 (**7m**)	26	98	85

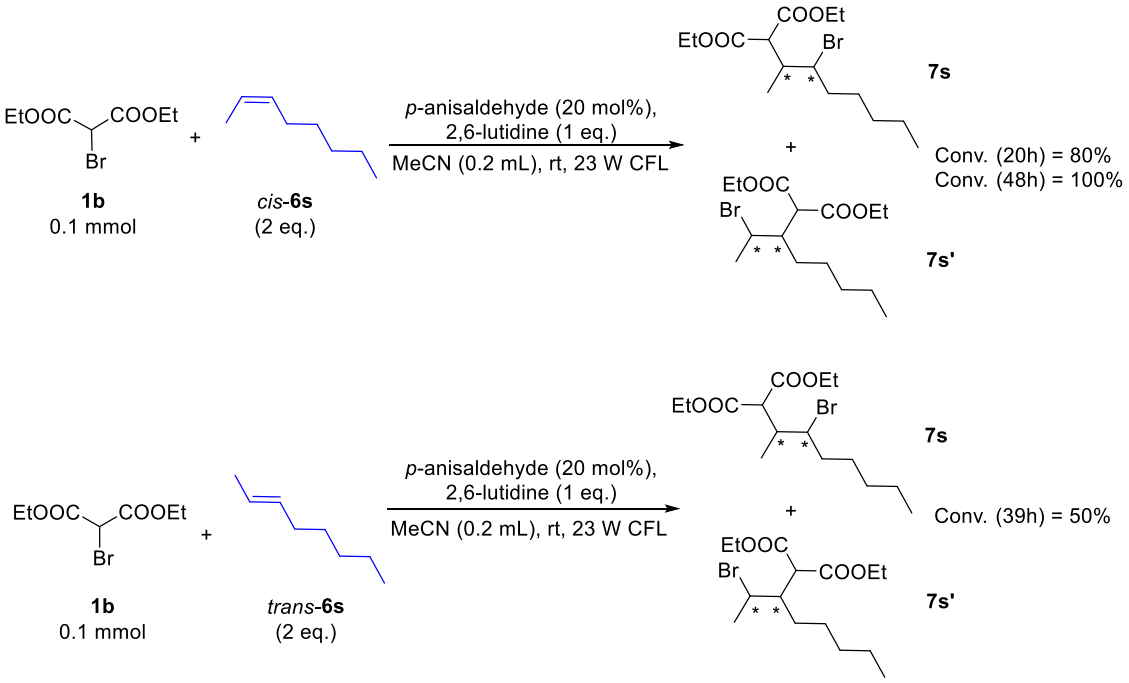
Entry	Product	Time (h)	Conv. (%)[b]	Yield (%)[c]
14	 (**7n**)	12	>99	97
15[f]	 (**7o**)	85	60	42
16	 (**7p**)	13	>99	87
17	 (**7q**)	96	70	60
18	 (**7r**)	15	>99	82

[a] Reaction conditions: **1b** (0.1 mmol), **6** (0.2 mmol), *p*-anisaldehyde (20 mol%), 2,6-lutidine (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1b** and **7**. [c] Yield of isolated product after flash-chromatography. [d] Reaction set up on doubled scale. [e] Starting from *cis*-cyclooctene. [f] **6o** (0.4 mmol).

The reaction worked perfectly for non-polarized terminal aliphatic olefins without any functional groups (entries 1-3) and also bearing an aromatic ring (entry 4). The transformation showed to be tolerant to the presence of a variety of functional groups like bromide (entry 8), ketone (entry 9), alcohol (entry 10), carbamate (entry 11), esters (entries 12, 13), epoxide (entry 14) and ether (entry 15). Also α-methyl substituted terminal olefins can be used in this process (entry 16) achieving very good results. We tested also 3-butyn-1-ol (entry 17); and even if the reaction was much slower, it was interesting to see that we can extend this process also to alkynes. Finally we tested limonene as a substrate of the reaction obtaining selectively the ATRA product on the terminal bond (**7r**) with 82% yield in 15 hours, without detecting any product involving the trisubstituted internal double bond in the reaction.

Encouraged by the wide scope in both the olefinic and halide partners, and by the good results achieved in terms of yield, we decided to test also internal olefins, which usually are typically more difficult to react in ATRA reactions. Under the same mild reaction conditions the cyclic substrates 2-norbornene, cyclohexene and cyclooctene led to the corresponding functionalized compounds with excellent yields (Table 36,

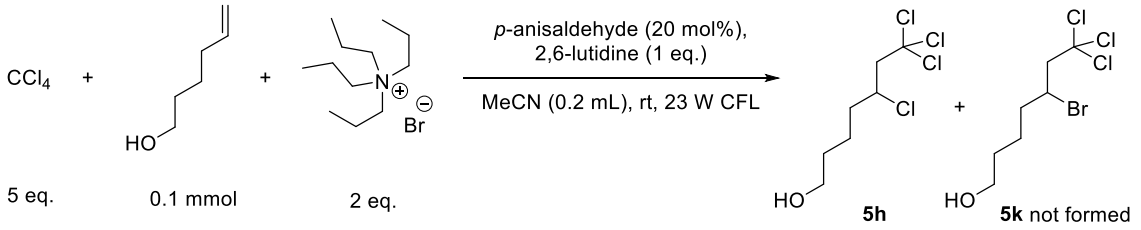
entries 5-7). We were pleased to see that in the case of the even more challenging linear internal olefin, both *cis*- and *trans*-octene afforded the desired transformation employing our reaction conditions (Scheme 40). It is noteworthy that the *cis* isomer appeared to be more reactive than the *trans*. Unfortunately in both cases there were not any regio- or stereo-control and both regioisomers were formed in both diastereoisomers.



Scheme 40

Additionally, we performed a scale-up of the reaction (by a factor of 100) between diethyl bromomalonate (10 mmol) and 1-hexen-5-ol isolating the product in 98.6% yield and recovering 91% of *p*-anisaldehyde. The reaction time increased to 44 hours instead of 15 probably because the same source of irradiation as for the small scale 0.1 mmol reaction was used, so only one 23 W CFL bulb.

In order to explore the possibility of a polar pathway participating in the reaction mechanism, we performed the reaction adding to the mixture tetrabutylammoniun bromide (Scheme 41). In these conditions if a carbocation is formed during the reaction, the bromide should be incorporated to give product **5k**, otherwise only product **5h** would be produced through a pure radical pathway.

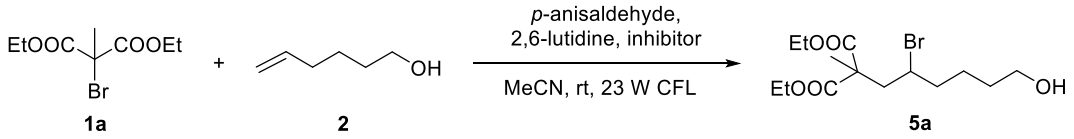


Scheme 41

Since only product **5h** was observed, we could infer that only a radical mechanism was present in this organocatalytic photochemical ATRA reaction.

We set up different reactions aimed to prove the radical pathway and to further study the mechanism. First, we set up the model reaction in the presence of radical scavengers such as 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT), and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) or in the presence of the good electron-acceptor 1,4-dinitrobenzene (Table 37); in all the cases the reaction was strongly inhibited, confirming the radical nature of the process. Unfortunately, the addition of radical scavengers didn't lead to the trapping of any intermediate.

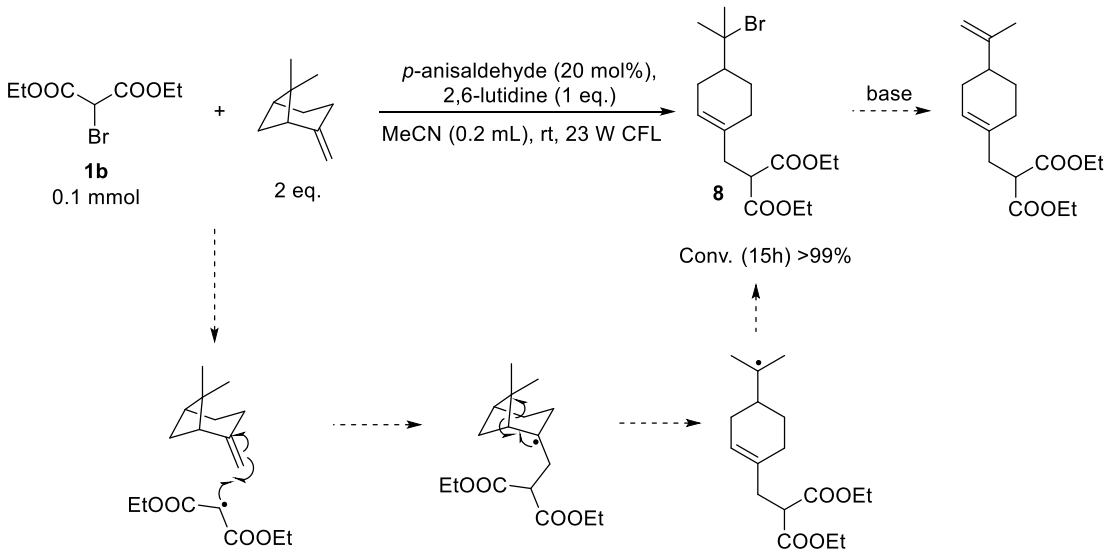
Table 37: Study of the formation of radicals in the presence of radical and electron transfer inhibitors.[a]



Entry	Inhibitor	Time (h)	Conv. (%)[b]
1	-	24	>99
2	BHT	24	-
3	TEMPO	24	-
4	1,4-Dinitrobenzene	24	-

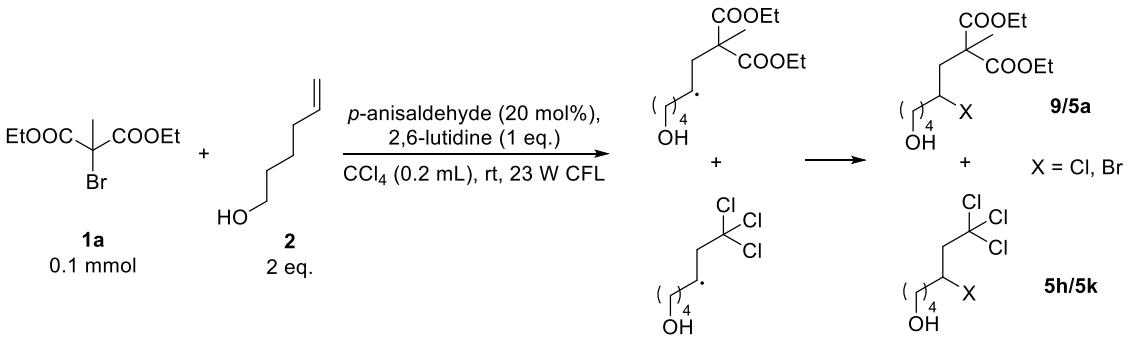
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), *p*-anisaldehyde (20 mol%), 2,6-lutidine (0.1 mmol), inhibitor (0.1 mmol), acetonitrile (0.2 mL), rt, irradiation with a 23 W CFL bulb placed around 10 cm far from the reaction, freeze-pump-thaw repeated three times.. [b] Determined by ^{1}H NMR of the crude mixture from the relative amounts of **1a** and **5a**.

Another proof of the presence of a radical pathway was found in the reaction carried out with β-pinene. After the addition of the malonate radical to the double bond, a ring opening rearrangement of the structure, a process well known for radical intermediates, took place followed by the addition of the bromine (Scheme 42). This reaction also provides evidence against the involvement of concerted mechanism.



Scheme 42

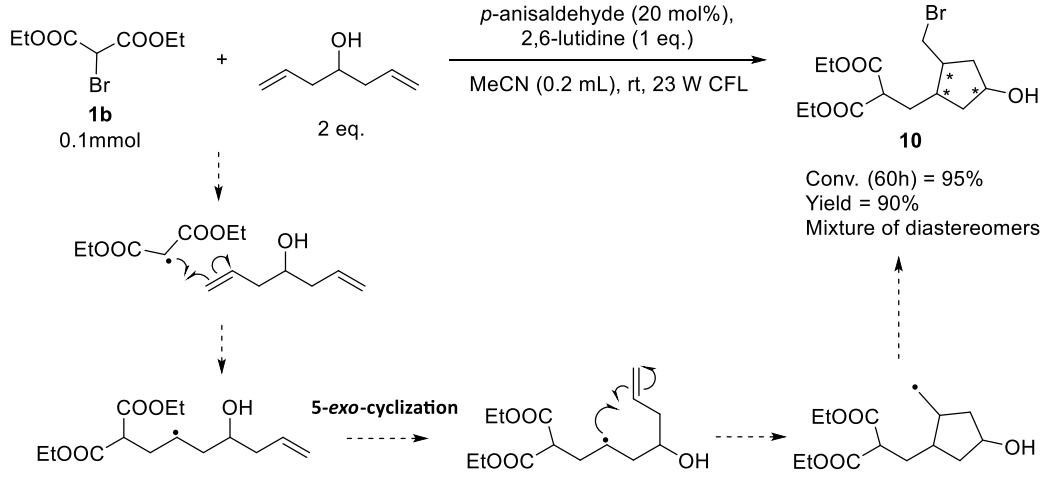
A further demonstration that the reaction is not concerted was gained performing the model reaction between olefin **2** and **1a** in carbon tetrachloride as solvent, instead of acetonitrile (Scheme 43). In these conditions, two carbon-centered secondary radical intermediates may be formed as both diethyl 2-bromo-2-methylmalonate and carbon tetrachloride are valid substrates for this reaction. These intermediates can abstract both a bromine or a chlorine atom forming four possible products. In fact, this crossover experiment afforded the four possible products excluding the possibility of a concerted mechanism.



Scheme 43

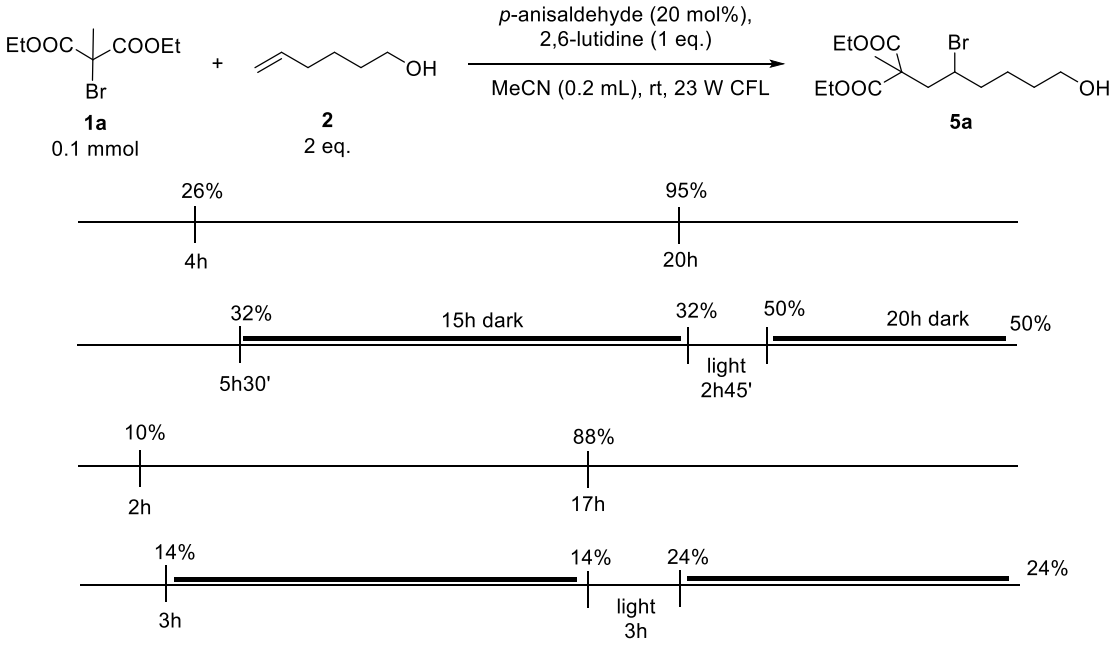
The use of 1,6-heptadien-4-ol as the olefin might give the formation of different products: the single addition to one double bond, the addition to both the double bonds or the cyclization. The intermediate formed can be imagined to cyclize by intramolecular addition to the second double bond to form a 5-membered ring or a 6-membered ring. Usually 5-*exo* cyclizations are highly favoured in radical mechanisms;

conversely 6-*endo* cyclizations are typical in polar mechanisms where 5-*exo* cyclizations cannot occur. When performing the reaction with bromomalonate, we obtained the 5-membered cyclized product as reported in Scheme 44, consistent with ring closure of a radical.



Scheme 44

In order to have additional information on the mechanism, the requirement of light irradiation throughout the reaction progress and on the probable contribution of a radical chain, we carried out the reaction alternating periods of irradiation with dark periods (Scheme 45).



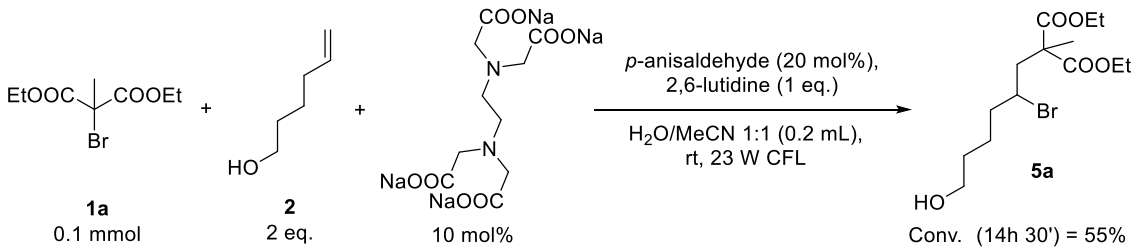
Scheme 45

In our experiments, the reactions stopped immediately when light was excluded during the dark periods, initiating again when irradiation was restored. These observations tell us that the light is essential for the reaction to proceed and suggests that if a radical chain mechanism is present, it would have very short propagating chains. The proper way to establish the presence, absence or the extent of a radical chain is the determination of the quantum yield; these mesurements will be done in the near future during the mechanistic studies that are still in progress.

All the data reported in the lines of Scheme 45 were produced by different parallel and identical reactions. The reason is that taking an aliquot from one reaction requires the opening of the Schlenk tube and, even if taking care of excluding oxygen during the sampling, there is the risk of interrupting a chain if present. So, for example, the data reported before and after a dark period come from two different reactions set up in exactly the same conditions.

From the results obtained we could also infer that there is not an induction period since the reaction gave conversion from the first few hours.

To be sure of the absence of metal impurities that could catalyse the reaction we performed it in the presence of EDTA sodium salt able to chelate metals (Scheme 46). The reaction proceeded thus excluding the hypothesis of the catalytic metal impurity. Additionally, the model reaction was performed with freshly distilled reagents, alkyl halide, olefin, aldehyde, base and solvent, in new glassware, with the same excellent results. The reproducibility of the protocol, the fact that not all the aldehydes were able to catalyse the process and that the reaction without aldehyde didn't occur, together with the other experimental information make us be certain that an impurity could not be responsible for the reactivity under study.



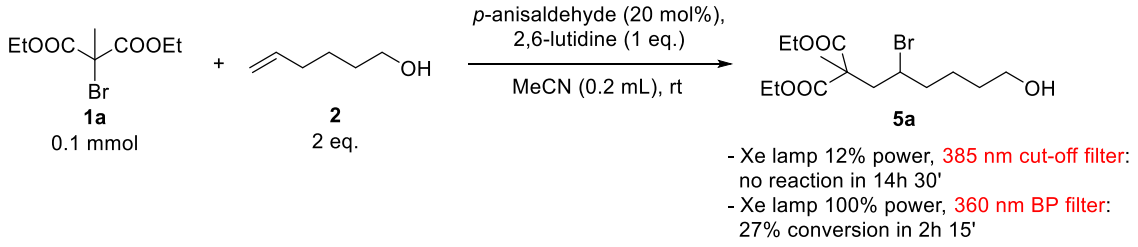
Scheme 46

Even if the reaction was not coloured (only sometimes yellowish after many hours) we measured the absorption spectra of the reaction components in order to

investigate the possibility of the formation of an EDA complex able to promote the reaction. We recorded the absorption spectra of all the possible mixtures of the reagents in many different concentrations but none of them absorbed in the visible. In the UV region, the interpretation of the results was complicated because the concentrations used in the reaction were too high for recording a UV absorption spectra without saturating the detector of the spectrophotometer, while decreasing too much the concentration in order to allow a proper analysis could eliminate the possibility of formation of weak complexes that are usually very sensitive to concentration.

The light is very important for this reaction as the transformation does not occur at all in the dark even if heated at 100°C in DMF or at reflux in toluene for several hours. The model reaction was set up on the roof of the institute using illumination by the sun, instead of the 23 W CFL bulb used in the laboratory set-up, providing 91% of conversion in 9 hours using only 5 mol% of *p*-anisaldehyde. We rationalized this increased reactivity based on the much higher light intensity of the sun compared to that of a household bulb and maybe also on a plausible increase of the temperature of the mixture.

With the aim of understanding which was the useful wavelength able to promote reactivity we set up a series of experiments using a Xenon lamp equipped with different light filters (Scheme 47).



Scheme 47

First we set up the reaction using a 385 nm cut-off filter excluding completely the UV and near UV wavelengths; the power of the lamp was set to 12% in order to be closer to the light intensity of a 23 W CFL bulb at 15 cm far from the reaction. In these conditions the reaction did not proceed. We carried out the same reaction using a 360 nm band-pass filter which allows irradiation from 355 to 365 nm to get through, obtaining 27% of conversion of the alkyl halide in 2 hours and 15 minutes, thus

demonstrating that these near UV wavelengths were the ones able to promote the process.

In fact all the CFL bulbs have a residual UV emission peak centred at 360 nm and probably this near-UV light is the one able to promote the reaction under study. The emission spectrum of one of the lamps that were used in the laboratory is shown in Figure 21 in which the peak responsible of this organocatalytic photochemical ATRA reaction to alkenes is highlighted.

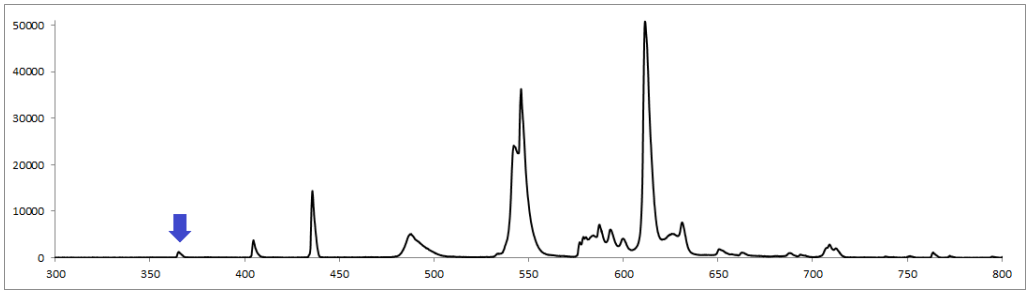


Figure 21

4. Conclusions

We developed the first organocatalytic photochemical ATRA reaction. This photochemical transformation offers a new synthetic methodology for the rapid construction of highly functionalized complex molecules in a single step by introduction of two functional groups in adjacent carbons of a simple olefin. This process has a broad scope that includes mono- and di- substituted olefins both terminal and internal. Also alkynes are able to react smoothly in these conditions. Furthermore the presence of many functional groups is tolerated in the olefinic partner. The direct introduction of several functional groups such as fluorinated fragments, alcohol, nitrile, ester and halide, which are excellent synthetic targets for further functionalization, into a simple olefin is allowed by the very mild and extremely selective reaction developed.

We were able to scale up the reaction, an achievement not common for organocatalytic processes which usually show poor ability to adjust to scales higher than those used for reaction development (usually less than 1 mmol). This established its potential for a synthetic practical use.

The absence of pricey transition-metal catalysts, toxic reagents, or harsh reaction conditions makes this reaction attractive from economic, environmental and safety perspectives.

Although the most obvious mechanism for this transformation is the classical ATRA pathway, given the novelty of the reaction, further studies on the mechanism of the photochemical event are still in progress.

5. Experimental section

General Information

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal.

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI).

General Procedures

All reactions were set up under an argon or nitrogen atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased and the reaction mixtures were degassed by three cycles of freeze-pump-thaw. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were employed, using UV light as the visualizing agent and basic aqueous potassium permanganate ($KMnO_4$) stain solutions, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials. Reagents were purchased at the highest commercial quality from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification, unless otherwise stated. All the reagents used within this study are commercially available

except of *tert*-butyl allylcarbamate obtained from the Boc-protection of allylamine.

General Procedures for the Photochemical Organocatalytic Atom Transfer Radical Addition to Alkenes

1. General Procedure for the Photochemical Organocatalytic Atom Transfer Radical Addition to Alkenes

A 10 mL Schlenk tube was charged with the solvent (CH_3CN, 0.5 M referring to the alkyl halide), olefin (2 eq.), 2,6-lutidine (1 eq.), the alkyl halide (1 eq.) and *p*-anisaldehyde (20 mol%). The reaction mixture was degassed via freeze pump thaw (x 3 times), and the vessel refilled with argon or nitrogen. After the reaction mixture was thoroughly degassed, the vial was sealed and positioned approximately 10 cm away from the light source. A household full spectrum 23 W compact fluorescent light (CFL) bulb was used for irradiating the reaction mixture. The reaction can be monitored by analysis (^1H NMR spectroscopy) of an aliquot taken from the reaction mixture under inert atmosphere. After stirring for the indicated time, the crude mixture was loaded directly into the silica gel column. Purification by flash column chromatography affords the functionalized compound in the stated yield.

2. On Water-Procedure for the Photochemical Organocatalytic Atom Transfer Radical Addition to Alkenes

A 10 mL Schlenk tube was charged with the solvent (H_2O, 0.5 M referring to the alkyl halide), olefin (2 eq.), the alkyl halide (1 eq.) and *p*-anisaldehyde (20 mol%). The reaction mixture was degassed via freeze pump thaw (x 3 times), and the vessel refilled with argon or nitrogen. After the reaction mixture was thoroughly degassed, the vial was sealed and positioned approximately 10 cm away from the light source. A household full spectrum 23 W compact fluorescent light (CFL) bulb was used for irradiating the reaction mixture. After stirring for the indicated time, the crude mixture was extracted with DCM (x3), the solvent was removed under pressure and the crude was loaded into the silica gel column. Purification by flash column chromatography affords the functionalized compound in the stated yield.

Diethyl 2-methyl-2-(2-bromo-6-hydroxyhexyl)malonate (5a)

The general procedure was followed using diethyl 2-bromo-2-methylmalonate (0.1 mmol, 19 μL, 1 eq.), MeCN (200 μL), 5-hexen-1-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 19 h

the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (30.9 mg, 88% yield) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.20-4.16 (m, 4H), 4.10-4.05 (m, 1H), 3.67-3.65 (t, *J* = 6.2 Hz 2H), 2.60-2.50 (m, 2H), 1.90-1.83 (m, 2H), 1.67-1.51 (m, 4H), 1.49 (s, 3H), 1.27-1.24 2x (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 171.7, 62.7, 61.7, 61.5, 53.1, 51.6, 44.5, 40.2, 31.9, 23.7, 20.0, 14.0, 13.9. HRMS (-ve CI): calculated for $C_{14}H_{25}BrNaO_5$ (M+Na): 375.0778, found: 375.0790.

Diethyl 2-(2-bromo-6-hydroxyhexyl)malonate (5b)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 5-hexen-1-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 15 h the reaction showed complete conversion of the bromo malonate. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (33.4 mg, 98% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.19 (m, 4H), 4.09 – 3.99 (m, 1H), 3.81 (dd, J = 10.2, 4.2 Hz, 1H), 3.69 (t, J = 6.0 Hz, 2H), 2.49 (ddd, J = 14.8, 10.2, 3.1 Hz, 1H), 2.28 (ddd, J = 14.8, 10.7, 4.2 Hz, 1H), 1.97 – 1.86 (m, 2H), 1.72 – 1.51 (m, 4H), 1.34 – 1.25 2x(t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.8, 62.6, 61.7, 61.6, 54.6, 50.6, 39.1, 37.8, 31.9, 23.8, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{13}H_{23}BrNaO_5$ (M+Na): 361.0627, found: 361.0621.

Ethyl 4-bromo-8-hydroxy-2-methyloctanoate (5c)

The general procedure was followed using ethyl-2-bromopropionate (0.1 mmol, 13 μL), MeCN (200 μL), 5-hexen-1-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 74 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 9:1 hexane:AcOEt) afforded the title compound (22 mg, 78% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.09 (m, 4H), 4.10 – 3.99 (m, 2H), 3.73 – 3.62 (m, 4H), 2.94 – 2.80 (m, 1H), 2.83 – 2.70 (m, 1H), 2.36 – 2.14 (m, 2H), 1.93 – 1.75 (m, 6H), 1.69 – 1.50 (m, 10H), 1.33 – 1.24 2x(t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 176.0, 62.63, 62.61, 60.6, 60.5, 56.1,

54.9, 43.1, 42.1, 39.4, 39.0, 38.1, 37.9, 32.0, 23.9, 23.7, 18.2, 16.1, 14.23, 14.21. HRMS (+ve ESI): calculated for $C_{11}H_{21}BrNaO_3$ (M+Na): 303.0559, found: 303.0566.

Diethyl 2-bromo-2-(2-bromo-6-hydroxyhexyl)malonate (5d)

The general procedure was followed using diethyl dibromomalonate (0.1 mmol, 19 μL, 1 eq.), MeCN (200 μL), 1-hexen-5-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 40 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 15:1 hexane:AcOEt) afforded the title compound (29.5 mg, 71% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 – 4.18 (m, 5H), 3.69 (t, *J* = 5.9 Hz, 2H), 2.98 (dd, *J* = 16.0, 8.5 Hz, 1H), 2.88 (dd, *J* = 16.0, 3.4 Hz, 1H), 2.03 – 1.81 (m, 2H), 1.71 – 1.53 (m, 4H), 1.37 – 1.27 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.8, 63.5, 63.3, 62.6, 61.8, 51.2, 46.4, 39.5, 31.9, 23.6, 13.8, 13.7. HRMS (+ve ESI): calculated for $C_{13}H_{22}Br_2NaO_5$ (M+Na): 438.9726, found: 438.9740.

Ethyl 4-bromo-2-fluoro-8-hydroxyoctanoate (5e)

The general procedure was followed using ethyl bromofluoroacetate (0.1 mmol, 11.8 μL, 1 eq.), MeCN (200 μL), 1-hexen-5-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 48 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (17.1 mg, 60% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 – 5.04 (m, 1H), 4.38 – 4.25 (m, 2H), 4.27 – 4.14 (m, 1H), 3.69 (t, *J* = 6.0 Hz, 2H), 2.58 – 2.42 (m, 1H), 2.41 – 2.22 (m, 1H), 2.04 – 1.81 (m, 2H), 1.77 – 1.49 (m, 5H), 1.39 – 1.27 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.3, 169.2, 169.0, 88.0, 87.8, 86.6, 86.3, 62.5, 61.9, 61.8, 51.68, 51.66, 50.7, 50.6, 41.8, 41.6, 41.4, 41.2, 39.0, 38.1, 31.9, 31.8, 23.8, 23.7, 14.12, 14.10. HRMS (+ve ESI): calculated for $C_{10}H_{18}BrFNaO_3$ (M+Na): 307.0316, found: 307.0314.

2,2,4-Tribromooctane-1,8-diol (5f)

The general procedure was followed using 2,2,2-tribromoethanol (0.1 mmol, 28.2 mg, 1 eq.), MeCN (200 μL), 1-hexen-5-ol (0.2 mmol, 24 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 20 h the reaction showed complete conversion of the alkyl halide. Purification by flash column

chromatography (gradient eluent from hexane to 15:1 hexane:AcOEt) afforded the title compound (36.1 mg, 94% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 – 4.21 (m, 1H), 4.19 (d, *J* = 12.9 Hz, 1H), 4.05 (d, *J* = 12.9 Hz, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.24 (dd, *J* = 16.3, 6.6 Hz, 1H), 3.00 (dd, *J* = 16.3, 3.7 Hz, 1H), 2.18 (s, 2H), 2.08 – 1.91 (m, 2H), 1.75 – 1.53 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.9, 62.6, 54.2, 52.0, 39.8, 31.8, 23.6. HRMS (+ve ESI): calculated for $C_8H_{15}O_2{}^{79}Br_2$ (M+Na): 300.9433, found: 300.9443.

4-Bromo-8-hydroxyoctanenitrile (5g)

The general procedure was followed using bromoacetonitrile (0.2 mmol, 13 μL, 1 eq.), MeCN (400 μL), 1-hexen-5-ol (0.4 mmol, 48 μL, 2 eq.), 2,6-lutidine (0.2 mmol, 24 μL, 1 eq.) and *p*-anisaldehyde (0.04 mmol, 4.8 μL, 20 mol%). After 20 h the reaction showed 95% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 15:1 hexane:AcOEt) afforded the title compound (37.5 mg, 85% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 – 4.02 (m, 1H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.70 – 2.57 (m, 2H), 2.26 – 2.15 (m, 1H), 2.15 – 2.00 (m, 1H), 2.00 – 1.80 (m, 2H), 1.71 – 1.52 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.8, 62.4, 54.7, 38.6, 34.5, 31.8, 23.8, 16.0. HRMS (+ve ESI): calculated for $C_8H_{15}BrNO$ (M+H): 220.0332, found: 220.0321.

5,7,7,7-Tetrachloroheptan-1-ol (5h)

The general procedure was followed using CCl_4 (0.5 mmol, 48 μL, 5 eq.), MeCN (200 μL), 5-hexen-1-ol (0.1 mmol, 12 μL, 1 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 42 h the reaction showed complete conversion of the olefin. Purification by flash column chromatography (gradient eluent from hexane to 9:1 hexane:AcOEt) afforded the title compound (20.1 mg, 79% yield) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 – 4.22 (m, 1H), 3.78 – 3.62 (m, 2H), 3.30 (dd, J = 15.7, 5.7 Hz, 1H), 3.15 (dd, J = 15.7, 4.3 Hz, 1H), 2.08 – 1.81 (m, 2H), 1.77 – 1.50 (m, 4H), 1.36 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.9, 62.6, 62.2, 57.6, 38.8, 31.9, 22.4. HRMS (APCI): calculated for (M-2HCl-OH)+: 163.0076, found: 163.0074.

7,7,8,8,9,9,10,10,11,11,12,12,12-Tridecafluoro-5-iodododecan-1-ol (5i)

The on water-procedure was followed using perfluorohexyl iodide (0.2 mmol, 44 μL, 2 eq.) H_2O (200 μL), 5-hexen-1-ol (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02

mmol, 2.4 μL, 20 mol%). After 23 h the reaction showed complete NMR yield (1,3,5-trimethoxy benzene as internal standard). Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (51.2 mg, 94% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 – 4.31 (m, 1H), 3.71 (t, J = 5.9 Hz, 2H), 3.05 – 2.71 (m, 2H), 1.97 – 1.76 (m, 2H), 1.76 – 1.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5 , 41.6 (t, J = 20.9 Hz), 40.0 (d, J = 2.1 Hz), 31.5 , 26.0 , 20.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.9 (t, J = 10.0 Hz, 3F), -111.3 – -112.3 (m, 1F), -114.2 – -115.2 (m, 1F), -121.7 – -122.0 (m, 2F), -122.8 – -123.1 (m, 2F), -123.6 – -123.9 (m, 2F), -126.1 – -126.4 (m, 2F). HRMS (+ve APCI): calculated for $C_{12}H_{11}F_{13}I$ (M-H_2O): 528.9698, found: 528.9692.

Diethyl 2-(2-bromodecyl)malonate (7a)

The general procedure was followed using diethyl bromomalonate (0.2 mmol, 17 μL, 1 eq.), MeCN (400 μL), 1-decene (0.4 mmol, 76 μL, 2 eq.), 2,6-lutidine (0.2 mmol, 24 μL, 1 eq.) and *p*-anisaldehyde (0.04 mmol, 4.8 μL, 20 mol%). After 12 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (65.4 mg, 86% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 – 4.17 (m, 4H), 4.09 – 3.94 (m, 1H), 3.80 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.48 (ddd, *J* = 14.8, 10.3, 3.1 Hz, 1H), 2.26 (ddd, *J* = 14.9, 10.7, 4.2 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.62 – 1.50 (m, 1H), 1.50 – 1.38 (m, 1H), 1.34 – 1.23 (m, 11H), 0.92 – 0.86 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.8, 61.7, 61.6, 55.0, 50.6, 39.4, 37.9, 31.8, 29.4, 29.2, 28.9, 27.4, 22.6, 14.1, 14.06, 14.02. HRMS (+ve ESI): calculated for $C_{17}H_{31}BrNaO_4$ (M+Na): 401.1298, found: 401.1309.

Diethyl 2-(2-bromo-3-cyclopentylpropyl)malonate (7b)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), allylcyclopentane (0.2 mmol, 29 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 16 h the reaction showed 96% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (32.3 mg, 92% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 – 4.18 (m, 4H), 4.10 – 3.98 (m, 1H), 3.83 (dd, J = 10.3, 4.2 Hz, 1H), 2.52 (ddd, J = 14.8, 10.2, 3.1 Hz, 1H), 2.25 (ddd, J = 14.8, 10.6, 4.2 Hz, 1H),

2.16 – 2.05 (m, 1H), 2.01 (ddd, J = 14.6, 8.8, 6.0 Hz, 1H), 1.89 – 1.74 (m, 3H), 1.68 – 1.51 (m, 4H), 1.33 – 1.24 2x(t, J = 7.2 Hz, 3H), 1.19 – 1.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.8, 61.7, 61.6, 54.3, 50.6, 45.9, 38.2, 38.1, 32.5, 31.9, 25.0, 25.0, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{15}H_{25}BrNaO_4$ (M+Na): 371.0834, found: 371.0828.

Diethyl 2-(2-bromo-2-cyclohexylethyl)malonate (7c)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), vinylcyclohexane (0.2 mmol, 27 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 15 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (30.9 mg, 89% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 – 4.09 (m, 4H), 3.96 (ddd, *J* = 11.3, 4.2, 2.6 Hz, 1H), 3.80 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.47 (ddd, *J* = 14.8, 10.7, 2.6 Hz, 1H), 2.28 (ddd, *J* = 15.0, 11.3, 3.8 Hz, 1H), 1.89 – 1.75 (m, 4H), 1.74 – 1.62 (m, 1H), 1.62 – 1.56 (m, 1H), 1.37 – 1.21 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 168.9, 61.8, 61.7, 61.6, 50.8, 44.9, 35.2, 30.6, 29.2, 26.2, 26.1, 26.0, 14.1, 14.0. . HRMS (+ve ESI): calculated for $C_{15}H_{25}BrNaO_4$ (M+Na): 371.0828, found: 371.0830.

Diethyl 2-(2-bromo-4-phenylbutyl)malonate (7d)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 4-phenyl-1-butene (0.2 mmol, 30 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 23 h the reaction showed 97% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (25.9 mg, 70% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.26 – 7.19 (m, 3H), 4.28 – 4.14 (m, 4H), 4.04 – 3.94 (m, 1H), 3.81 (dd, J = 10.0, 4.4 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.84 – 2.74 (m, 1H), 2.51 (ddd, J = 14.8, 10.0, 3.2 Hz, 1H), 2.35 (ddd, J = 14.9, 10.5, 4.4 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.7, 140.6, 128.51, 128.48, 126.2, 61.7, 61.6, 54.0, 50.6, 41.0, 37.9, 33.6, 14.0. HRMS (+ve ESI): calculated for $C_{17}H_{23}BrNaO_4$ (M+Na): 393.0677, found: 393.0672.

Diethyl 2-(3-bromobicyclo[2.2.1]heptan-2-yl)malonate (7e)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), norbornene (0.2 mmol, 18.8 mg, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 12 h the reaction showed 97% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (29.6 mg, 89% yield) as a colourless oil in a mixture of two diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (dd, J = 7.0, 1.9 Hz, 1H), 4.33 – 4.12 (m, 8H), 4.11 – 4.03 (m, 1H), 3.61 (d, J = 12.1 Hz, 1H), 3.15 (d, J = 11.0 Hz, 1H), 2.64 – 2.53 (m, 2H), 2.51 – 2.43 (m, 1H), 2.38 – 2.29 (m, 1H), 2.10 – 1.98 (m, 3H), 1.98 – 1.89 (m, 1H), 1.76 – 1.43 (m, 6H), 1.39 – 1.23 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.4, 168.1, 167.7, 61.8, 61.62, 61.60, 61.5, 60.8, 57.8, 55.7, 55.5, 52.3, 48.0, 47.0, 44.6, 41.4, 40.0, 34.7, 34.2, 30.0, 29.6, 26.8, 23.6, 14.12, 14.05, 13.9. HRMS (+ve ESI): calculated for $C_{14}H_{21}BrNaO_4$ (M+Na): 355.0521, found: 355.0515.

Diethyl 2-(2-bromocyclohexyl)malonate (7f)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), cyclohexene (0.2 mmol, 20 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 95 h the reaction showed 78% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 30:1 hexane:AcOEt) afforded the title compound as a mixture of two diastereomers (24.1 mg, 75% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 – 4.72 (m, 1H), 4.33 – 4.16 (m, 9H), 4.14 (d, *J* = 3.7 Hz, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.40 – 2.30 (m, 1H), 2.28 – 2.13 (m, 2H), 2.05 – 1.86 (m, 4H), 1.84 – 1.72 (m, 4H), 1.58 – 1.39 (m, 6H), 1.32 – 1.26 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.4, 168.1, 167.9, 61.54, 61.51, 61.4, 61.1, 58.4, 57.4, 56.4, 54.3, 46.3, 42.0, 38.8, 34.8, 28.5, 27.2, 25.4, 25.3, 24.7, 20.2, 14.15, 14.09, 14.07, 14.06. HRMS (+ve ESI): calculated for $C_{13}H_{21}BrNaO_4$ (M+Na): 343.0515, found: 343.0521.

Diethyl 2-(2-bromocyclooctyl)malonate (7g)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), *cis*-cyclooctene (0.2 mmol, 26 μL, 2 eq.), 2,6-lutidine (0.1 mmol,

12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 14 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 30:1 hexane:AcOEt) afforded the title compound (mixture of two diastereomers) (33.8 mg, 97% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 – 4.44 (m, 1H), 4.43 – 4.34 (m, 1H), 4.28 – 4.14 (m, 8H), 3.26 (dd, *J* = 8.5, 3.1 Hz, 2H), 2.48 – 2.16 (m, 8H), 2.14 – 2.02 (m, 2H), 1.95 – 1.60 (m, 10H), 1.53 – 1.36 (m, 6H), 1.31 – 1.28 (m, 12H).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 168.74, 168.72, 61.3, 61.29, 61.25, 58.8, 58.7, 56.6, 56.2, 37.8, 37.7, 36.5, 36.0, 34.7, 34.0, 29.12, 29.05, 28.3, 28.2, 26.7, 26.2, 25.3, 24.0, 14.1. HRMS (+ve ESI): calculated for $C_{15}H_{25}BrNaO_4$ (M+Na): 371.0828, found: 371.0833.

Diethyl 2-(2,7-dibromoheptyl)malonate (7h)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 7-Bromo-1-heptene (0.2 mmol, 30.5 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 88 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (38.5 mg, 92% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.19 (m, 4H), 4.06 – 3.98 (m, 1H), 3.81 (dd, J = 10.3, 4.2 Hz, 1H), 3.44 (t, J = 6.7 Hz, 2H), 2.48 (ddd, J = 14.9, 10.3, 3.1 Hz, 1H), 2.28 (ddd, J = 14.9, 10.7, 4.2 Hz, 1H), 1.94 – 1.85 (m, 4H), 1.67 – 1.57 (m, 1H), 1.56 – 1.43 (m, 3H), 1.35 – 1.25 2x(t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.8, 61.7, 61.6, 54.6, 50.6, 39.2, 37.9, 33.6, 32.5, 27.5, 26.6, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{14}H_{24}Br_2NaO_4$ (M+Na): 436.9939, found: 436.9934.

Diethyl 2-(2-bromo-5-oxohexyl)malonate (7i)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 5-hexen-2-one (0.2 mmol, 23 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 16 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (29.5 mg, 88% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 – 4.16 (m, 4H), 4.13 – 3.97 (m, 1H), 3.77 (dd, *J* = 10.0, 4.5 Hz, 1H), 2.82 – 2.61 (m, 2H), 2.48 (ddd, *J* = 14.8, 9.9, 3.3 Hz, 1H), 2.31 (ddd, *J* = 14.9,

10.4, 4.5 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.18 (s, 3H), 2.10 – 1.98 (m, 1H), 1.34 – 1.25 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 168.8, 168.6, 61.75, 61.69, 53.9, 50.5, 41.3, 38.0, 32.8, 30.1, 14.04, 14.01. HRMS (+ve ESI): calculated for $C_{13}H_{21}BrNaO_5$ (M+Na): 359.0465, found: 359.0463.

Diethyl 2-(2-bromo-4-hydroxy-4-methylhexyl)malonate (7j)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 3-methyl-5-hexen-3-ol (0.2 mmol, 27 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 19 h the reaction showed 95% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (31.6 mg, 89% yield) as a colourless oil in a mixture of the two diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 – 4.18 (m, 10H), 3.81 (dd, J = 10.3, 4.0 Hz, 2H), 2.77 – 2.59 (m, 2H), 2.37 – 2.20 (m, 4H), 2.16 – 2.04 (m, 2H), 1.91 (bs, 1H), 1.76 (bs, 1H), 1.63 – 1.50 (m, 4H), 1.35 – 1.24 (m, 12H), 1.25 (s, 3H), 1.23 (s, 3H), 0.98 – 0.89 2x(t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.01, 168.95, 168.88, 168.84, 72.92, 72.88, 61.73, 61.71, 61.70, 61.68, 50.64, 50.56, 50.03, 50.01, 49.9, 49.8, 39.3, 39.2, 35.5, 34.8, 26.6, 26.0, 14.1, 14.0, 8.2, 8.1. HRMS (+ve ESI): calculated for $C_{14}H_{25}BrNaO_5$ (M+Na): 375.0783, found: 375.0778.

Diethyl 2-(2-bromo-3-((tert-butoxycarbonyl)amino)propyl)malonate (7k)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), Boc-allylamine (0.2 mmol, 31.4 mL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 111 h the reaction showed 84% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (31.0 mg, 78% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (bs, 1H), 4.32 – 4.18 (m, 4H), 4.19 – 4.05 (m, 1H), 3.76 (dd, J = 9.5, 5.0 Hz, 1H), 3.62 – 3.45 (m, 2H), 2.50 (ddd, J = 14.9, 9.5, 3.7 Hz, 1H), 2.29 (ddd, J = 15.0, 10.1, 5.1 Hz, 1H), 1.47 (s, 9H), 1.37 – 1.23 2x(t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 168.5, 155.6, 79.9, 61.8, 61.7, 53.3, 50.2, 47.1, 34.6, 28.3, 14.04, 14.01. HRMS (+ve ESI): calculated for $C_{15}H_{26}BrNNaO_6$ (M+Na): 418.0841, found: 418.0836.

1,1-Diethyl 11-methyl 3-bromoundecane-1,1,11-tricarboxylate (7l)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), methyl undec-10-enoate (0.2 mmol, 47 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 16 h the reaction showed 94% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (33.9 mg, 78% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.17 (m, 4H), 4.07 – 3.97 (m, 1H), 3.81 (dd, J = 10.3, 4.2 Hz, 1H), 3.69 (s, 3H), 2.48 (ddd, J = 14.9, 10.3, 3.1 Hz, 1H), 2.33 (t, J = 7.5 Hz, 2H), 2.27 (ddd, J = 14.8, 10.7, 4.2 Hz, 1H), 1.93 – 1.81 (m, 2H), 1.69 – 1.59 (m, 2H), 1.60 – 1.51 (m, 1H), 1.51 – 1.40 (m, 1H), 1.36 – 1.27 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 169.0, 168.8, 61.7, 61.6, 55.0, 51.4, 50.6, 39.4, 37.9, 34.1, 29.2, 29.12, 29.08, 28.9, 27.4, 24.9, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{19}H_{33}BrNaO_6$ (M+Na): 459.1358, found: 459.1353.

Diethyl 2-(6-acetoxy-2-bromohexyl)malonate (7m)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 5-hexenyl acetate (0.2 mmol, 32 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 26 h the reaction showed 98% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (32.5 mg, 85% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.17 (m, 4H), 4.09 (t, J = 6.3 Hz, 2H), 4.07 – 3.97 (m, 1H), 3.80 (dd, J = 10.3, 4.2 Hz, 1H), 2.48 (ddd, J = 14.7, 10.3, 3.1 Hz, 1H), 2.27 (ddd, J = 14.8, 10.7, 4.2 Hz, 1H), 2.07 (s, 3H), 1.94 – 1.86 (m, 2H), 1.72 – 1.60 (m, 3H), 1.60 – 1.47 (m, 1H), 1.34 – 1.24 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 168.9, 168.8, 64.1, 61.7, 61.6, 54.4, 50.5, 39.0, 37.9, 27.9, 24.0, 21.0, 14.1, 14.0. HRMS (+ve ESI): calculated $C_{15}H_{25}BrNaO_6$ (M+Na): 403.0732, found: 403.0727.

Diethyl 2-(2-bromo-4-(oxiran-2-yl)butyl)malonate (7n)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 1,2-epoxy-5-hexene (0.2 mmol, 23 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 12 h the reaction showed complete conversion of the alkyl halide. Purification by flash column

chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (32.8 mg, 97% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.16 (m, 4H), 4.15 – 3.97 (m, 1H), 3.83 – 3.77 (m, 1H), 3.01 – 2.89 (m, 1H), 2.79 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.37 – 2.22 (m, 1H), 2.11 – 1.92 (m, 2H), 1.88 – 1.72 (m, 1H), 1.70 – 1.49 (m, 1H), 1.33 – 1.26 2x (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 168.7, 61.73, 61.66, 54.1, 53.8, 51.5, 51.2, 50.5, 46.93, 46.90, 37.9, 37.8, 35.9, 35.4, 30.6, 30.2, 14.04, 14.01. HRMS (+ve ESI): calculated for $C_{13}H_{21}BrNaO_5$ (M+Na): 359.0465, found: 359.0467.

Diethyl 2-(2-bromo-3-methoxypropyl)malonate (7o)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), allyl methyl ether (0.4 mmol, 37.6 μL, 4 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 85 h the reaction showed 60% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 19:1 hexane:AcOEt) afforded the title compound (13.2 mg, 42% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 – 4.19 (m, 4H), 4.20 – 4.11 (m, 1H), 3.78 (dd, J = 10.1, 4.5 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.42 (s, 3H), 2.62 (ddd, J = 14.8, 10.1, 3.5 Hz, 1H), 2.27 (ddd, J = 15.0, 10.5, 4.6 Hz, 1H), 1.34 – 1.28 2x(t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.7, 76.7, 61.7, 61.7, 58.9, 50.2, 49.9, 34.4, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{11}H_{19}BrNaO_5$ (M+Na): 333.0308, found: 333.0309.

Diethyl 2-(2-bromo-2-methylundecyl)malonate (7p)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 2-methyl-1-undecene (0.2 mmol, 44 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 13 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 30:1 hexane:AcOEt) afforded the title compound (35.4 mg, 87% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 – 4.16 (m, 4H), 3.75 (dd, *J* = 6.3, 5.2 Hz, 1H), 2.60 (dd, *J* = 15.3, 5.2 Hz, 1H), 2.49 (dd, *J* = 15.2, 6.3 Hz, 1H), 1.87 (ddd, *J* = 14.2, 11.3, 5.1 Hz, 1H), 1.76 (ddd, *J* = 14.2, 11.0, 5.3 Hz, 1H), 1.68 (s, 3H), 1.59 – 1.44 (m, 2H), 1.34 – 1.24 (m, 18H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.4, 71.2, 61.7,

50.1, 45.8, 43.4, 31.9, 31.0, 29.6, 29.52, 29.45, 29.3, 25.7, 22.7, 14.1, 14.0. HRMS (+ve ESI): calculated for $C_{19}H_{35}BrNaO4$ (M+Na): 429.1611, found: 429.1608.

Diethyl 2-(2-bromo-4-hydroxybut-1-en-1-yl)-2-methylmalonate (7q)

The general procedure was followed using diethyl 2-bromo-2-methylmalonate (0.1 mmol, 19 μL, 1 eq.), MeCN (200 μL), 3-butyn-1-ol (0.2 mmol, 15 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 96 h the reaction showed 70% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 30:1 hexane:AcOEt) afforded the title compound (19.4 mg, 60% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 4.39 – 4.11 (m, 4H), 3.95 – 3.77 (m, 1H), 2.75 – 2.57 (m, 2H), 1.76 (t, *J* = 6.1 Hz, 1H), 1.65 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 132.8, 127.8, 62.2, 60.5, 55.6, 39.3, 23.1, 13.9. HRMS (+ve ESI): calculated for $C_{12}H_{19}BrNaO_5$ (M+Na): 345.0308, found: 345.0305.

Diethyl 2-(2-bromo-2-(4-methylcyclohex-3-en-1-yl)propyl)malonate (7r)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), *R* (+)-limonene (0.2 mmol, 32 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 15 h the reaction showed complete conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound (30.7 mg, 82% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 – 5.28 (m, 1H), 4.32 – 4.16 (m, 4H), 3.84 – 3.72 (m, 1H), 2.70 (ddd, *J* = 20.4, 15.3, 4.5 Hz, 1H), 2.52 (ddd, *J* = 16.0, 15.3, 6.9 Hz, 1H), 2.32 – 1.93 (m, 5H), 1.82 – 1.72 (m, 1H), 1.71 – 1.59 (m, 6H), 1.54 – 1.38 (m, 1H), 1.34 – 1.22 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.74, 169.71, 169.4, 134.2, 133.9, 120.0, 119.7, 76.3, 76.2, 61.81, 61.77, 61.7, 50.0, 49.9, 46.5, 46.3, 41.4, 40.7, 30.9, 28.41, 28.38, 27.9, 27.8, 26.0, 25.6, 23.1, 14.0. HRMS (+ve ESI): calculated for $C_{17}H_{27}BrNaO_4$ (M+Na): 397.0985, found: 397.0985.

Diethyl 2-((4-(2-bromopropan-2-yl)cyclohex-1-en-1-yl)methyl)malonate (8)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), (-)-β-pinene (0.2 mmol, 31 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 15 h the reaction

showed full conversion. Purification by flash column chromatography (gradient eluent from hexane to 20:1 hexane:AcOEt) afforded the title compound as a colourless oil.

Diethyl 2-(2-(bromomethyl)-4-hydroxycyclopentyl)malonate (10)

The general procedure was followed using diethyl bromomalonate (0.1 mmol, 17 μL, 1 eq.), MeCN (200 μL), 3-butyn-1-ol (0.2 mmol, 15 μL, 2 eq.), 2,6-lutidine (0.1 mmol, 12 μL, 1 eq.) and *p*-anisaldehyde (0.02 mmol, 2.4 μL, 20 mol%). After 60 h the reaction showed 95% conversion of the alkyl halide. Purification by flash column chromatography (gradient eluent from hexane to 30:1 hexane:AcOEt) afforded the title compound (31.5 mg, 90% yield) as a colourless oil.

List of Publications

A New Robust and Efficient Ion-Tagged Proline Catalyst Carrying an Amide Spacer for the Asymmetric Aldol Reaction - *Adv. Synth. Catal.* **2011**, 353, 3234-3240.

A Liquid-Liquid Biphasic Homogeneous Organocatalytic Aldol Protocol Based on the Use of a Silica Gel Bound Multulayered Iinic Liquid Phase - *ChemCatChem* **2012**, 4, 1000-1006.

A New Family of Conformationally Constrained Bicyclic Diarylprolinol Silyl Ethers as Organocatalysts - *Adv. Synth. Catal.* **2012**, 354, 3428-3434.

Electrosteric Activation Using Ion-Tagged Prolines. A Combined Experimental and Computational Investigation – *ChemCatChem* **2013**, 5, 2913-2924.

Organocatalytic Conjugate Addition of Nitroalkanes to 3-Ylidene Oxindoles: a stereocontrolled Diversity Oriented Route to Oxindole Derivatives – *J. Org. Chem.* **2013**, 78, 12049-12064.

Bibliography

[1] Books on organocatalysis: (a) Berkessel A., Gröger H., *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis* (**2005**), Wiley-VCH; (b) Dalko P. I., *Enantioselective Organocatalysis – Reactions and Experimental Procedures* (**2007**), Wiley-VCH.

[2] Reviews on organocatalysis: (a) MacMillan D. W. C., *Nature* **2008**, 455, 304-308; (b) Gaunt M. J., Johansson C. C. C., McNally A., Vo N. T., *Drug Discovery Today* **2007**, 12, 8-27; (c) Seayad J., List B., *Org. Biomol. Chem.* **2005**, 3, 719-724; (d) Dalko P. I., Moisan L., *Angew. Chem. Int. Ed.* **2004**, 43, 5138-5175.

[3] (a) Pracejus H., *Justus Liebigs Ann. Chem.* **1960**, 634, 9-22; (b) Pracejus H., Mäthe H., *J. Prakt. Chem.* **1964**, 24, 195-205.

[4] (a) Eder U., Sauer G., Wiechert R., *Angew. Chem. Int. Ed.* **1971**, 10, 496-497; (b) Hajos Z. G., Parrish D. R., *J. Org. Chem.* **1974**, 39, 1615-1621.

[5] (a) Oku J., Inoue S., *J. Chem. Soc., Chem. Commun.* **1981**, 229-230; (b) Oku J., Ito N., Inoue S., *Macromol. Chem.* **1982**, 183, 579-589.

[6] (a) Juliá S., Guixer J., Masana J., Rocas J., Colonna S., Annuziata R., Molinari H., *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317-1324; (b) Juliá S., Masana J., Vega J. C., *Angew. Chem. Int. Ed.* **1980**, 19, 929-931.

[7] List B., Lerner R. A., Barbas III C. F. , *J. Am. Chem. Soc.* **2000**, 122, 2395-2396.

[8] Ahrendt K. A., Borths C. J., MacMillan D. W. C., *J. Am. Chem. Soc.* **2000**, 122, 4243-4244.

[9] Melchiorre P., Marigo M., Carlone A., Bartoli G., *Angew. Chem. Int. Ed.* **2008**, 47, 6138-6171.

[10] Mukherjee S., Yang J. W., Hoffmann S., List B., *Chem. Rev.* **2007**, 107, 5471-5569.

[11] Erkkilä A., Majander I., Pihko P. M., *Chem. Rev.* **2007**, 107, 5416-5470.

[12] Beeson T. D., Mastracchio A., Hong J., Ashton K., MacMillan D. W. C., *Science* **2007**, 316, 582-585.

[13] Nicewicz D. A., MacMillan D. W. C., *Science* **2008**, 322, 77-80.

[14] Melchiorre P., *Angew. Chem. Int. Ed.* **2012**, 51, 9748-9770.

[15] (a) Jurberga I. D., Chatterjeea I., Tannerta R., Melchiorre P., *Chem. Commun.* **2013**, 49, 4869-4883; (b) Jianga H, Albrechtab Ł., Jørgensen K. A., *Chem. Sci.* **2013**, 4, 2287-2300; (c) Bertelsen S., Jørgensen K. A., *Chem. Soc. Rev.* **2009**, 38, 2178-2189.

[16] (a) Doyle A. G., Jacobsen E. N., *Chem. Rev.* **2007**, 107, 5713-5743; (b) Taylor M. S., Jacobsen E. N., *Angew. Chem. Int. Ed.* **2006**, 45, 1520-1543.

[17] (a) Brak K., Jacobsen E. N., *Angew. Chem. Int. Ed.* **2013**, 52, 534-561; (b) Brière J., Oudeyer S., Dallab V., Levacher V., *Chem. Soc. Rev.* **2012**, 41, 1696-1707.

[18] Ooi T., Maruoka K., *Angew. Chem. Int. Ed.* **2007**, 46, 4222-4266.

[19] Mahlau M., List B., *Angew. Chem. Int. Ed.* **2013**, 52, 518-533.

[20] Anslyn E. V., Dougherty D. A., *Modern Physical Organic Chemistry* (**2006**), University Science Books, Sausalito.

[21] Rueping M., Kuenkel A., Atodiresei I., *Chem. Soc. Rev.* **2011**, 40, 4539-4549.

[22] (a) Sharma K., Sunoj R. B., *Angew. Chem. Int. Ed.* **2010**, 49, 6373-6377; (b) Schmid M. B., Zeitler K., Gschwind R. M., *Angew. Chem. Int. Ed.* **2010**, 49, 4997-5003; (c) Ajitha M. J., Suresh C. H., *J. Mol. Catal. A-Chem.* **2011**, 345, 37-43; (d) Schmid M. B., Zeitler K., Gschwind R. M., *J. Org. Chem.* **2011**, 76, 3005-3015.

[23] (a) Bahmanyar S., Houk K. N., *Org. Lett.* **2003**, 5, 1249-1251; (b) Bahmanyar S., Houk K. N., Martin H. J., List B., *J. Am. Chem. Soc.* **2003**, 125, 2475-2479; (c) Hoang L., Bahmanyar S., Houk K. N., List B., *J. Am. Chem. Soc.* **2003**, 125, 16-17; (d) Bahmanyar S., Houk K. N., *J. Am. Chem. Soc.* **2001**, 123, 12911-12912; (e) Bahmanyar S., Houk K. N., *J. Am. Chem. Soc.* **2001**, 123, 11273-11283.

[24] (a) Aratake S., Itoh T., Okano T., Nagae N., Sumiya T., Shoji M., Hayashi Y., *Chem. Eur. J.* **2007**, 13, 10246-10256; (b) Gu L. Q., Yu M. L., Wu X. Y., Zhang Y. Z., Zhao G., *Adv. Synth. Catal.* **2006**, 348, 2223-2228; (c) Giacalone F., Gruttadauria M., Agrigento P., Lo Meo P., Noto R., *Eur. J. Org. Chem.* **2010**, 5696-5704; (d) Guizzetti S., Benaglia M., Pignataro L., Puglisi A., *Tetrahedron: Asymmetry* **2006**, 17, 2754-2760; (e) Chen X. H., Luo S. W., Tang Z., Cun L. F., Mi A. Q., Jiang Y. Z., Gong L. Z., *Chem. Eur. J.* **2007**, 13, 689-701; (f) Maya V., Raj M., Singh V. K., *Org. Lett.* **2007**, 9, 2593-2595; (g) Cobb A. J. A., Shaw D. M., Longbottom D. A., Gold J. B., Ley S. V., *Org. Biomol. Chem.* **2005**, 3 , 84-96; (h) Giacalone F., Gruttadauria M., Lo Meo P., Riela S., Noto R., *Adv. Synth. Catal.* **2008**, 350, 2747-2760; (i) Notz W., Tanaka F., Barbas III C. F., *Acc. Chem. Res.* **2004**, 37, 580-591; (j) Bellis E., Kokotos G., *Tetrahedron* **2005**, 61, 8669-8676; (k) Hayashi Y., Sumiya

T., Takahashi J., Gotoh H., Urushima T., Shoji M., *Angew. Chem.* **2006**, 118, 972-975; (l) List B., Pojarliev P., Castello C., *Org. Lett.* **2001**, 3, 573-575; (m) Huang J., Zhang X., Armstrong D. W., *Angew. Chem. Int. Ed.* **2007**, 46, 9073-9077.

[25] Benaglia M., Cinquini M., Cozzi F., Puglisi A., Celentano G., *Adv. Synth. Catal.* **2002**, 344, 533-542.

[26] (a) Gruttadauria M., Salvo A. M. P., Giacalone F., Agrigento P., Noto R., *Eur. J. Org. Chem.* **2009**, 5437-5444; (b) Gruttadauria M., Giacalone F., Noto R., *Chem. Soc. Rev.* **2008**, 37, 1666-1688; (c) Kehat T., Portnoy M., *Chem. Commun.* **2007**, 2823-2825; (d) Font D., Jimeno C., Pericas M. A., *Org. Lett.* **2006**, 8, 4653-4655.

[27] Huo C., Chan T. H., *Chem. Soc. Rev.* **2010**, 39, 2977-3006.

[28] Lombardo M., Trombini C., *ChemCatChem* **2010**, 2, 135-145.

[29] (a) Mase N., Barbas III C. F., *Org. Biomol. Chem.* **2010**, 8, 4043-4050; (b) Barbas III C. F., Heine A., Zhong G., Hoffmann T., Gramatikova S., Bjçrnestedt R., List B., Anderson J., Stura E. A., Wilson I. A., Lerner R. A., *Science* **1997**, 278, 2085-2092.

[30] Bartlett G. J., Porter C. T., Borkakoti N., Thornton J. M., *J. Mol. Biol.* **2002**, 324, 105-121.

[31] Warshel A., Sharma P. K., Kato M., Xiang Y., Liu H., Olsson M. H. M., *Chem. Rev.* **2006**, 106, 3210-3235.

[32] Noujeim N., Leclercq L., Schmitzer A. R., *Curr. Org. Chem.* **2010**, 14, 1500-1516.

[33] (a) Lombardo M., Easwar S., Pasi F., Trombini C., *Adv. Synth. Catal.* **2009**, 351, 276-282; (b) Lombardo M., Pasi F., Easwar S., Trombini C., *Synlett* **2008**, 2471-2474.

[34] Gruttadauria M., Giacalone F., Noto R., *Adv. Synth. Catal.* **2009**, 351, 33-57.

[35] Zotova N., Franzke A., Armstrong A., Blackmond D. G., *J. Am. Chem. Soc.* **2007**, 129, 15100-15101.

[36] Notz W., List B., *J. Am. Chem. Soc.* **2000**, 122, 7386-7387.

[37] Samanta S., Liu J., Dodda R., Zhao C., *Org. Lett.* **2005**, 7, 5321-5323.

[38] Tang Z., Yang Z., Cun L., Gong L., Mi A., Jiang Y., *Org. Lett.* **2004**, 6, 2285-2287.

[39] (a) Kumar A., Singh S., Kumar V., Chimni S. S., *Org. Biomol. Chem.* **2011**, 9, 2731-2742; (b) Czarnecki P., Plutecka A., Gawroński J., Kacprzak K., *Green Chem.* **2011**, 13, 1280-1287; (c) Demuynck A. L. W., Peng L., de Clippel F., Vanderleyden J., Jacobs P. A., Selsa B. F., *Adv. Synth. Catal.* **2011**, 353, 725-732; (d) Paradowska J., Rogozińska M.,

Mlynarski J., *Tetrahedron Lett.* **2009**, 50, 1639-1641; (e). Xu X., Wang Y., Gong L., *Org. Lett.* **2007**, 9, 4247-4249.

[40] (a) Buchmeiser M. R., *Chem. Rev.* **2009**, 109, 303-321; (b) Fraile J. M., García J. I., Mayoral J. A., *Chem. Rev.* **2009**, 109, 360-417; (c) Trindade A. F., Gois P. M. P., Afonso C. A. M., *Chem. Rev.* **2009**, 109, 418-514; (d) Lu J., Toy P. H., *Chem. Rev.* **2009**, 109, 815-838; (e) Shylesh S., Schünemann V., Thiel W. R., *Angew. Chem. Int. Ed.* **2010**, 49, 3428-3459; (f) Collis E. A. C., Horváth I. T., *Catal. Sci. Technol.* **2011**, 1, 912-919.

[41] Mayr M., Mayr B., Buchmeiser M. R., *Angew. Chem. Int. Ed.* **2001**, 40, 3839-3842.

[42] Lombardo M., Quintavalla A., Chiarucci M., Trombini C., *Synlett* **2010**, 1746-1765.

[43] (a) Keim W., *Chem. Ing. Tech.* **1984**, 56, 850-853; (b) Keim W., *Green Chem.* **2003**, 5, 105-111.

[44] (a) Chiappe C., Pieraccini D., *J. Phys. Org. Chem.* **2005**, 18, 275-297; (b) Weingärtner H., *Angew. Chem. Int. Ed.* **2008**, 47, 654-670; (c) Marciniak A., *Int. J. Mol. Sci.* **2010**, 11, 1973-1990; (d) Werner S., Haumann M., Wasserscheid P., *Annu. Rev. Chem. Biomol. Eng.* **2010**, 1, 203-230.

[45] (a) Mehnert C. P., *Chem. Eur. J.* **2005**, 11, 50-56; (b) Shi F., Zhang Q., Li D., Deng Y., *Chem. Eur. J.* **2005**, 11, 5279-5288; (c) Riisager A., Fhermann R., Haumann M., Wasserscheid P., *Top. Catal.* **2006**, 40, 91-102; (d) Sievers C., Jimenez O., Müller T. E., Steuernagel S., Lercher J. A., *J. Am. Chem. Soc.* **2006**, 128, 13990-13991; (e) Burguete M. I., Galindo F., Garcia-Verdugo E., Karbass N., Luis S. V., *Chem. Commun.* **2007**, 3086-3088; (f) Mikkola J. T., Virtanen P. P., Kordás K., Karhu H., Salmi T. O., *Appl. Catal. A* **2007**, 328, 68-76.

[46] Cancogni D., Mandoli A., Jumde R. P., Pini D., *Eur. J. Org. Chem.* **2012**, 1336-1345.

[47] Giacalone F., Gruttadauria M., Lo Meo P., Riela S., Noto R., *Adv. Synth. Catal.* **2008**, 350, 2747-2760.

[48] Tsuboi S., Nishiyama E., Furutani H., Utaka M., Takeda A., *J. Org. Chem.* **1987**, 52, 1359-1362.

[49] (a) List B., *Tetrahedron* **2002**, 58, 5573-5590; (b) List B., *Acc. Chem. Res.* **2004**, 37, 548-557; (c) List B., *Chem. Commun.* **2006**, 819-824; (d) Marigo M., Jørgensen K. A., *Chem. Commun.* **2006**, 2001-2011; (e) Guillena G., Ramón D. J., *Tetrahedron: Asymmetry* **2006**, 17, 1465-1492.

[50] Lelais G., MacMillan D. W. C., *Aldrichimica Acta* **2006**, 39, 79-87.

[51] Hayashi Y., Gotoh H., Hayashi T., Shoji M., *Angew. Chem. Int. Ed.* **2005**, 44, 4212-4215.

[52] Marigo M., Wabnitz T. C., Fielenbach D., Jørgensen K. A., *Angew. Chem. Int. Ed.* **2005**, 44, 794-797.

[53] (a) Jensen K. L., Dickmeiss G., Jiang H., Albrecht Ł., Jørgensen K. A., *Acc. Chem. Res.* **2012**, 45, 248-264; (b) Palomo C., Mielgo A., *Angew. Chem. Int. Ed.* **2006**, 45, 7876-7880; (c) Palomo C., Mielgo A., *Chem. Asian J.* **2008**, 3, 922-948; (d) Meninno S., Lattanzi A., *Chem. Commun.* **2013**, 49, 3821-3832.

[54] Haindl M. H., Schmid M. B., Zeitler K., Gschwind R. M., *RSC Advances* **2012**, 2, 5941-5943.

[55] Holland M. C., Paul S., Schweizer W. B., Bergander K., Mück-Lichtenfeld C., Lakhdar S., Mayr H., Gilmour R., *Angew. Chem. Int. Ed.* **2013**, 52, 7967-7971.

[56] Schmid M. B., Zeitler K., Gschwind R. M., *Chem. Sci.* **2011**, 2, 1793-1803.

[57] Xie H., Zu L., Li H., Wang J., Wang W., *J. Am. Chem. Soc.* **2007**, 129, 10886-10894.

[58] (a) Hayashi Y., Itoh T., Ishikawa H., *Angew. Chem. Int. Ed.* **2011**, 50, 3920-3924; (b) Ghosh S. K., Zheng Z., Ni B., *Adv. Synth. Catal.* **2010**, 352, 2378-2382; (c) Mager I., Zeitler K., *Org. Lett.* **2010**, 12, 1480-1483; (d) Wang Y., Li P., Liang X., Zhang T. Y., Ye J., *Chem. Commun.* **2008**, 1232-1234; (e) Zu L., Xie H., Li H., Wang J., Wang W., *Adv. Synth. Catal.* **2007**, 349, 2660-2664; (f) Palomo C., Landa A., Mielgo A., Oiarbide M., Puente A., Vera S., *Angew. Chem. Int. Ed.* **2007**, 46, 8431-8435.

[59] Jia Z., Jiang H., Li J., Gschwend B., Li Q., Yin X., Grouleff J., Chen Y., Jørgensen K. A., *J. Am. Chem. Soc.* **2011**, 133, 5053-5061.

[60] Patora-Komisarska K., Benohoud M., Ishikawaa H., Seebach D., Hayashi Y., *Helv. Chim. Acta* **2011**, 94, 719-745.

[61] Sigman M. S., Jacobsen E. N., *J. Am. Chem. Soc.* **1998**, 120, 4901-4902.

[62] (a) Schreiner P. R., Wittkopp A., *Org. Lett.* **2002**, 4, 217-220; (b) Schreiner P. R., Wittkopp A., *Chem. Eur. J.* **2003**, 9, 407-414.

[63] (a) Siau W., Wang J., *Catal. Sci. Technol.* **2011**, 1, 1298-1310; (b) Ting A., Goss J. M., McDougal N. T., Schaus S. E., "Brønsted Base Catalysts", *Topics in Current Chemistry*, **2010**, Springer, 145-200.

[64] Okino T., Hoashi Y., Takemoto Y., *J. Am. Chem. Soc.* **2003**, 125, 12672-12673.

[65] Wynberg H., Heider R., *Tetrahedron Lett.* **1975**, 16, 4057-4060.

[66] Connon S. J., *Chem. Commun.* **2008**, 2499-2510.

[67] Li B., Jiang L., Liu M., Chen Y., Ding L., Wu Y., *Synlett* **2005**, 603-606.

[68] Vakulya B., Varga S., Csámpai A., Soós T., *Org. Lett.* **2005**, 7, 1967-1969.

[69] (a) McCooey S. H., Connon S. J., *Angew. Chem. Int. Ed.* **2005**, 44, 6367-6370; (b) Ye J., Dixon D. J., Hynes P. S., *Chem. Commun.* **2005**, 4481-4483.

[70] (a) Millemaggi A., Taylor R. J. K., *Eur. J. Org. Chem.* **2010**, 4527-4547; (b) Bhrigu B., Pathak, D., Siddiqui N., Alam M. S., Ahsan, W., *Int. J. Pharm. Sci. Drug Res.* **2010**, 2, 229-235; (c) Fensome A., Adams W. R., Adams A. L., Berrodin T. J., Cohen J., Huselton C., Illenberger A., Kern J. C., Hudak V. A., Marella M. A., Melenski E. G., McComas C. C., Mugford C. A., Slayden O. D., Yudt M., Zhang Z., Zhang P., Zhu Y., Winneker R. C., Wrobel J. E., *J. Med. Chem.* **2008**, 51, 1861-1873; (d) Canner J., Sobo M., Ball S., Hutzen B., DeAngelis S., Willis W., Studebaker A. W., Ding K., Wang S., Yang D., Lin J., *Br. J. Cancer* **2009**, 101, 774-781; (e) Shangary S., Qin D., McEachern D., Liu M., Miller R. S., Qiu S., Nikolovska-Coleska Z., Ding K., Wang G., Chen J., Bernard D., Zhang J., Lu Y., Gu Q., Shah R. B., Pienta K. J., Ling X., Kang S., Guo M., Sun Y., Yang D., Wang S., *Proc. Natl. Acad. Sci. U. S. A.* **2008**, 105, 3933-3938; (f) Rottmann M., McNamara C., Yeung B. K. S., Lee M. C. S., Zou B., Russell B., Seitz P., Plouffe D. M., Dharia N. V., Tan J., Cohen S. B., Spencer K. R., González-Páez G. E., Lakshminarayana S. B., Goh A., Suwanarusk R., Jegla T., Schmitt E. K., Beck H., Brun R., Nosten F., Renia L., Dartois V., Keller T. H., Fidock D. A., Winzeler E. A., Diagana T. T., *Science* **2010**, 329, 1175-1180.

[71] (a) Albrecht B. K., Williams R. M., *Org. Lett.* **2003**, 5, 197-200; (b) Lin H., Danishefsky S. J., *Angew. Chem. Int. Ed.* **2003**, 42, 36-51; (c) Greshock T. J., Grubbs A. W., Jiao P., Wicklow D. T., Gloer J. B., Williams R. M., *Angew. Chem. Int. Ed.* **2008**, 47, 3573-3577; (d) Reisman S. E., Ready J. M., Weiss M. M., Hasuoka A., Hirata M., Tamaki K., Ovaska T. V., Smith C. J., Wood J. L., *J. Am. Chem. Soc.* **2008**, 130, 2087-2100; (e) Galliford C. V., Scheidt K. A., *Angew. Chem. Int. Ed.* **2007**, 46, 8748-8758; (f) Marti C., Carreira E. M., *Eur. J. Org. Chem.* **2003**, 2209-2219; (g) Trost B. M., Brennan M. K., *Synthesis* **2009**, 18, 3003-3025.

[72] (a) Ma S., Han X., Krishnan S., Virgil S. C., Stoltz B. M., *Angew. Chem. Int. Ed.* **2009**, 48, 8037-8041; (b) Trost, B. M., Zhang Y., *Chem. Eur. J.* **2011**, 17, 2916-2922; (c) Trost B. M., Cramer N., Silverman S. M., *J. Am. Chem. Soc.* **2007**, 129, 12396-12397; (d) Kato Y., Furutachi M., Chen Z., Mitsunuma H., Matsunaga S., Shibasaki M., *J. Am. Chem. Soc.*

2009, 131, 9168-9169; (e) Antonchick A. P., Gerding-Reimers C., Catarinella M., Schürmann M., Preut H., Ziegler S., Rauh D., Waldmann H., *Nat. Chem.* **2010**, 2, 735-740.

[73] (a) Dalpozzo R., Bartoli G., Bencivenni G., *Chem. Soc. Rev.* **2012**, 41, 7247-7290; (b) Ball-Jones N. R., Badillo J. J., Franz A. K., *Org. Biomol. Chem.* **2012**, 10, 5165-5181; (c) Singh G. S., Desta Z. Y., *Chem. Rev.* **2012**, 112, 6104-6155; (d) Hong L., Wang R., *Adv. Synth. Catal.* **2013**, 355, 1023-1052; (e) Zhou F., Liu Y., Zhou J., *Adv. Synth. Catal.* **2010**, 352, 1381-1407.

[74] (a) Corey E. J., Guzman-Perez A., *Angew. Chem. Int. Ed.* **1998**, 37, 388-401; (b) Douglas C. J., Overman L. E., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5363-5367; (c) Peterson E. A., Overman L. E., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 11943-11948; (d) Trost B. M., Jiang C., *Synthesis* **2006**, 3, 369-396; (e) Bella M., Gasperi T., *Synthesis* **2009**, 10, 1583-1614.

[75] Aitken L. S., Arezki N. R., Dell'Isola A., Cobb A. J. A., *Synthesis* **2013**, 45, 2627-2648.

[76] Liu L., Wu D., Zheng S., Li T., Li X., Wang S., Li J., Li H., Wang W., *Org. Lett.* **2012**, 14, 134-137.

[77] Pesciaioli F., Righi P., Mazzanti A., Bartoli G., Bencivenni G., *Chem. Eur. J.* **2011**, 17, 2842-2845.

[78] (a) Liu L., Zhang S., Xue F., Lou G., Zhang H., Ma S., Duan W., Wang W., *Chem. Eur. J.* **2011**, 17, 7791-7795; (b) Zhang Y., Li Z. J., Xu H. S., Zhang Y., Wang W., *RSC Advances* **2011**, 1, 389-392; (c) Li M., Zhang J., Huang X., Wu B., Liu Z., Chen J., Li X., Wang X., *Eur. J. Org. Chem.* **2011**, 5237-5241; (d) Prathima P. S., Srinivas K., Balaswamy K., Arundhathi R., Reddy G. N., Sridhar B., Rao M. M., Likhar P. R., *Tetrahedron: Asymmetry* **2011**, 22, 2099-2103.

[79] (a) Chen X., Zhu W., Qian W., Feng E., Zhou Y., Wang J., Jiang H., Yao Z., Liu H., *Adv. Synth. Catal.* **2012**, 354, 2151-2156; (b) Retini M., Bergonzini G., Melchiorre P., *Chem. Commun.* **2012**, 48, 3336-3338; (c) Li X., Zhang B., Xi Z., Luo S., Cheng J., *Adv. Synth. Catal.* **2010**, 352, 416-424; (d) Bui T., Syed S., Barbas III C. F., *J. Am. Chem. Soc.* **2009**, 131, 8758-8759; (e) Cui B., Han W., Wu Z., Zhang X., Yuan W., *J. Org. Chem.* **2013**, 78, 8833-8839.

[80] Duan S., Lu H., Zhang F., Xuan J., Chen J., Xiao W., *Synthesis* **2011**, 12, 1847-1852.

[81] For some examples of C-3 acting as nucleophile, see: (a) Ohmatsu K., Kiyokawa M., Ooi T., *J. Am. Chem. Soc.* **2011**, 133, 1307-1309; (b) Ogawa S., Shibata N., Inagaki J., Nakamura S., Toru T., Shiro M., *Angew. Chem. Int. Ed.* **2007**, 46, 8666-8669; (c) Jiang K., Peng J., Cui H., Chen Y., *Chem. Commun.* **2009**, 3955-3957; (d) Tian X., Jiang K., Peng J., Du W., Chen Y., *Org. Lett.* **2008**, 10, 3583-3586; (e) He R., Ding C., Maruoka K., *Angew. Chem. Int. Ed.* **2009**, 48, 4559-4561; (f) Li X., Luo S., Cheng J., *Chem. Eur. J.* **2010**, 16, 14290-14294; (g) Zhang T., Cheng L., Hameed S., Liu L., Wang D., Chen Y., *Chem. Commun.* **2011**, 47, 6644-6646.

[82] Bordwell F. G., Fried H. E., *J. Org. Chem.* **1991**, 56, 4218-4223.

[83] (a) Okino T., Hoashi Y., Furukawa T., Xu X., Takemoto Y., *J. Am. Chem. Soc.* **2005**, 127, 119-125; (b) Li H., Wang Y., Tang L., Wu F., Liu X., Guo C., Foxman B. M., Deng L., *Angew. Chem. Int. Ed.* **2005**, 44, 105-108; (c) Hamza A., Schubert G., Soós T., Pápai I., *J. Am. Chem. Soc.* **2006**, 128, 13151-13160.

[84] Liao Y., Liu X., Wu Z., Cun L., Zhang X., Yuan W., *Org. Lett.* **2010**, 12, 2896-2899.

[85] (a) Zhu Q., Lu Y., *Angew. Chem. Int. Ed.* **2010**, 49, 7753-7756; (b) Lee H. J., Kang S. H., Kim D. Y., *Synlett* **2011**, 1559-1562.

[86] (a) Li X., Li Y., Peng F., Wu S., Li Z., Sun Z., Zhang H., Shao Z., *Org. Lett.* **2011**, 13, 6160-6163; (b) Ding M., Zhou F., Liu Y.L., Wang C., Zhao X., Zhou J., *Chem. Sci.* **2011**, 2, 2035-2039; (c) Liu X., Wu Z., Du X., Zhang X., Yuan W., *J. Org. Chem.* **2011**, 76, 4008-4017.

[87] (a) Pesciaioli F., Tian X., Bencivenni G., Bartoli G., Melchiorre P., *Synlett* **2010**, 11, 1704-1708; (b) Wang L., Peng L., Bai J., Huang Q., Xu X., Wang L., *Chem. Commun.* **2010**, 46, 8064-8066.

[88] (a) Bencivenni G., Wu L., Mazzanti A., Giannichi B., Pesciaioli F., Song M., Bartoli G., Melchiorre P., *Angew. Chem. Int. Ed.* **2009**, 48, 7200-7203; (b) Jiang K., Jia Z., Chen S., Wu L., Chen Y., *Chem. Eur. J.* **2010**, 16, 2852-2856; (c) Jiang K., Jia Z., Yin X., Wu L., Chen Y., *Org. Lett.* **2010**, 12, 2766-2769; (d) Galzerano P., Bencivenni G., Pesciaioli F., Mazzanti A., Giannichi B., Sambri L., Bartoli G., Melchiorre P., *Chem. Eur. J.* **2009**, 15, 7846-7849; (e) Companyó X., Zea A., Alba A. R., Mazzanti A., Moyano A., Rios R., *Chem. Commun.* **2010**, 46, 6953-6955; (f) Noole A., Oseka M., Pehk T., Öeren M., Järving I., Elsegood M. R. J., Malkov A. V., Lopp M., Kanger T., *Adv. Synth. Catal.* **2013**, 355, 829-835.

[89] Tietze L. F., *Chem. Rev.* **1996**, 96, 115-136.

[90] For reviews on organocatalytic domino reactions, see: (a) Enders D., Grondal C., Hüttl M. R. M., *Angew. Chem. Int. Ed.* **2007**, 46, 1570-1581; (b) Pellissier H., *Adv. Synth. Catal.* **2012**, 354, 237-294.

[91] Grondal C., Jeanty M., Enders D., *Nat. Chem.* **2010**, 2, 167-178.

[92] Honga L., Wang R., *Adv. Synth. Catal.* **2013**, 355, 1023-1052.

[93] Goudedranche S., Raimondi W., Bugaut X., Constantieux T., Bonne D., Rodriguez J., *Synthesis* **2013**, 45, 1909-1930.

[94] Quintavalla A., Lombardo M., Sanap S. P., Trombini C., *Adv. Synth. Catal.* **2013**, 355, 938-946.

[95] (a) Rajkumar S., Shankland K., Brown G. D., Cobb A. J. A., *Chem. Sci.* **2012**, 3, 584-588; (b) Rajkumar S., Shankland K., Goodman J. M., Cobb A. J. A., *Org. Lett.* **2013**, 15, 1386-1389.

[96] (a) Zhou B., Yang Y., Shi J., Luo Z., Li Y., *J. Org. Chem.* **2013**, 78, 2897-2907; (b) Jiang K., Jia Z., Yin X., Wu L., Chen Y., *Org. Lett.* **2010**, 12, 2766-2769; (c) Jiang K., Jia Z., Chen S., Wu L., Chen Y., *Chem. Eur. J.* **2010**, 16, 2852-2856.

[97] (a) Albertshofer K., Tan B., Barbas III C. F., *Org. Lett.* **2012**, 14, 1834-1837; (b) Li Y., Li X., Peng F., Li Z., Wu S., Sun Z., Zhang H., Shao Z., *Org. Lett.* **2011**, 13, 6200-6203; (c) Chandler B. D., Roland J. T., Li Y., Sorensen E. J., *Org. Lett.* **2010**, 12, 2746-2749.

[98] Noole A., Ilmarinen K., Järving I., Lopp M., Kanger T., *J. Org. Chem.* **2013**, 78, 8117-8122.

[99] Malhotra S., Balwani S., Dhawan A., Singh B. K., Kumar S., Thimmulappa R., Biswal S., Olsen C. E., Van der Eycken E., Prasad A. K., Ghosh B., Parmar V. S., *Med. Chem. Commun.* **2011**, 2, 743-751.

[100] Cao S., Zhang X., Wei Y., Shi M., *Eur. J. Org. Chem.* **2011**, 2668-2672.

[101] Sun W., Zhu G., Wu C., Hong L., Wang R., *Chem. Eur. J.* **2012**, 18, 6737-6741.

[102] Tan B., Hernández-Torres G., Barbas III C. F., *J. Am. Chem. Soc.* **2011**, 133, 12354-12357.

[103] (a) Jia Z., Jiang H., Li J., Gschwend B., Li Q.-Z., Yin X., Grouleff J., Chen Y., Jørgensen K. A., *J. Am. Chem. Soc.* **2011**, 133, 5053-5061; (b) Tan B., Candeias N. R., Barbas III C. F., *J. Am. Chem. Soc.* **2011**, 133, 4672-4675.

[104] Liu Y., Nappi M., Arceo E., Vera S., Melchiorre P., *J. Am. Chem. Soc.* **2011**, 133, 15212-15218.

[105] Tan B., Zeng X., Leong W. W. Y., Shi Z., Barbas III C. F., Zhong G., *Chem. Eur. J.* **2012**, 18, 63-67.

[106] Halskov K. S., Johansen T. K., Davis R. L., Steurer M., Jensen F., Jørgensen K. A., *J. Am. Chem. Soc.* **2012**, 134, 12943-12946.

[107] Kodukulla R. P. K., Trivedi G. K., Vora J. D., Mathur H. H., *Synth. Commun.* **1994**, 24, 819-832.

[108] Rajkumar S., Shankland K., Brown G. D., Cobb A. J. A., *Chem. Sci.* **2012**, 3, 584-588.

[109] Griesser H., Öhrlein R., Schwab W., Ehrler R., Jäger V., *Org. Synth.* **2000**, 77, 236.

[110] Kharasch M. S., Engelmann H., Mayo F. R., *J. Org. Chem.* **1937**, 2, 288-302.

[111] (a) Kharasch M. S., Jensen E. V., Urry W. H., *Science* **1945**, 102, 128-128; (b) Kharasch M. S., Jensen E. V., Urry W. H., *J. Am. Chem. Soc.* **1945**, 67, 1626-1626.

[112] De Malde M., Minisci F., Pallini U., Volterra E., Quilico A., *Chim. Ind. (Milan, Italy)* **1956**, 38, 371-382.

[113] (a) Minisci F., *Gazz. Chim. Ital.* **1961**, 91, 386-389; (b) Minisci F., Pallini U., *Gazz. Chim. Ital.* **1961**, 91, 1030-1036; (c) Minisci F., Galli R., *Tetrahedron Lett.* **1962**, 3, 533-538; (d) Minisci F., Galli R., *Chim. Ind. (Milan, Italy)* **1963**, 45, 1400-1401; (e) Minisci F., Cecere M., Galli R., *Gazz. Chim. Ital.* **1963**, 93, 1288-1294.

[114] Muñoz-Molina J. M., Belderrain T. B., Pérez P. J., *Eur. J. Inorg. Chem.* **2011**, 3155-3164.

[115] Clark A. J., *Chem. Soc. Rev.* **2002**, 31, 1-11.

[116] (a) Eckenhoff W. T., Pintauer T., *Catalysis Reviews: Science and Engineering* **2010**, 1-59; (b) Pintauer T., *Eur. J. Inorg. Chem.* **2010**, 2449-2460.

[117] (a) Eckenhoff W. T., Garrity S. T., Pintauer T., *Eur. J. Inorg. Chem.* **2008**, 563-571; (b) Eckenhoff W. T., Pintauer T., *Dalton Trans.* **2011**, 40, 4909-4917; (c) Quebatte L., Thommes K., Severin K., *J. Am. Chem. Soc.* **2006**, 128, 7440-7441.

[118] Stevens C. V., Van Meenen E., Masschelein K. G. R., Eeckhout Y., Hooghe W., D'hondt B., Nemykinb V. N., Zhdankin V. V., *Tetrahedron Lett.* **2007**, 48, 7108-7111.

[119] Wang J., Matyjaszewski K., *J. Am. Chem. Soc.* **1995**, 117, 5614-5615.

[120] Kato M., Kamigaito M., Sawamoto M., Higashimura T., *Macromolecules* **1995**, 28, 1721-1723.

[121] (a) Matyjaszewski K., Xia J., *Chem. Rev.* **2001**, 101, 2921-2990; (b) Patten T. E, Matyjaszewski K., *Acc. Chem. Res.* **1999**, 32,895-903; (c) Tsarevsky N. V, Matyjaszewski K., *Chem. Rev.* **2007**, 107, 2270-2299.

[122] Pintauer T., Matyjaszewski K., *Chem. Soc. Rev.* **2008**, 37, 1087-1097.

[123] (a) Prier C. K., Rankic D. A., MacMillan D. W. C., *Chem. Rev.* **2013**, 113, 5322-5363; (b) Xi Y., Yia H., Lei A., *Org. Biomol. Chem.* **2013**, 11, 2387-2403; (c) Narayanam J. M. R., Stephenson C. R. J., *Chem. Soc. Rev.* **2011**,40, 102-113; (d) Yoon T. P., Ischay M. A., Du J., *Nat. Chem.* **2010**, 2, 527-532.

[124] (a) Nguyen J. D., Tucker J. W., Konieczynska M. D., Stephenson C. R. J., *J. Am. Chem. Soc.* **2011**, 133, 4160-4163; (b) Wallentin C., Nguyen J. D., Finkbeiner P., Stephenson C. R. J., *J. Am. Chem. Soc.* **2012**, 134, 8875-8884.

[125] Arceo E., Jurberg I. D., Álvarez-Fernández A., Melchiorre P., *Nat. Chem.* **2013**, 5, 750-756.

[126] (a) Russell G. A., Janzen E. G., Strom E. T., *J. Am. Chem. Soc.* **1964**, 86, 1807-1814; (b) Kornblum N., *Angew. Chem. Int. Ed.* **1975**, 14, 734-745; (c) Bunnett J. F., Singh P., *J. Org. Chem.* **1981**, 46, 5022-5025; (d) Russell G. A., Mudryk B., Jawdosiuk M., *J. Am. Chem. Soc.* **1981**, 103, 4611-4613; (e) Ashby E. C., Argyropoulos J. N., Richard Meyer G., Goel A. G., *J. Am. Chem. Soc.* **1982**, 104, 6788-6789; (f) Ashby E. C., Park W., *Tetrahedron Let.* **1983**, 24, 1667-1670; (g) Ashby E. C., Argyropoulos J. N., *J. Org. Chem*. **1985**, 50, 3274-3283; (h) Gassman P. G., Bottorff K. J., *J. Org. Chem.* **1988**, 53, 1097-1100.

[127] http://research.chem.psu.edu/brpgroup/pKa_compilation.pdf

List of Abbreviations

Ac	Acetyl
ACDC	Asymmetric Counteranion-Directed Catalysis
AIBN	Azobisisobutyronitrile
Ar	Aryl
ATRA	Atom Transfer Radical Addition
ATRC	Atom Transfer Radical Cyclization
ATRP	Atom Transfer Radical Polymerization
BF_4	Tetrafluoroborate
BHT	2,6-Bis(1,1-dimethylethyl)-4-methylphenol
BINOL	1,1'-Bi-2-naphthol
bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
CA	Chloroacetic acid
Cbz	Benzyloxycarbonyl
CFL	Compact Fluorescent Light
CSP	Chiral Stationary Phase
DBU	1,5-Diazabiciclo[5.4.0]undec-5-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFPA	α,α-Difluorophenylacetic acid
DFT	Density Functional Theory
DMAP	*N*-dimethylamino pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E^+	Electrophile

ECD	Electronic Circular Dichroism
EDA	Electron Donor-Acceptor
ee	Enantiomeric excess
EI	Electron Ionization
ESI	Electrospray Ionization
Et	Ethyl
EWG	Electron Withdrawing Group
GC	Gas Chromatography
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HPLC-MS	High Performance Liquid Chromatography – Mass Spectrometry
HRMS	High-Resolution Mass Spectrometry
IPA	Isopropyl alcohol
i-Pr	Isopropyl
IL	Ionic Liquid
LUMO	Lowest Unoccupied Molecular Orbital
KHMDS	Potassium hexamethyldisilazane
Me	Methyl
mlc-SILP	Multilayered covalently bonded Supported Ionic Liquids Phases
MNBA	4-Methyl-2-nitrobenzoic acid
MS-TOF	Mass Spectrometry – Time-of-flight
MTBE	Methyl *tert*-butyl ether
NMR	Nuclear Magnetic Resonance
NTf_2	Bis(trifluoromethane)sulfonimide or bistriflimide
Nu:	Nucleophile
OFBA	*o*-Fluorobenzoic acid
OR	Optical Rotation
Ox	Oxidant
PF_6	Hexafluorophosphate
Ph	Phenyl
PTC	Phase-Transfer Catalysis
R	Alkyl

Ra-Ni	Raney Nickel
rt	Room temperature
SET	Single Electron Transfer
SILP	Supported Ionic Liquid Phases
So:	SOMOphile
SOMO	Singly Occupied Molecular Orbital
t-Bu	*tert*-butyl
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5- dimethanol
TCE	Tetrachloroethylene
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMC	Transition Metal Catalysed
TMS	Trimethylsilyl
TUC	Takemoto's thiourea catalyst
UV	Ultraviolet