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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Bifunctional catalysis

Darren J. Dixon

Editorial

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Bifunctional catalysis concerns the use of low molecular weight, structurally defined molecules possessing two distinct functional groups to bring about new reactivity and/or selectivity in a reaction of interest. The reactions are typically polar addition reactions of pronucleophiles and electrophiles where, ideally, simple low-cost starting materials are converted into high-value, stereochemically defined products through the action of the bifunctional catalyst system.

Many bifunctional catalysts possess either Lewis or Brønsted basic functionality and a hydrogen-bond donor group suitably positioned over a chiral scaffold. Compared to single functional group catalysts, the cooperative effect of the two complementary functional groups can lead to new reactivity and stereocontrol in reactions that were previously challenging or unprecedented. With multiple points of diversity in the two functional groups and the chiral scaffold, these catalysts can be readily tuned to optimise reactivity and selectivity in synthetically relevant reactions. Furthermore, owing to the great number of pronucleophiles and electrophiles that are available, the number of polar addition reactions that are amenable to catalysis through the action of bifunctional catalysts is enormous, and consequently, the field continues to expand at an impressive pace.

The present Thematic Series serves to highlight the current state-of-the-art of bifunctional catalysis from new bifunctional catalyst design and development, their application in new asymmetric metholodgy development, to their application in natural product and drug target synthesis. The creativity and productivity of the researchers in the field in general, and the breadth of highly stereoselective reactions reported in this series in particular, is truly impressive, and I would like to express my sincere gratitude to all of the many contributors.

Darren J. Dixon

Oxford, April 2016

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Organocatalytic and enantioselective Michael reaction between α-nitroesters and nitroalkenes. *Syn*/*anti*-selectivity control using catalysts with the same absolute backbone chirality

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Full Research Paper

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Abstract

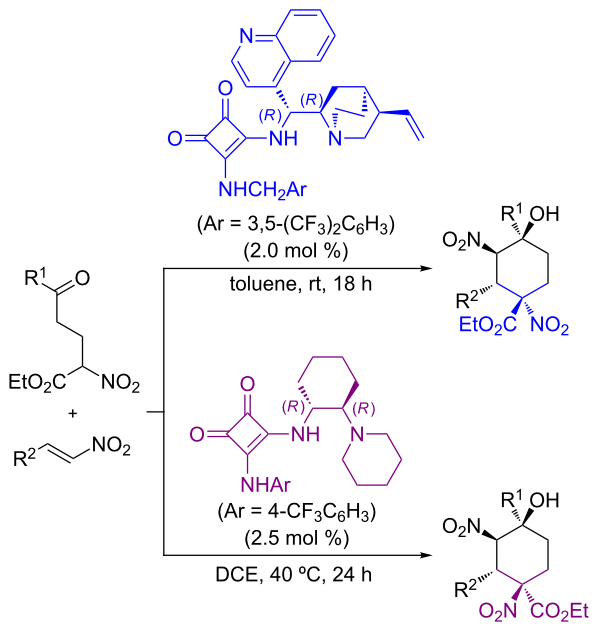
The asymmetric and catalytic Michael reaction between α-nitroesters and nitroalkenes has been studied in the presence of two bifunctional catalysts both containing the same absolute chirality at the carbon backbone. The reaction performed in similar conditions allows us to control the *syn* or *anti* selectivity of the Michael adduct obtaining good yields and high enantiocontrol in all cases.

Introduction

The absolute stereochemistry of a molecule has a paramount influence on the properties that this compound will have when interacting with biological systems [1]. As a consequence, the last decades have witnessed an enormous progress directed toward the development of synthetic methodology for the preparation of chiral molecules as single enantiomers with a well-defined three-dimensional arrangement. In this scenario, asymmetric catalysis arises as a key methodology for chemical production of enantiomerically enriched chiral compounds in terms of atom economy and reduced waste generation [2-6]. Nowadays, many very effective methodologies exist that allow the formation of a chiral compound as a single enantiomer. However, and despite the advances made in the field, an important challenge arises when a molecule containing multiple stereocentres has to be prepared because the access to all possible stereoisomers is not usually straightforward. While obtaining one or other mirror image of the target molecule can also be easily achieved by selecting the correct enantiomer of the catalyst, the relative configuration is typically governed by intrinsic factors associated to the mechanistic profile of the reaction and very often the formation of the major diastereoisomer is determined from the very beginning of the reaction and

therefore access to any stereoisomer at will from the same set of starting materials with full absolute and relative stereocontrol is not trivial. Previous reports show that the diastereoselection can be directed by different approaches that include the modification of reaction conditions [7-9], the incorporation of additives or co-catalysts [10-13], the modification of some structural features of the substrate [14,15], the use of two catalysts that are structurally different to each other and that can also operate independently through a single transition state with minimal matched/mismatched interactions [16-22] or finally the concurrent use of two cycle-specific catalysts, in which each of them is exclusively involved in the formation of one stereocentre and therefore has to overcome the stereochemical bias exerted by the stereocentres generated in the previous steps [23-26].

In this context, we have recently reported a catalytic and enantioselective Michael/Michael cascade reaction in which α-nitro-δ-ketoesters react with nitroalkenes to provide densely functionalized cyclohexanes in excellent yield and stereoselectivity (Scheme 1) [27]. This reaction made use of bifunctional tertiary amine/squaramide catalysts [28-32] and, interestingly, we found that catalysts containing the same backbone chirality provided different diastereoisomers, thus allowing the development of a diastereodivergent process.



Scheme 1: Diastereodivergent cascade Michael/Michael reaction using catalysts with the same absolute chirality reported in our group.

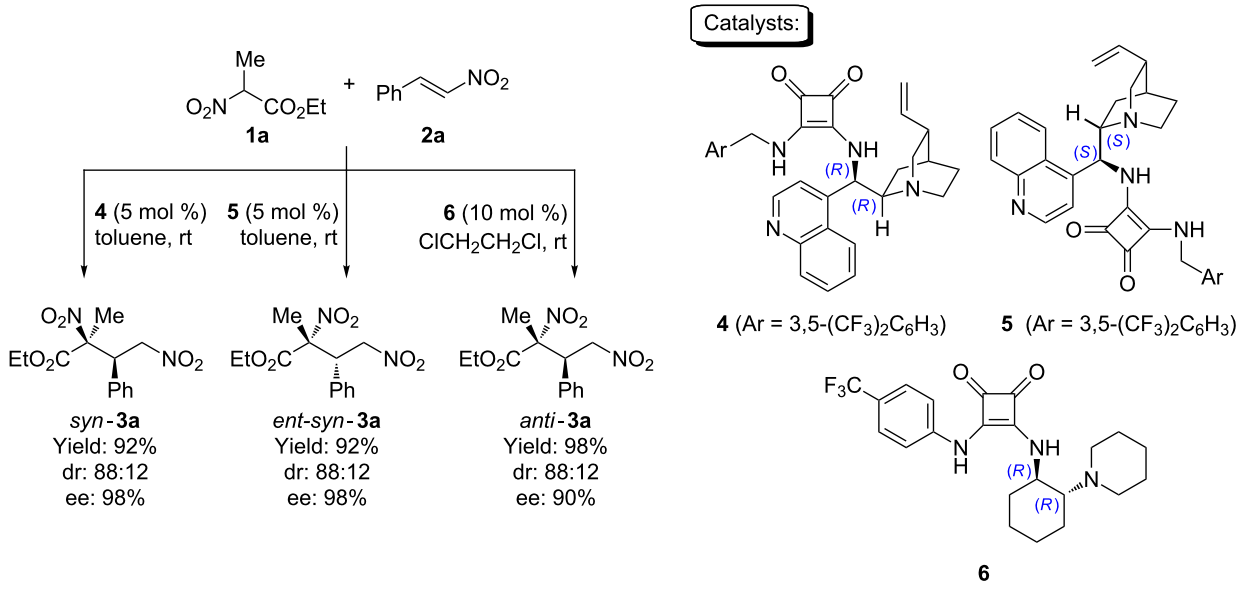
In this report, we wish to present the extension of this behaviour to the Michael reaction between α-substituted nitroacetates and nitroalkenes. The Michael reaction is regarded as a fundamental tool for the formation of C–C bonds during the synthesis of complex molecules [33-35], in particular, being able to control both the simple and the facial stereoselection of those versions in which two stereocentres are generated in the reaction become of special utility to synthetic chemists. In this case, using two different bifunctional tertiary amine/squaramide organocatalysts [36-61] with the same absolute chirality, the stereochemical outcome of the reaction can be controlled to provide the corresponding Michael adducts with two stereocentres, one of them being quaternary, and allowing the preparation of the desired diastereoisomer at will.

Results and Discussion

We started our work by first applying the conditions optimized for our recently reported cascade process to the reaction between ethyl 2-nitropropanoate (**1a**) and β-nitrostyrene (**2a**). As it can be seen in Scheme 2, the use of catalyst **4** led to the formation of the *syn*-diastereoisomer *syn*-**3a** in excellent yield, an acceptable 88:12 dr and 98% ee. As expected, the use of the pseudoenantiomeric catalyst **5** provided the corresponding enantiomer *ent*-*syn*-**3a** with similar results. Moving to cyclohexanediamine-based catalyst **6** resulted in the same behaviour as observed in our previous report, isolating the other possible diastereoisomer *anti*-**3a** in good yield, 88:12 dr and 90% ee.

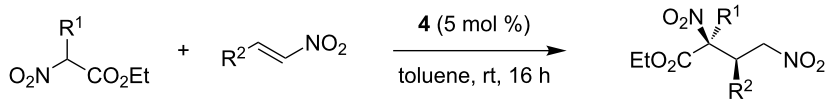
Once we had confirmed the good performance of the reaction in this intermolecular Michael reaction, we proceeded to evaluate the scope of this transformation in order to establish whether this method could be useful and general for a variety of nitroalkene Michael acceptors and nitroacetate donors. For this reason, we initially studied the reaction using squaramide **4** as catalyst that leads to the formation of *syn*-**3** adducts. In this sense, and as it can be seen in Table 1, the reaction performed excellently in almost all the cases studied. In particular, when the reaction was conducted using nitrostyrene derivatives as Michael acceptors, the corresponding adducts **3a–k** were isolated cleanly, in high yields, diastereo- and enantioselectivities regardless the electronic nature of the aromatic substituent of the nitrostyrene reagent. Indeed, the reaction using nitrostyrenes containing electron-donating groups at any of the position of the aryl ring led to the formation of the corresponding adducts (*syn*-**3a–f**) in excellent yield, good diastereoselectivities and enantiomeric excesses over 95% (Table 1, entries 2–6).

When nitrostyrenes containing electron-withdrawing groups were tested, the reaction proceeded equally well (Table 1, entries 7–11), although a slight decrease in the yield was observed for those cases in which the substituent was placed at the *ortho*-position (Table 1, entries 7 and 10). Heteroaromatic substituents at the nitroalkene reagent were also tested and



Scheme 2: Diastereodivergent enantioselective Michael reaction using ethyl 2-nitropropanoate and β-nitrostyrene as model substrates.

Table 1: Enantio- and diastereoselective Michael reaction between nitroesters **1** and nitroalkenes **2** catalysed by **4**.[a]



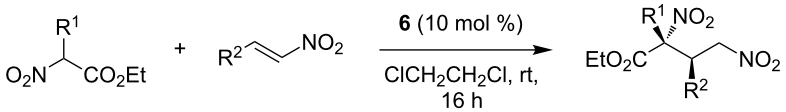
Entry	R^1	R^2	Product	Yield[b]	dr[c]	ee (%)[d]
1	Me	Ph	*syn*-**3a** [27]	92	88:12	98
2	Me	4-MeC_6H_4	*syn*-**3b**	85	89:11	97
3	Me	2-MeOC_6H_4	*syn*-**3c**	79	82:18	96
4	Me	3-MeOC_6H_4	*syn*-**3d**	92	88:12	96
5	Me	4-MeOC_6H_4	*syn*-**3e**	86	87:13	>99
6	Me	4-BnOC_6H_4	*syn*-**3f**	85	86:14	97
7	Me	2-ClC_6H_4	*syn*-**3g**	80	88:12	98
8	Me	3-ClC_6H_4	*syn*-**3h**	92	86:14	97
9	Me	4-ClC_6H_4	*syn*-**3i**	97	88:12	97
10	Me	2-BrC_6H_4	*syn*-**3j**	75	85:15	97
11	Me	4-BrC_6H_4	*syn*-**3k**	92	87:13	97
12	Me	2-furyl	*syn*-**3l**	80	86:14	93
13	Me	2-thienyl	*syn*-**3m**	86	93:7	96
14	Me	$(MeO)_2CH$	*syn*-**3n**	96	80:20	96
15	Et	Ph	*syn*-**3o**	92	86:14	98
16	Et	4-MeOC_6H_4	*syn*-**3p**	88	84:16	97
17	Et	4-BrC_6H_4	*syn*-**3q**	78	78:22	95

[a]All reactions were carried out on a 0.1 mmol scale of **1** and **2** in toluene (1 M) at room temperature using 5.0 mol % of **4** as catalyst. [b]Yield of pure Michael adducts as mixture of diastereoisomers after flash column chromatographic purification. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC on a chiral stationary phase (see experimental part in Supporting Information File 1 for details).

those also reacted very efficiently, leading to the formation of adduct *syn*-**3l**–**m** in high yield and good stereoselection (Table 1, entries 12 and 13). Functionalized nitroalkene **2n** also performed well in the reaction, providing the corresponding addition product *syn*-**3n** in good yield and high diastereo- and enantioselectivity (Table 1, entry 14). Disappointingly, when we tested β-alkyl-substituted nitroalkenes (R^2 = iPr or *n*-Pr) we could not identify the formation of the desired addition product, and a complex mixture of products was obtained as a consequence of the very likely decomposition of these rather unstable nitroalkene reagents. Finally, we also surveyed the use of a nitroacetate donor with a bulkier substituent such as **1b** which also performed very well in the reaction with *trans*-β-nitrostyrene (**2a**), *para*-methoxy-*trans*-β-nitrostyrene (**2e**) or *para*-bromo-*trans*-β-nitrostyrene (**2k**), yielding the corresponding products *syn*-**3o–q** with comparable results to those obtained with Michael donor **1a** (Table 1, entries 15–17).

Next, we proceeded to evaluate the scope of the reaction leading to diastereomeric adducts *anti*-**3** (Table 2) using bifunctional cyclohexanediamine/squaramide catalyst **6** which, as mentioned before, is based on a chiral backbone with the same absolute chirality as **4**. The reaction conditions used for this reaction were those already observed to be optimal in our previous work for the cascade Michael/Henry reaction using this catalyst, that involved changing the solvent to 1,2-dichloroethane [27]. As it happened in the previous case, we could observe that the reaction performed well in all cases tested and, in general, with a similar level of chemical efficiency and stereocontrol, although in comparison with the **4**-catalyzed version, enantioselectivities are normally around 5–10% lower if we analyse case by case. As it can be seen in Table 2, nitrostyrenes containing electron-withdrawing or electron-donating groups at the aromatic moiety performed similarly well in all cases, regardless the position of the substituents (Table 2, entries 1–11) and also heteroaryl moieties were well tolerated in the reaction (Table 2, entries 12 and 13). In the same line, functionalized nitroalkene **2n** could also be successfully used in the reaction leading to adduct *anti*-**3n** in good yield, diastereo- and enantioselectivity (Table 2, entry 14). The use of bulkier ethyl 2-nitrobutanoate (**1b**) as Michael donor also led to good results for three representative nitroalkenes (Table 2, entries 15–17), although in the case of nitroalkene **2e** a somewhat lower enantiomeric excess was obtained. Finally,

Table 2: Enantio- and diastereoselective Michael reaction between nitroesters **1** and nitroalkenes **2** catalysed by **6**.[a]



1a,b **2a–n** *anti*-**3a–q**

Entry	R^1	R^2	Product	Yield[b]	dr[c]	ee (%)[d]
1	Me	Ph	*anti*-**3a** [27]	98	88:12	90
2	Me	4-MeC_6H_4	*anti*-**3b** [62]	94	85:15	84
3	Me	2-$MeOC_6H_4$	*anti*-**3c**	95	90:10	86
4	Me	3-$MeOC_6H_4$	*anti*-**3d**	92	86:14	86
5	Me	4-$MeOC_6H_4$	*anti*-**3e** [62]	92	86:14	78
6	Me	4-$BnOC_6H_4$	*anti*-**3f**	90	86:14	81
7	Me	2-ClC_6H_4	*anti*-**3g** [62]	94	93:7	91
8	Me	3-ClC_6H_4	*anti*-**3h**	92	85:15	84
9	Me	4-ClC_6H_4	*anti*-**3i** [62]	91	83:17	84
10	Me	2-BrC_6H_4	*anti*-**3j** [62]	97	93:7	90
11	Me	4-BrC_6H_4	*anti*-**3k** [62]	93	83:17	84
12	Me	2-furyl	*anti*-**3l** [62]	94	80:20	80
13	Me	2-thienyl	*anti*-**3m**	98	87:13	80
14	Me	$(MeO)_2CH$	*anti*-**3n**	96	76:24	84
15	Et	Ph	*anti*-**3o** [62]	94	87:13	90
16	Et	4-$MeOC_6H_4$	*anti*-**3p**	94	87:13	64
17	Et	4-BrC_6H_4	*anti*-**3q**	94	88:12	84

[a]All reactions were carried out on a 0.1 mmol scale of **1** and **2** in 1,2-dichloroethane (1 M) at room temperature using 10.0 mol % of **6** as catalyst. [b]Yield of pure Michael adducts as mixture of diastereoisomers after flash column chromatographic purification. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC on a chiral stationary phase (see experimental part in Supporting Information File 1 for details).

and as it happened in the reaction catalyzed by **4**, β-alkyl-substituted nitroalkenes were not suitable substrates for the reaction, probably due to their tendency to polymerize under the reaction conditions.

The absolute configuration was determined by X-ray analysis of products *anti*-**3a** and *syn*-**3o** for which suitable crystals could be obtained (Figure 1). The crystallographic analysis gave a (2*R*,3*R*) configuration for *anti*-**3a** [27] and a (2*S*,3*R*) for *syn*-**3o** [63] and this stereochemical assignment was extended to all other adducts prepared assuming an identical mechanistic pathway.

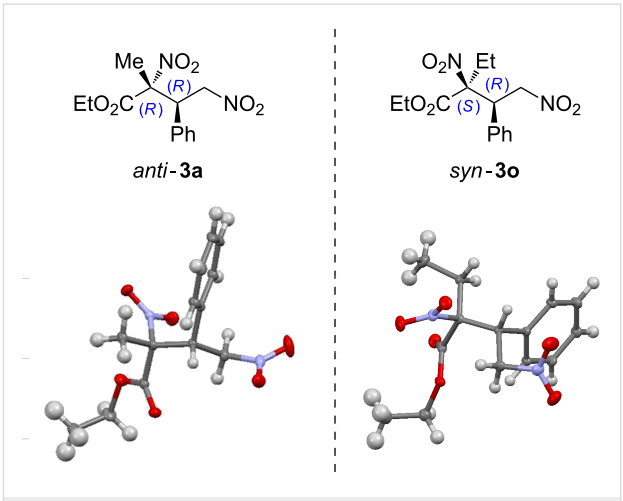
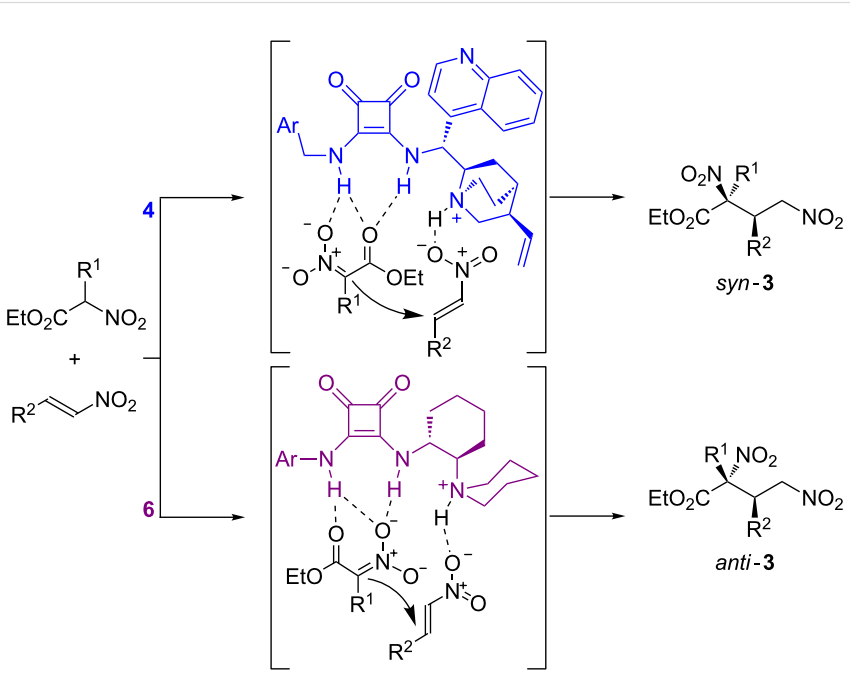


Figure 1: ORTEP diagrams for *anti*-**3a** and *syn*-**3o** respectively.

This configuration is also in agreement with a transition state for the Michael reaction such as the one proposed in Scheme 3 [64]. This involves the activation of the nucleophile by the squaramide moiety of the bifunctional catalysts **4** and **6** through the formation of multiple H-bonding interactions and the simultaneous interaction between the nitroalkene acceptor and the ammonium salt moiety, the latter being generated after the initial deprotonation of the pronucleophile. The different possibilities offered by the two catalysts **4** and **6** to form geometrically different H-bonded complexes with the nitroacetate enolate would account for the different simple diastereoselection observed in each case, in which the nitronate moiety exposes a different reactive prochiral face. These results are in good agreement with our previously reported work in which DFT calculations also showed that the difference in the steric bulk of the nitrogen substituents of the Brønsted basic site of the catalysts (the quinuclidine moiety in catalyst **4** and the piperidine scaffold in catalyst **6**) are the key parameters influencing this different arrangement for the nitroacetate pronucleophile [27].

Conclusion

We have developed an asymmetric catalytic diastereodivergent route for the synthesis of 2,4-dinitro esters taking advantage of the Michael addition of nitroalkenes and using two different bifunctional catalysts derived from cinchona alkaloids (catalyst



Scheme 3: Proposed models to explain the stereochemical outcome of the reaction.

4) or cyclohexadiamine (catalyst **6**). These catalysts, both with the same absolute backbone chirality, allow us to control the *syn* or *anti* selectivity obtaining the final products in good to excellent yields and with high enantioselectivity.

Supporting Information

Supporting Information File 1

Experimental details, analytical data, NMR spectra and HPLC traces of all compounds prepared.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-277-S1.pdf]

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Bifunctional phase-transfer catalysis in the asymmetric synthesis of biologically active isoindolinones

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Abstract

New bifunctional chiral ammonium salts were investigated in an asymmetric cascade synthesis of a key building block for a variety of biologically relevant isoindolinones. With this chiral compound in hand, the development of further transformations allowed for the synthesis of diverse derivatives of high pharmaceutical value, such as the Belliotti (*S*)-PD172938 and arylated analogues with hypnotic sedative activity, obtained in good overall total yield (50%) and high enantiomeric purity (95% ee). The synthetic routes developed herein are particularly convenient in comparison with the current methods available in literature and are particularly promising for large scale applications.

Introduction

Among the nitrogen heterocycles, the isoindolinone ring system is a favored scaffold, owing to the wide range of applications and pharmacological properties [1-3]. A relevant structural aspect is the presence of a substituent at the C3 position of the ring. A higher biological activity of the enantioenriched compounds with respect to racemic mixtures has been demonstrated for several 3-substituted isoindolinones, some of which are shown in Figure 1 [4-8]. For example, the enantioenriched isoindolinones **1** and **2** are benzodiazepine-receptor agonists for the treatment of anxiety [4-7]. Compound (*S*)-**3**, developed by

Belliotti et al. and known as PD172938, is a potent dopamine D_4 ligand [8] while hypnotic/sedative activity has been investigated only for *rac*-**4** [6,7]. In the last years, the development of the efficient, catalytic, asymmetric synthesis of 3-substituted isoindolinones became a research field of great interest among organic and medicinal chemists [9-23]. Nevertheless, the enantioenriched compounds **1**–**3** and their analogues have as of yet only been accessible via resolution approaches in less satisfactory overall yields (usually <10%). This is accompanied by the need of stoichiometric amounts of valuable chiral resolving agents, illustrating the need for more convenient strategies for large scale applications [4-8].

Recently, cascade reactions have received increasing attention due to the possibility of construction of complex scaffolds in operationally simple, one-pot procedures, starting from readily available materials [24-26]. In this context, our group recently introduced an interesting asymmetric organo-cascade reaction of 2-cyanobenzaldehyde (**5**) with malonate **6**. This resulted in enantioenriched 2-(1-oxoisoindolin-3-yl)malonate **7** which is supposed to serve as a potentially useful building block for further elaborations en route to the targets of medicinal interest (Figure 1). A high yield (usually >95%) and a maximum level of enantioselectivity of 74% ee were obtained but only in the presence of large amounts of cinchona alkaloid-based thiourea-containing organocatalysts (15 mol %) and after an unacceptably long reaction time (72 h) [21,22]. Readily available chiral ammonium salts (e.g., cinchona alkaloid-based or commercially available Maruoka catalysts) were also investigated, but the enantioselectivity was lower, reaching a maximum of 46% ee [23]. Gratifyingly, a very efficient heterochiral crystallization (these isoindolinones crystallize as racemic mixtures) allowed the isolation of the product in high enantiomeric excesses (>90% ee) and good overall yield, making the entire process attractive from a synthetic point of view [21,23]. However, several issues remain to be addressed when targeting the use of such a catalytic strategy to access the target compounds **1**–**4** in an efficient manner.

The availability of efficient catalytic processes is a fundamental requirement for the development of scalable synthetic routes of bioactive compounds. Thus, in the present work, we firstly reconsidered this cascade reaction, investigating novel *trans*-1,2-cyclohexane diamine-based bifunctional ammonium salts **8**. These catalysts were recently introduced by our groups in a variety of different reactions [27-29], as exemplified by a related aldol-initiated cascade reaction of glycine Schiff base with 2-cyanobenzaldehydes [29]. Then we decided to address the asymmetric synthesis of bioactive isoindolinones, identifying the chiral isoindolinone **9** as a very useful, key building block, as shown in Scheme 1.

Results and Discussion

Asymmetric cascade reaction of 2-cyanobenzaldehyde under phase-transfer conditions

As already discussed [21-23], the bifunctional nature of organocatalysts plays an important role in this reaction to attain satisfactory levels of enantioselectivity. The presence of additional hydrogen donors such as urea groups positively affected the enantioselectivity both in the presence of chiral base organo-catalysts and when using quaternary ammonium salts. In the latter case, however, only 46% ee was obtained using the bifunctional urea-containing ammonium salt catalyst introduced by Dixon's group [30]. Readily available commonly used quaternary ammonium salt catalysts gave racemic mixtures only, although high reactivity was generally observed [23].

Taking advantage of the high flexibility and efficiency of the developed synthetic route to **8** [27,29], a library of more than 20 structurally diversified chiral ammonium salts was tested in the

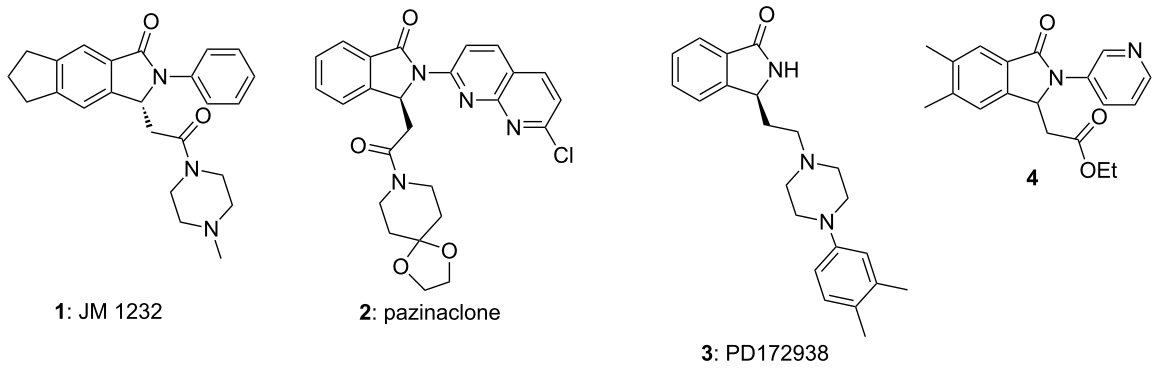
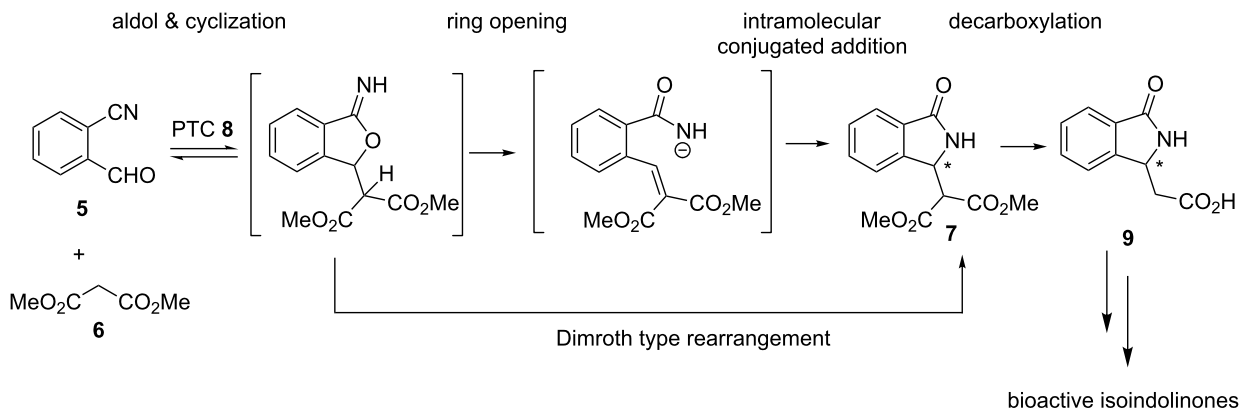
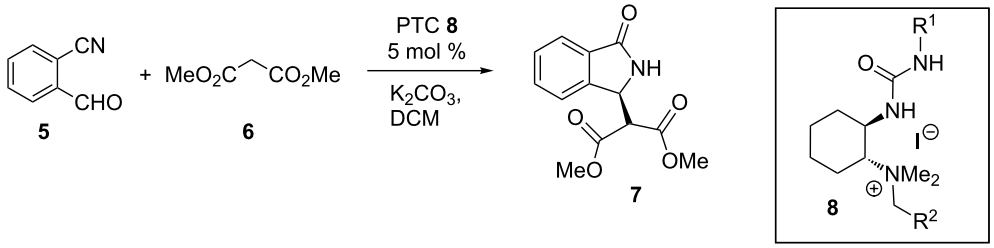


Figure 1: Some chiral, bioactive isoindolinones.



Scheme 1: This work: 1) *trans*-1,2-cyclohexane diamine-based bifunctional ammonium salts **8** in the asymmetric synthesis of **7**; 2) transformation of **7** into **9**; 3) asymmetric synthesis of bioactive isoindolinones.

Table 1: Catalyst screening in asymmetric cascade reactions of 2-cyanobenzaldehyde.



Entry	R^1	R^2	Yield (%)[a]	ee[b]
1	Ph	H	96	4
2	Ph	Ph	92	22
3	Ph	β-Np	91	20
4	Ph	4-*t*-Bu-C_6H_4	83	6
5	Ph	3,5-F_2-4-OMe-C_6H_2	92	26
6	Ph	α-Np	95	24
7	Ph	3-NO_2-C_6H_4	94	32
8	3-NO_2-C_6H_4	4-Br-C_6H_4	95	38
9	Cy	3,5-$(CF_3)_2$-C_6H_3	91	28
10	Et	3,5-$(CF_3)_2$-C_6H_3	94	28
11	3-NO_2-C_6H_4	Ph	92	32
12[c]	3-NO_2-C_6H_4	Ph	95	26
13	3-NO_2-C_6H_4	3,5-F_2-4-OMe-C_6H_2	94	40
14	3-NO_2-C_6H_4	4-*t*-Bu-C_6H_4	92	30
15	3-NO_2-C_6H_4	β-Np	95	34
16	3-NO_2-C_6H_4	3,5-$(CF_3)_2$-C_6H_3	96	66
17	**4-NO_2-C_6H_4**	**3,5-$(CF_3)_2$-C_6H_3**	**95**	**70**
18	(*R*)-PhCHCH$_3$	3,5-$(CF_3)_2$-C_6H_3	94	30
19	(*S*)-PhCHCH$_3$	3,5-$(CF_3)_2$-C_6H_3	96	28
20	2-Cl-5-NO_2-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	96	62
21	3,5-$(CF_3)_2$-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	96	64
22	3,5-$(CO_2Me)_2$-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	95	55
23	4-CF_3-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	96	60

[a]Isolated yields after 15 h reaction time using 5 mol % of the catalysts. [b]Determined by HPLC on chiral stationary phase. [c]The thiourea was tested.

model cascade reaction of 2-cyanobenzaldehyde with dimethyl malonate at room temperature (Table 1). We first identified the combination of DCM and solid K_2CO_3 as the best-suited solvent–base system for this reaction, however etheral or aromatic solvents or aqueous (alternative) bases generally gave significantly lower selectivities (this was carefully double-checked once the most active catalyst was identified). High yields were usually observed (>90%) when running the reaction for one night using 5 mol % of the catalyst. Good levels of enantioselectivity (up to 70% ee) were obtained when strong electron-withdrawing groups are present on both the urea and ammonium sides of the catalyst (Table 1, entries 16, 17, and 21). Electron-neutral or bulky aryl groups on the ammonium side, as well as the introduction of a naphthyl group, did not result in any improvement of the enantioselectivity. Also, the presence of aliphatic groups on the urea side did not allow us to improve the catalyst performance and a similar selectivity was obtained upon incorporation of more electron-rich aryl groups R^1. The initial tests also showed that ureas are more selective than thioureas (Table 1, entry 12). Thus further optimization was carried out with ureas only, finally identifying the catalyst **8a** (R^1 = 4-NO_2-C_6H_4, R^2 = 3,5-$(CF_3)_2$-C_6H_3) as the most promising one (Table 1, entry 17). It should also be noted that control experiments with catalyst derivatives containing only either a quaternary ammonium or a urea group proved the need for both of these functionalities to obtain satisfactory levels of enantioselectivity.

As mentioned before, the combination of solid K_2CO_3 as the base and DCM as the solvent was identified as the best system for this reaction and other reaction parameters (catalyst and base amounts, temperature, molar concentration) were systematically investigated next. Table 2 summarizes the most relevant results. Base amounts of 0.25–1 equiv (with respect to aldehyde **5**) can be used without affecting the enantioselectivity, but this results in a slightly reduced reaction rate when using less base. By varying the temperature, dilution, and catalyst loading, as shown in Table 2, **7** was finally obtained with 78% ee and in almost quantitative yield with a reasonably short reaction time when using only 2.5 mol % of the catalyst at −10 °C (Table 2, entry 9). Keeping in mind the fact that significantly larger amounts of catalyst and much longer reaction times were required to achieve a somewhat comparable selectivity and yield with organocatalysts found in the literature [21-23], these results encouraged us to use this methodology to access larger quantities of **8** next.

Thus, under the conditions of entry 9 in Table 2, the reaction was successfully scaled up to a practical 2 mmol scale with unchanged efficiency. After crystallization, we were able to obtain reasonable quantities of (*S*)-**7** with 95% ee and an overall yield of 77%. The availability of both the enantiomers of the catalysts is another important advantage because of the possibility to obtain both the enantiomers of chiral bioactive compounds. In this case, we focused on (*R,R*)-**8a**, which afforded the required (*S*)-**7** (the absolute configuration has been previously determined by vibrational circular dichroism) [31].

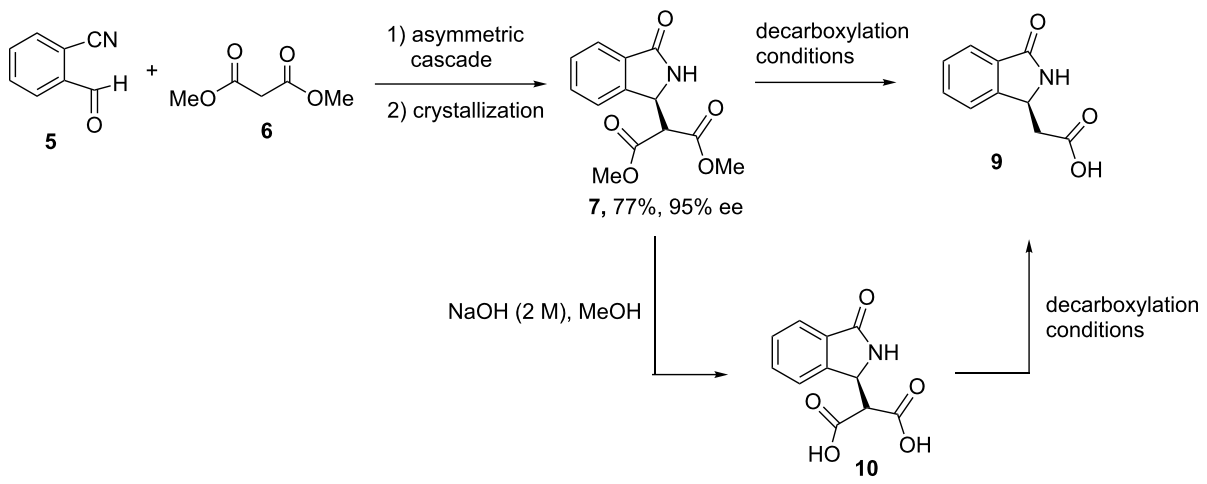
Asymmetric synthesis of **9** by decarboxylation of (*S*)-**7**

Although several methods to obtain *rac*-**9** are available [32-36], it is worth noting that the asymmetric synthesis of **9** is one of the major obstacles when targeting the synthesis of chiral isoindolinones. The recently introduced intramolecular aza-Michael reactions of 2-substituted acrylates gave very poor enantioselectivity (ee <10%) [9], while racemic analogues of **9** were resolved in the past in very low yields [4]. This disappointing picture prompted us to find a viable access route to enantioenriched **9**. We thus investigated the decarboxylation of the chiral dimethyl 2-(*S*)-(1-oxoisoindolin-3-yl)malonate ((*S*)-**7**), according to Scheme 2. We firstly focused on two well-known mild procedures in order to avoid the classical harsh acidic

Table 2: Optimization of the asymmetric cascade reaction.

Entry	Catalyst **8a** mol %	*T* (°C)	[**5**][a]	Time (h)	Yield (%)[b]	ee[c]
1	5 mol %	rt	0.033	15	95	70
2	5 mol %	0°C	0.033	15	95	75
3	5 mol %	−10°C	0.033	15	95	76
4	5 mol %	−20°C	0.033	15	95	60
5	5 mol %	0°C	0.067	6	92	73
6	5 mol %	0°C	0.017	15	91	64
7	10 mol %	rt	0.017	15	94	72
8	2.5 mol %	0°C	0.067	6	93	73
9	**2.5 mol %**	**−10°C**	**0.067**	**10**	**98**	**78**

[a]Aldehyde molar concentration. [b]Isolated yields. [c]Determined by HPLC on chiral stationary phase.



Scheme 2: Asymmetric cascade, crystallization and decarboxylation reaction.

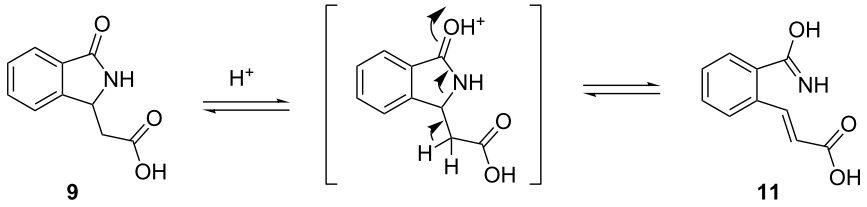
conditions. Disappointingly, modifications of the Krapcho decarboxylation performed with a $LiCl/H_2O/DMF$ mixture under reflux [36,37] led to partial racemization of the recovered methyl ester of **9** (60% ee), although high yields were observed (Table 3, entry 1). Then, in another attempt, the malonic acid **10** was subjected to the reaction with carbonyldiimidazole (CDI) under different conditions but also in combination with a piperazine. This method has been reported for a number of malonic acids [38] to afford the respective monoacid or directly the mono-amide derivative when the decarboxylation is performed in the presence of amines. However, we were not able to isolate the target compounds since we observed very low conversions and decomposition products. Therefore, we focused on the classical procedures carried out under acidic conditions. Luckily, the decarboxylation of both diester **7** and diacid **10** was particularly encouraging when performed in 6 M HCl solution at reflux in a very short reaction time. This gave the chiral acid **9** in high yield with essentially no loss in ee (Table 3, entries 4 and 8).

On the other hand, partial racemization was detected at longer reaction times (Table 3, entries 2, 3 and 7). This somewhat matched the time-dependent loss in ee observed by Allin et al. in the *N*-deprotection with H_2SO_4 of other chiral 3-substituted isoindolinones [39]. The racemization probably occurs on the product **9**, via the mechanism reported in Scheme 3, as a slower process than the decarboxylation itself. The cleavage of the C–N bond and the formation of the acyclic intermediates **11** with the consequent loss of chirality is probably favored by the protonation of the C=O group of the lactam. A similar *retro*-Michael racemization mechanism can be envisioned for the Krapcho decarboxylation, in which the Lewis acid Li^+ can coordinate the lactam group. In principle, racemization could also occur on **7**. However, under the optimized conditions, the decar-

Table 3: Optimization of the decarboxylation reaction.

Entry	Conditions	Substrate	*T* (°C)	Time	Yield (%)[a]	ee[b]
1[c]	Krapcho decarboxylation	**7**	reflux	2 h	85	60 (37)[d]
2	HCl 6N	**7**	60	96 h	51	36 (60)[d]
3	HCl 6N	**7**	reflux	1 h	96	91 (3)[d]
4	HCl 6N	**7**	reflux	30 min	90	95 (0)[d]
5	CDI/NaOH	**10**	rt	24 h	–	–
6	HCl 3M	**10**	50	24 h	–	–
7	HCl 1M	**10**	80	3 h	46	85 (10)[d]
8	HCl 6M	**10**	reflux	15 min	97	95 (0)[d]

[a]Isolated yield. [b]Determined by HPLC on chiral column on methyl ester. [c]The methyl ester of **9** was obtained. [d]$\Delta ee = ee_{\mathbf{5}} - ee_{\mathbf{6}}$.



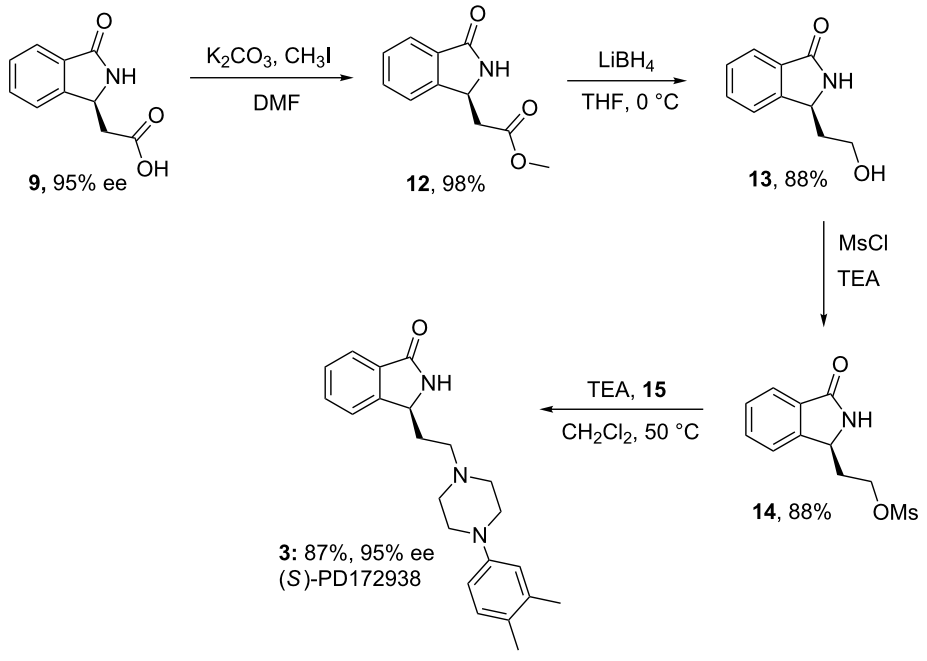
Scheme 3: Proposed racemization pathways of isoindolinones **9** via *retro*-Michael process.

boxylation is a faster process and **7** or **10** have never been recovered. Since the decarboxylation does not directly affect the stereocenter, we can confidently assign the absolute configuration of (−)-**9** as (*S*).

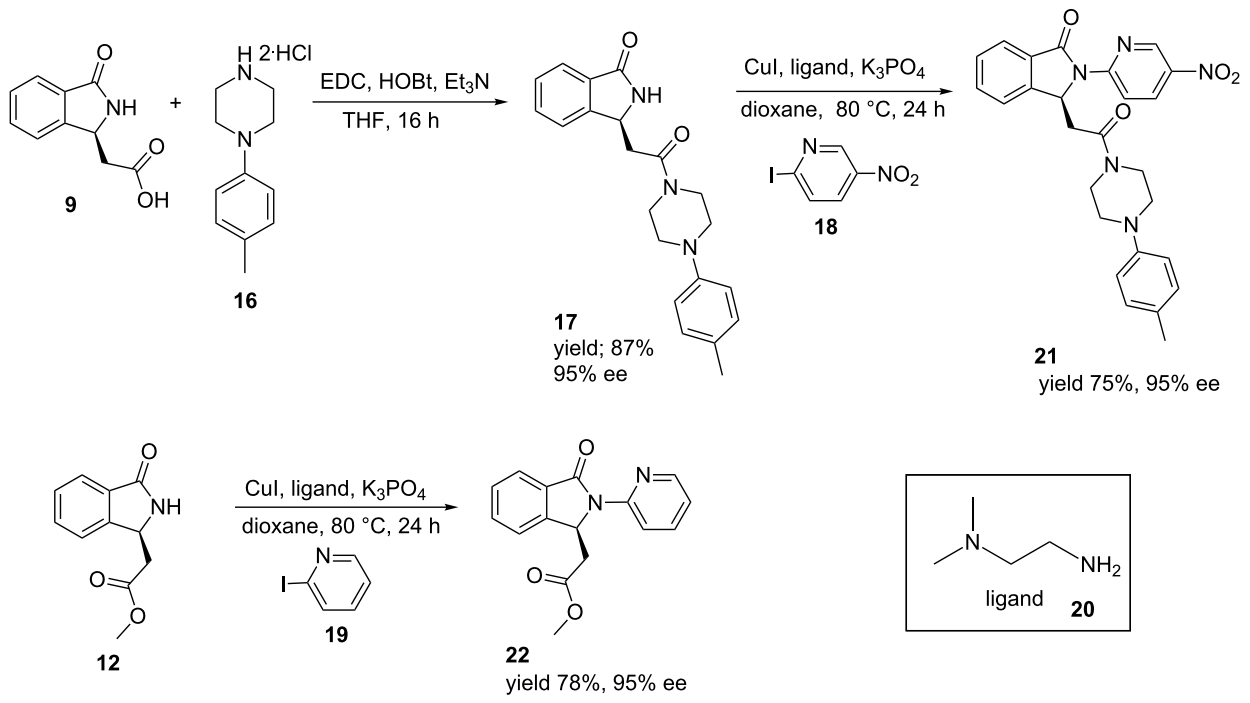
Asymmetric synthesis of bioactive isoindolinones

Inspired by well-known synthetic routes of racemic derivatives [4,5,8,36], (*S*)-**9** was found to be particularly useful in the asymmetric synthesis of a series of chiral intermediates and bioactive isoindolinones. Firstly, we focused on the reduction of methyl ester **12** to give the chiral alcohol **13**. In this case, $LiBH_4$ was particularly effective, leading to **13**in high yield, and most importantly, without a reduction in ee value. To our knowledge, this is the first asymmetric synthesis of **13**. On the other hand, $NaBH_4$, previously employed by Belliotti [8] for the reduction of *rac*-**12**, gave less satisfactory results. Then **13** was subjected to reaction with mesyl chloride and the subsequent displacement with 1-(3,4-(dimethylphenyl)pyperazine (**15**) gave **3**, the potent dopamine D_4 ligand (*S*)-PD172938, in high overall yield (51%), with 95% ee (Scheme 4).

Then, the amide **16**, which is of particular interest in the field of benzodiazepine-receptor agonists, was efficiently obtained by condensation of the chiral acid (*S*)-**9** with the commercially available piperazine **16**. Since most of the bioactive isoindolinones have a heteroaromatic group on the lactam, we focused on the CuI arylation of amides developed by Buchwald [40], previously applied by us to racemic derivatives [36]. Thus, we reacted the two model chiral isoindolinones **12** and **17** (bearing an ester and amide moiety in the side chains, respectively) with two different 2-iodopyridines **18** and **19**. This was done in the presence of CuI and *N*,*N*-dimethylethylenediamine (**20**) as the ligand in dioxane, improving the previous version developed on the racemates (Scheme 5) [36]. This method also allowed us to obtain the analogues **21** and **22** of the bioactive



Scheme 4: Asymmetric synthesis of (*S*)-PD172938.



Scheme 5: Coupling of chiral acid **9** with *p*-tolylpiperazine and CuI arylation of chiral isoindolinones.

isoindolinones described in Figure 1 in high overall yield (50%) without loss in enantiomeric purity.

Conclusion

Recently developed (*R,R*)-1,2-cyclohexanediamine-based bifunctional ammonium salts were investigated in the cascade reaction of 2-cyanobenzaldehyde with dimethyl malonate for the synthesis of (*S*)-2-(1-oxoisoindolin-3-yl)malonate. Very high yields and good enantioselectivities were obtained with only 2.5 mol % of the catalyst, improving previous versions performed in the presence of bifunctional organocatalysts and other readily available ammonium salts. Then, decarboxylation of this compound and further transformations allowed the synthesis of the Belliotti (*S*)-PD172938 and of other derivatives with diverse biological activities, in about 50% overall yield with 95% ee. Since the developed routes are particularly convenient in comparison to other syntheses reported in literature, further optimization and the synthesis of other bioactive isoindolinones are ongoing in our laboratory.

Experimental

(*S*)-Dimethyl 2-(1-oxoisoindolin-3-yl)malonate (7). A mixture of 2-cyanobenzaldehyde **5** (262 mg, 2 mmol), K_2CO_3 (276 mg, 2 mmol) and (*R,R*)-catalyst **8a** (27 mg, 0.05 mmol, 2.5 mol %) was dissolved in dichloromethane (30 mL, 0.066 M) and cooled to −10 °C while stirring. Within a period of 2 min, dimethyl malonate **6** (245 µL, 2.4 mmol, 1.2 equiv) was added. After 10 h (reaction monitored by TLC), the reaction mixture was filtered through a plug of Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, heptanes/ethyl acetate 1:1) giving the product as a colorless oil in 98% yield (520 mg, 1.96 mmol) and ee 78%. The enantiomers were separated by HPCL using the following conditions: Chiralcel AD-H, *n*-hexane/iPrOH 70:30, 1.0 mL/min, 10 °C, 12.3 min (minor; *R*-enantiomer), 25.5 min (major; *S*-enantiomer). The product was dissolved in a mixture of dichloromethane (6 mL) and heptanes (4 mL) and after crystallization overnight at −20 °C, the solid was filtered off and the solution containing the enantioenriched compound was evaporated and analyzed by chiral HPLC. The resulting enantioenriched product was obtained as a colourless oil in 77% overall yield (400 mg, 1.51 mmol, 95% ee). The spectroscopic data are in agreement with that reported in literature [21,22]. Chiralpack AD column, hexane/iPrOH 8:2, 0.8 mL/min, λ = 254 nm, *t* = 19.4 min, *t* = 29.3 min.

(*S*)-2-(1-Oxoisoindolin-3-yl)acetic acid (9) from 7. A flask containing a solution of isoindolinone **7** (320 mg, 1.20 mmol) and HCl 6 M (2 mL) was immersed in a preheated oil bath and refluxed for 30 min. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give compound **9**, which was purified with silica gel using ethyl acetate. Com-

pound **9** was obtained as a white solid (208 mg, 1.09 mmol, 90%). Mp 170–171 °C (from ethyl acetate); ESIMS (*m*/*z*): 190.18 $(M - H)^-$; $[\alpha]_D^{22}$ −21 (*c* 1.0, methanol); Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33; found: C, 62.72; H, 4.78; N, 7.01; ^{1}H NMR (300 MHz, CD_3OD) 7.76 (d, *J* = 7.5 Hz, 1H), 7.65–7.53 (m, 2H), 7.51–7.48 (m, 1H), 5.09–4.99 (m, 1H), 2.97–2.89 (m, 1H), 2.68–2.48 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.6, 171.2, 146.8, 131.9, 131.3, 128.1, 122.9, 122.6, 53.4, 38.3. The enantiomeric excess was determined by derivatization of the compound into methyl ester **12** or amide **16**.

Supporting Information

Supporting Information File 1

Complete experimental details and procedures, spectroscopic data, copies of ^{1}H NMR, ^{13}C NMR and HPLC traces.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-279-S1.pdf]

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Catalytic asymmetric formal synthesis of beraprost

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Full Research Paper

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Abstract

The first catalytic asymmetric synthesis of the key intermediate for beraprost has been achieved through an enantioselective intramolecular oxa-Michael reaction of an α,β-unsaturated amide mediated by a newly developed benzothiadiazine catalyst. The Weinreb amide moiety and bromo substituent of the Michael adduct were utilized for the C–C bond formations to construct the scaffold. All four contiguous stereocenters of the tricyclic core were controlled via Rh-catalyzed stereoselective C–H insertion and the subsequent reduction from the convex face.

Introduction

Prostacyclin (PGI_2, Figure 1) is a physiologically active compound known to inhibit platelet activation and also acting as an effective vasodilator [1-3]. In addition to these properties, PGI_2 derived from new vessels has attracted much attention due to its ability to promote axonal remodeling of injured neuronal networks after central nervous system disease [4,5]. However, PGI_2 possesses an unstable enol ether moiety, which can be hydrolyzed even under neutral aqueous conditions, resulting in a loss of pharmacological action [6-8]. Therefore, an increasing number of more stable PGI_2 derivatives have been developed. Among these, beraprost (**1**) has already been used as a pharmaceutical or under clinical trial in several countries for the treatment of arteriosclerosis obliterans and pulmonary hypertension [9]. Beraprost can be dosed orally as its sodium salt, and sold as a mixture of four diastereomers (**1a**, *ent*-**1a**, **1b**, and *ent*-**1b**) [10-13], although it was reported that each of the isomers have different activities [11]. In order to reduce the adverse effects while maintaining the pharmacological activities, an effective route for the asymmetric synthesis of **1** is highly sought after, and such methodologies should also lead to the expanded clinical application of **1**, as well as the development of more active derivatives.

Due to the unique tricyclic core of **1**, which bears four contiguous stereocenters, various approaches for the synthesis of key intermediate **2** (Scheme 1) have been reported [14-23], including a few asymmetric syntheses relying on the optical resolution of racemic intermediates [16-18,23]. Herein we

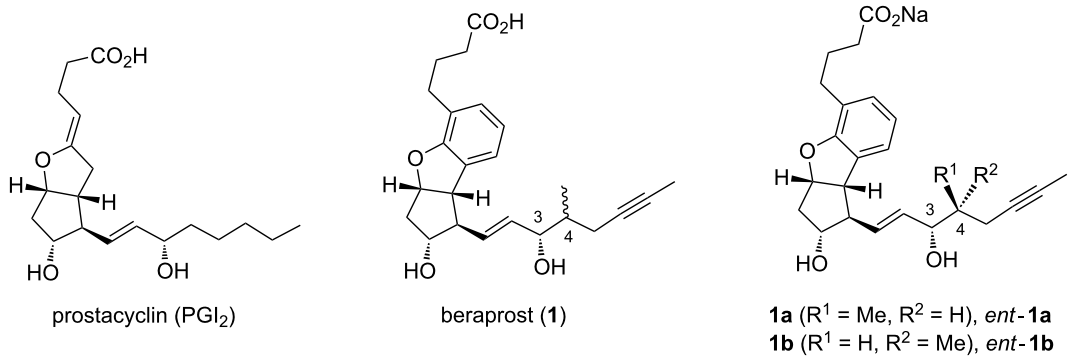
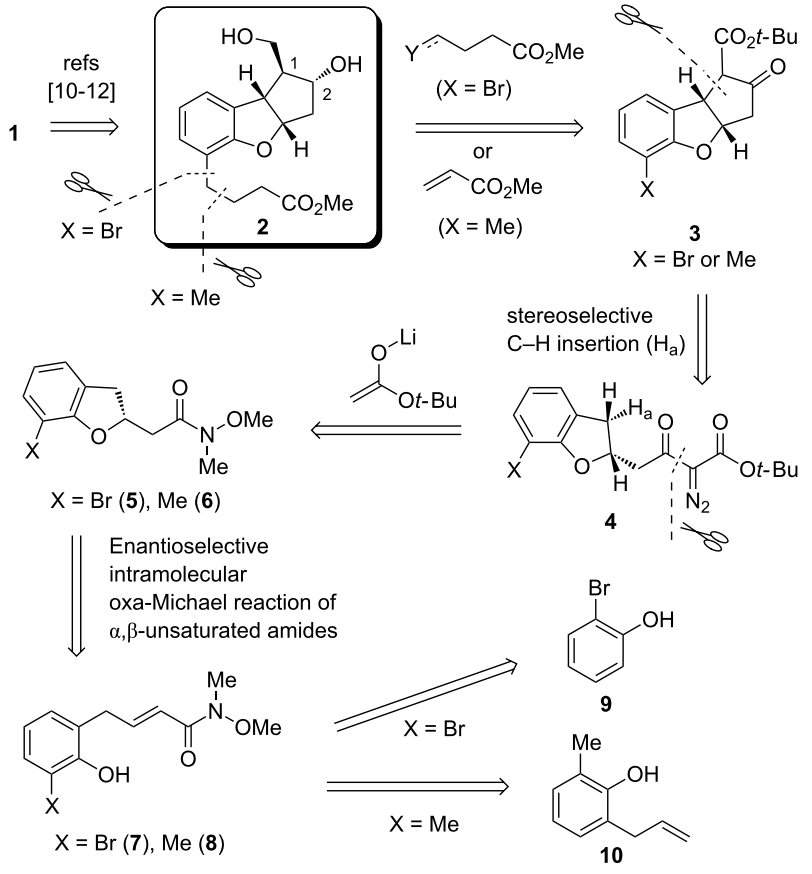


Figure 1: Structure of PGI_2 and beraprost (**1**).

report the first catalytic asymmetric synthesis of the key intermediate **2** through organocatalyzed-enantioselective intramolecular oxa-Michael reaction [24-26].

Results and Discussion

Our retrosynthetic analysis for **2** is shown in Scheme 1, with the derivatization of **2** to beraprost (**1**) having already been reported. We planned to introduce the ester side chain on the aromatic ring at a later stage, utilizing radical-mediated reactions with acrylate [22] when the functional group (X) at the *ortho* position was methyl, or via coupling reactions with C4 units when X was a bromo substituent. The *cis*-fused tricyclic core of **3** was assumed to be constructed by a stereoselective C–H insertion of diazoester **4**, which can be readily prepared from the Weinreb amides **5** or **6** via Claisen condensation followed by diazo-transfer reaction. The chiral dihydrobenzofuran

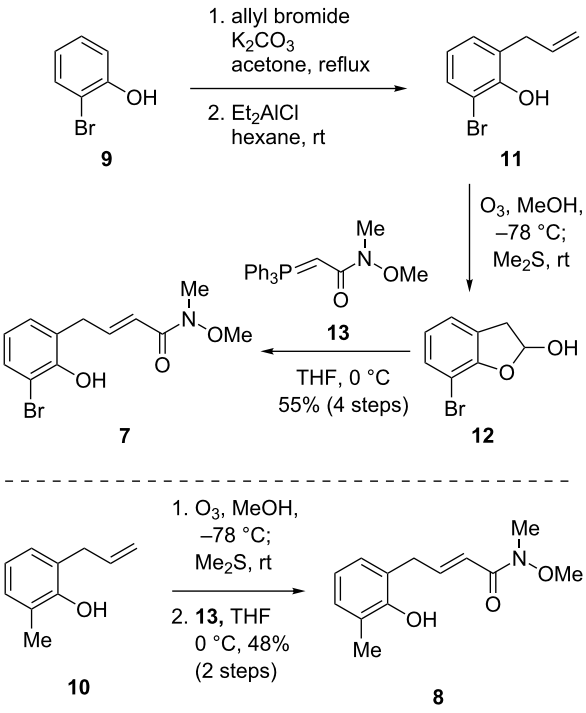


Scheme 1: Retrosynthetic analysis of beraprost (**1**).

scaffold (**5** or **6**) could be synthesized by asymmetric intramolecular oxa-Michael reaction (AIOM) of α,β-unsaturated amides **7** or **8**. Such reactions are generally considered to be challenging due to low nucleophilicity of the oxygen nucleophile and relatively unreactive Michael acceptors [27-33]. We envisioned that our recently developed powerful hydrogen bond (HB)-donor bifunctional organocatalyst [33] could promote the desired reaction of **7** or **8**, which can be synthesized from commercial sources **9** or **10**. Overall, the proposed strategy offers an efficient construction of all stereocenters of tricyclic core **2**, based on the initially established chiral stereocenter, as the configuration at the C1 and C2 positions of **2** would presumably be controlled by face-selective reduction of ketone **3**.

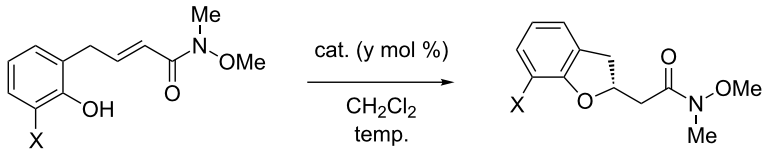
The Michael precursor **7** could be readily prepared from *ortho*-bromophenol (**9**, Scheme 2). *O*-Allylation of **9** followed by Lewis acid-mediated Claisen rearrangement afforded *ortho*-allylphenol **11**, whose olefin moiety was ozonolyzed and subsequently treated with Wittig reagent **13** to provide amide **7** in 55% yield over four steps from **9**. Amide **8** was similarly synthesized in 48% yield from **10**.

With the Michael precursors in hand, we next investigated the key AIOM reaction of **7** and **8** (Table 1). When the methylated



Scheme 2: Preparation of Michael precursors **7** and **8**.

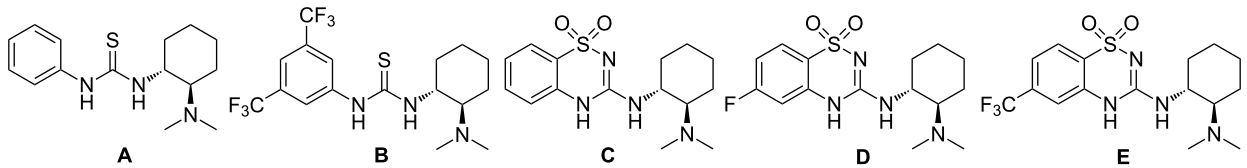
Table 1: Optimization of asymmetric intramolecular oxa-Michael reaction.



7 (X = Br)
8 (X = Me)

5 (X = Br)
6 (X = Me)

entry	X	cat.	y	temp	time (h)	yield (%)[a]	ee (%)[b]
1	Me	**A**	10	rt	192	95	90
2	Me	**B**	10	rt	72	90	91
3	Me	**C**	10	rt	72	90	93
4	Br	**B**	10	rt	72	82	75
5	Br	**C**	10	rt	120	72	70
6	Br	**D**	10	rt	120	92	80
7	Br	**E**	10	rt	96	83	85
8	Br	**E**	1	35	96	93	86

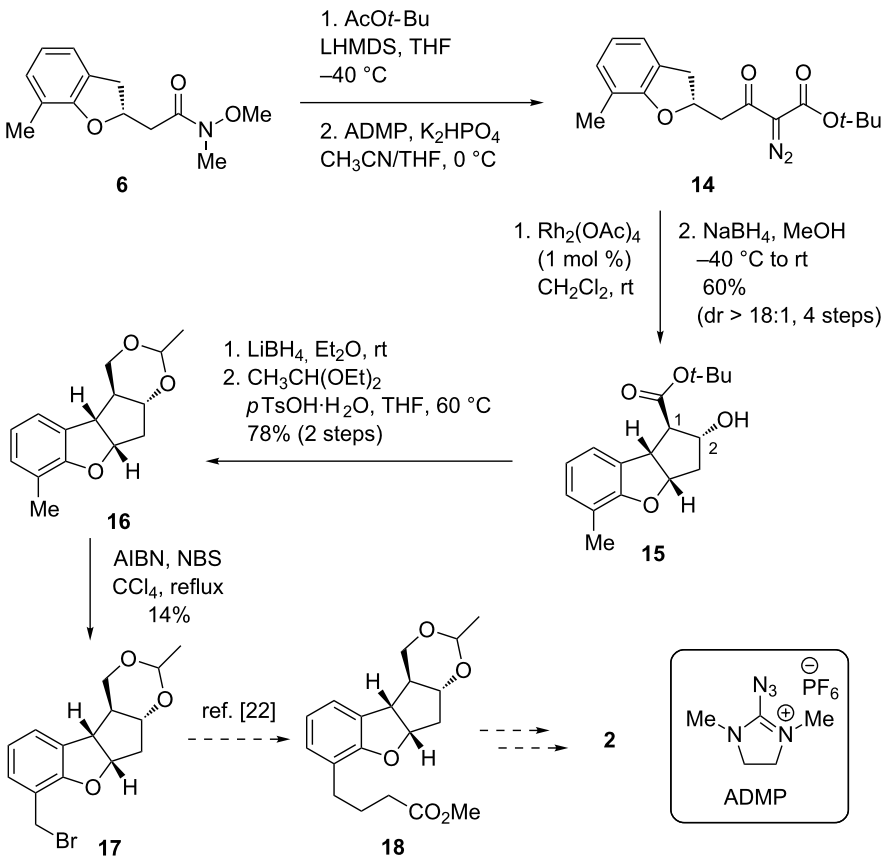


A **B** **C** **D** **E**

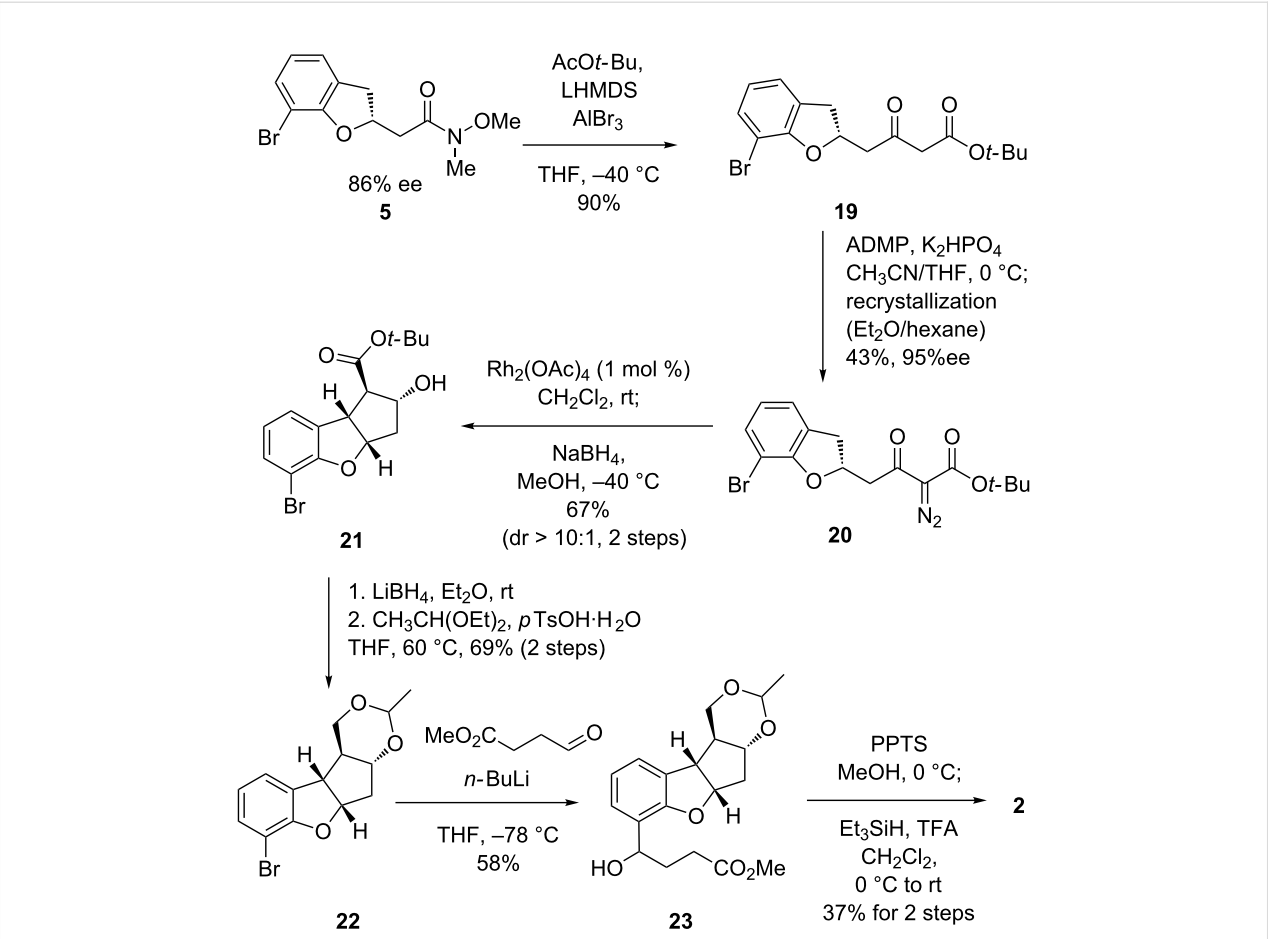
[a]Isolated yields. [b]Determined by HPLC.

substrate **7** was employed, the thiourea **B** [34,35] or benzothiadiazine **C** [33,36-38] catalysts efficiently promoted the reaction to furnish the dihydrobenzofuran **6** in 90% yield with high enantioselectivities (Table 1, entries 2 and 3). Conversely, thiourea **A** showed less catalytic activity, and the reaction required a much longer time for completion (Table 1, entry 1), indicating that the HB-donor moiety played an important role in facilitating the AIOM reaction. In addition, the AIOM reaction of bromo-substituted substrate **7** resulted in lower chemical yields (72–82%) and enantioselectivities (70–75% ee) even when catalysts **B** or **C** were employed for 72–120 hours (Table 1, entries 4 and 5). These results suggest that the relatively bulky bromo-substituent prevents recognition of the substrate by the catalyst. In order to improve recognition of the substrate through increased HB-donating abilities, we then tried catalyst **D** bearing a fluorine atom on the C6 position of the benzothiadiazine ring (Table 1, entry 6) [33]. As expected, both the chemical yield and enantioselectivity were improved, and the adduct **5** was obtained in 92% yield with 80% ee. In our preliminary DFT calculation, the HB-donor moiety would recognize an oxyanion generated from phenolic OH of substrates with tertiary amine moiety of the catalyst. It was also suggested that the SO_2 moiety of benzothiadiazine catalyst would interact with the *N*-methyl substituent of the substrate by a non-classical hydrogen-bonding [39], improving the catalytic activities (see Supporting Information File 1 for details). The absolute configuration of **5** and **6** were assigned as (2*R*) by reference from the previous work [32,33]. Encouraged by this result, we next designed the new catalyst **E** with a stronger electron-withdrawing CF_3 group on the aromatic ring, and applied it to the present AIOM reaction of **7** (Table 1, entry 7). To our delight, the enantioselectivity was improved to 85% ee while maintaining the high reactivity. Employing catalyst **E** we further investigated the reaction conditions and found that a scale-up synthesis can be performed using only 1 mol % of **E** with no loss of enantioselectivity, although gentle heating was required to ensure a high chemical yield (Table 1, entry 8).

With both the AIOM adducts **5** and **6** in hand, we next investigated the construction of the tricyclic core (Scheme 3 and Scheme 4). The cross-Claisen condensation of **6** with lithium *tert*-butyl acetate afforded the corresponding β-ketoester, which was then treated with 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP) [40-42] to give the diazoester **14**.



Scheme 3: First attempt at the synthesis of **2** from **6**.



Scheme 4: Achievement of a formal synthesis of **2**.

Rhodium catalysed C–H insertion [43,44] of **14** proceeded smoothly to furnish the tricyclic ketoester, which was found to be unstable to purification on column chromatography, presumably due to decomposition of the ketoester moiety. Therefore, the product was isolated as alcohol **15** after a one-pot reduction of the ketone moiety (60% in four steps from **6**), along with the minor diastereomer at C1 position (dr > 18:1). These results mean that the stereochemistry at the C2 position was fully controlled, presumably due to hydride attack from the less-hindered convex face. The relative configuration of **15** was unambiguously determined by NOESY analysis (see Supporting Information File 1 for details). As all four desired stereocenters were constructed, we next investigated the introduction of the ester side chain on the aromatic ring via benzylic bromination followed by elongation of the C3 unit [22]. To this end, the ester group at the C1 position of **15** was reduced by lithium borohydride, and the resultant 1,3-diol protected to give acetal **16** [16]. After various experiments, selective bromination of the methyl group on the aromatic ring of **16**, however, was found to be difficult due to competitive bromination of the electron-rich aromatic ring, and thus the desired bromide **17** was obtained in only 14% yield.

We then investigated an alternative route from adduct **5**, even though the enantiomeric excess of **5** (86% ee) was a little lower than that of adduct **6** (93% ee) (Scheme 4). Fortunately the diazoester **20**, as similarly derived as in Scheme 3, was obtained as a crystalline solid, and one recrystallization increased the ee to 95%. The tricyclic scaffold **21** with all four stereocenters of the desired configuration was synthesized in 67% yield (dr > 10:1) via the method established in Scheme 3. After derivatization to acetal **22** in 2 steps, we then turned our attention to the introduction of the C4 ester substituents. Amongst various different conditions investigated – including Pd-catalyzed coupling reactions – a halogen-lithium exchange and subsequent addition to methyl 4-oxobutanoate was found to be the best method to introduce the C4 subunit with reproducibility in the case of scale-up synthesis. Deprotection of the resultant ester **23** followed by reduction of the benzylic OH group finally afforded the key intermediate **2**.

Conclusion

We have developed the first asymmetric catalytic synthesis of the key intermediate for beraprost in 14 steps, via an organocatalyzed AIOM reaction of α,β-unsaturated amides. During the course of this study, it was revealed that a bromo substituent *ortho* to the phenolic OH group significantly decreased the reactivity and enantioselectivity. However, we found that the newly developed organocatalyst **E**, bearing increased HB-donating abilities, could improve both the reactivity and selectivity. In addition, the Weinreb amide moieties of the AIOM adduct were shown to be efficiently converted to β-ketoesters and diazoesters, a reactivity that could be further extended to various other molecular transformations. We believe that these findings could be applied to the synthesis of other biologically active oxo-heterocycles, and thus this is currently under investigation in our laboratory and will be reported in due course.

Experimental

General procedure for asymmetric oxa-Michael reaction

The benzothiadiazine catalyst **E** (8.6 mg, 0.022 mmol, 1 mol %) was added to a solution of **7** (661 mg, 2.20 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at 35 ºC for 96 h. The reaction mixture was then evaporated and the resulting crude residue purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate (60/40) to give the analytically pure compound **5** (614 mg, 93%). The enantiomeric ratio was determined by HPLC on a chiral stationary phase (86% ee).

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-285-S1.pdf]

Acknowledgements

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Asymmetric α-amination of β-keto esters using a guanidine–bisurea bifunctional organocatalyst

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Full Research Paper

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Abstract

An asymmetric α-amination of β-keto esters with azodicarboxylate in the presence of a guanidine–bisurea bifunctional organocatalyst was investigated. The α-amination products were obtained in up to 99% yield with up to 94% ee.

Introduction

Asymmetric α-amination of β-keto esters is an important synthetic route to optically active α-amino acid derivatives with chiral quaternary stereocenters [1,2]. Since an α-amino acid moiety is frequently found in biologically active compounds, considerable efforts have been made to achieve a stereoselective synthesis of this structure [3,4]. In particular, catalytic asymmetric α-amination of β-keto esters has been widely explored, using both metal catalysts and organocatalysts [5-18].

We have developed a series of guanidine–bis(thio)urea bifunctional organocatalysts, and have used them in a variety of asymmetric reactions [19,20]. Recently, we disclosed an α-hydroxylation of tetralone-derived β-keto esters **2** using guanidine–bisurea bifunctional organocatalyst **1a** in the presence of cumene hydroperoxide (CHP) as an oxidant (Figure 1a) [21]. This reaction provides the corresponding α-hydroxylation products **3** in high yield with high enantioselectivity. A computational study of the transition state of this reaction revealed that inter- and intramolecular hydrogen-bonding networks between catalyst and substrate are critical for obtaining high enantioselectivity [22]. Based upon these insights, we expected that guanidine–bisurea bifunctional organocatalyst **1** would be effective in promoting α-amination of β-keto esters as a result of interactions between guanidine and enolate of the β-keto ester, and between urea and azodicarboxylate (Figure 1b). Herein, we describe the catalytic asymmetric α-amination of β-keto esters with azodicarboxylates as a nitrogen source in the presence of **1**.

Results and Discussion

The reaction conditions for α-amination of β-keto ester **4a** in the presence of diethyl azodicarboxylate (DEAD) were optimized

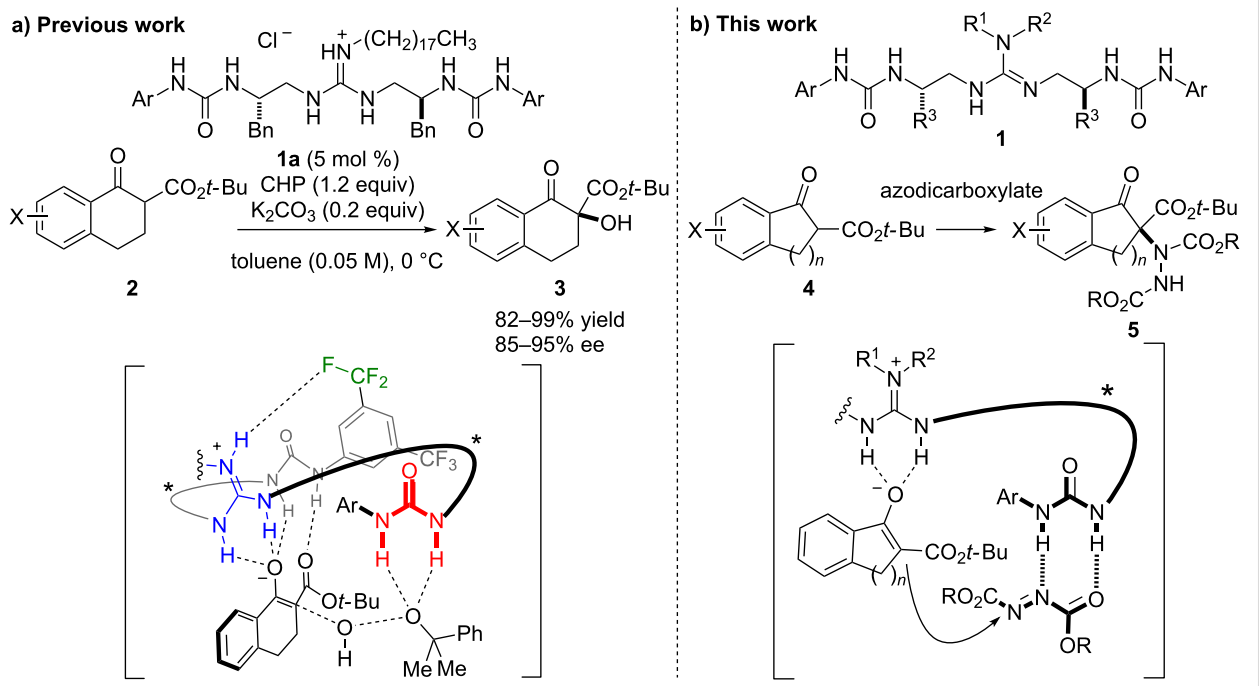
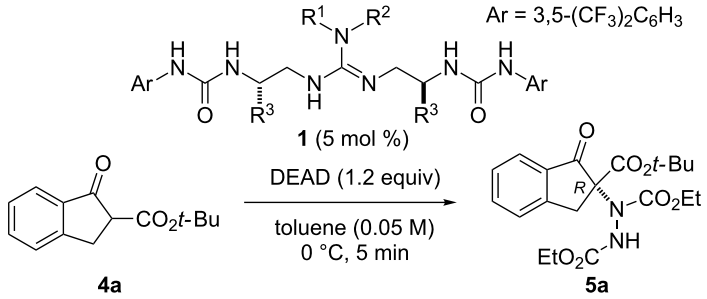


Figure 1: a) Asymmetric α-hydroxylation of **2** in the presence of **1a**. b) Asymmetric α-amination of **4** explored in this study.

as follows. First, we focused on the catalyst structure (Table 1) [23]. Initially, the R^3 substituent on the chiral spacer of the catalyst **1** was optimized (Table 1, entries 1–4). The catalyst with a benzyl group at R^3 (**1a**) afforded **5a** in excellent yield with moderate enantioselectivity for *R* configuration (Table 1, entry 1) [24,25]. When R^3 was changed to a phenyl group, the enantioselectivity was slightly increased to 59% ee (Table 1, entry 2). In the case of a methyl group, **5a** was obtained in 98%

Table 1: Optimization of catalyst structure.[a]



entry		catalyst **1**		α-amination product **5a**	
		R^1, R^2	R^3	yield (%)[b]	ee (%)[c]
1	**1a**	H, $-(CH_2)_{17}CH_3$	Bn	99	53
2	**1b**	H, $-(CH_2)_{17}CH_3$	Ph	94	59
3	**1c**	H, $-(CH_2)_{17}CH_3$	Me	98	50
4	**1d**	H, $-(CH_2)_{17}CH_3$	iPr	97	66
5	**1e**	$-(CH_2)_5-$	iPr	93	27
6	**1f**	$-(CH_2)_4-$	iPr	99	80

[a]Reaction conditions: **4a** (0.1 mmol), DEAD (0.12 mmol) and **1** (5 mol %) in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. DEAD = diethyl azodicarboxylate.

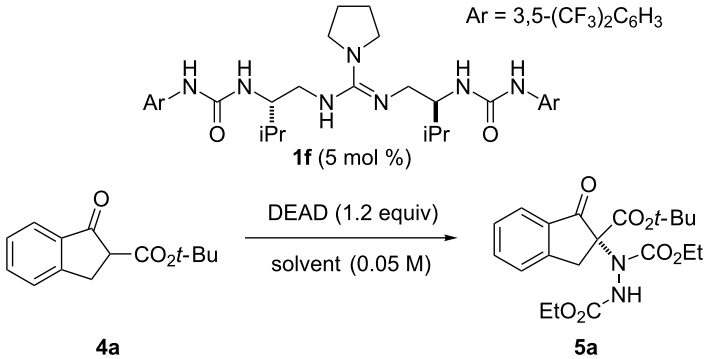
yield with 50% ee (Table 1, entry 3). An isopropyl group as R^3 group was most effective, affording **5a** with 66% ee (Table 1, entry 4). Next, we optimized R^1 and R^2 on the guanidine moiety (Table 1, entries 5 and 6). A catalyst bearing a six-membered ring at R^1 and R^2 (**1e**) gave excellent yield, but with only 27% ee (Table 1, entry 5). Interestingly, catalyst **1f** bearing a pyrrolidine ring at R^1 and R^2 showed the highest selectivity, and **5a** was obtained in 99% yield with 80% ee (Table 1, entry 6). Thus, we chose **1f** as the optimized catalyst for the reaction [26].

Next, we investigated various solvents, such as ethyl acetate, dichloromethane, acetonitrile and diethyl ether (Table 2, entries 1–5) for the reaction in the presence of catalyst **1f** (Table 2). The best result was obtained with diethyl ether, and **5a** was isolated in 95% yield with 85% ee (Table 2, entry 5). The enantioselectivity was improved to 90% ee by decreasing the reaction temperature to −40 °C without decrease in the yield (Table 2, entry 6). When the reaction was performed at −78 °C, the yield of **5a** was dropped to 91% (Table 2, entry 7).

As a further investigation, we optimized the ester moiety of the azodicarboxylate (Table 3). In addition to the ethyl ester (Table 3, entry 1), we examined benzyl, isopropyl, and *tert*-butyl ester as azodicarboxylate (Table 3, entries 2–4). By changing the ethyl ester to a benzyl or isopropyl ester, the amination products **6a** and **7a** were obtained in excellent yield, but the enantioselectivity was dropped to 64 and 79% ee, respectively (Table 3, entries 2 and 3). In the case of the *tert*-butyl ester, the reactivity of the azodicarboxylate was drastically decreased, and the reaction has not been completed after 48 h. The enantioselectivity of **8a** was also poor (Table 3, entry 4).

With the optimal reaction conditions in hand (Table 2, entry 6), we investigated the substrate scope for α-amination of β-keto esters (Scheme 1). First, various indanone-derived β-keto esters were examined. With electron-donating substituents such as methoxy and methyl, the corresponding amination products **5b**–**f** were obtained in high yield (72–99%) with high enantioselectivity (77–94% ee). In the case of substrates bearing electron-withdrawing groups, such as halogen atoms, the amination products **5g**–**j** were obtained with high enantioselectivity (73–86% ee). On the other hand, in the case of tetralone derivative **4k** and cyclopentanone derivative **4l**, the enantioselectivity of the products **5k** and **5l** was moderate to low (61% ee and 38% ee, respectively).

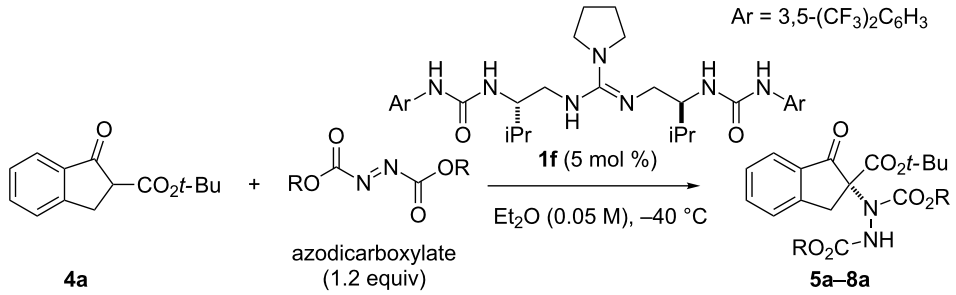
Table 2: Investigation of solvent effect.[a]



entry	solvent	time (min)	temp (°C)	α-amination product **5a**	
				yield (%)[b]	ee (%)[c]
1	toluene	5	0	99	80
2	EtOAc	5	0	99	78
3	DCM	30	0	99	75
4	MeCN	30	0	97	58
5	Et_2O	5	0	95	85
6	Et_2O	5	−40	99	90
7	Et_2O	30	−78	91	89

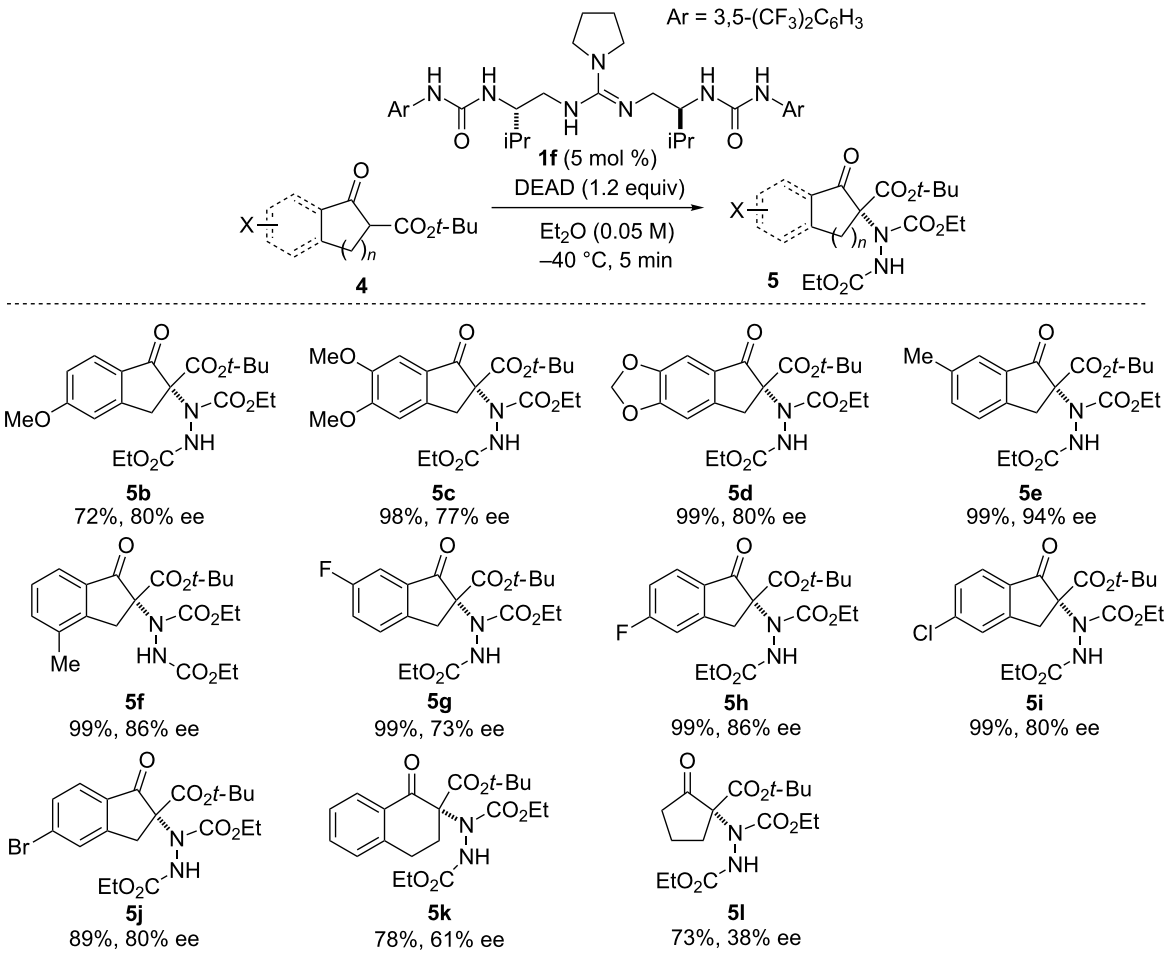
[a]Reaction conditions: **4a** (0.1 mmol), DEAD (0.12 mmol) and **1f** (5 mol %) in solvent (2.0 mL). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. DEAD = diethyl azodicarboxylate. EtOAc = ethyl acetate. DCM = dichloromethane. MeCN = acetonitrile. Et_2O = diethyl ether.

Table 3: Optimization of the ester moiety of azodicarboxylate.[a]



entry	azodicarboxylate	time	α-amination product		
	R			yield (%)[b]	ee (%)[c]
1	Et	5 min	**5a**	99	90
2	Bn	5 min	**6a**	98	64
3	iPr	30 min	**7a**	98	79
4	*t*-Bu	48 h	**8a**	58	44

[a]Reaction conditions: **4a** (0.1 mmol), azodicarboxylate (0.12 mmol) and **1f** (5 mol %) in Et_2O (2.0 mL) at −40 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.



Scheme 1: Substrate scope of α-amination.

To get insight into the transition state of the reaction, we performed a nonlinear effect (NLE) study (Figure 2) [27]. We found a linear relationship between % ee of **1f** and **5a** in the reaction. This result suggests that the stereoselectivity is controlled by the monomeric structure of **1f** [28-31]. Furthermore, to confirm the requirement of bifunctionality in catalyst **1**, we performed the α-amination reaction in the presence of carbamate **9** or triurea **10** as a catalyst (Scheme 2). In both cases, the enantioselectivity of the α-amination product **3a** was drastically decreased. These results clearly show that the guanidine and urea moieties in the catalyst **1f** are mandatory for obtaining high enantioselectivity, presumably interacting with the enolate of **4a** and DEAD, respectively.

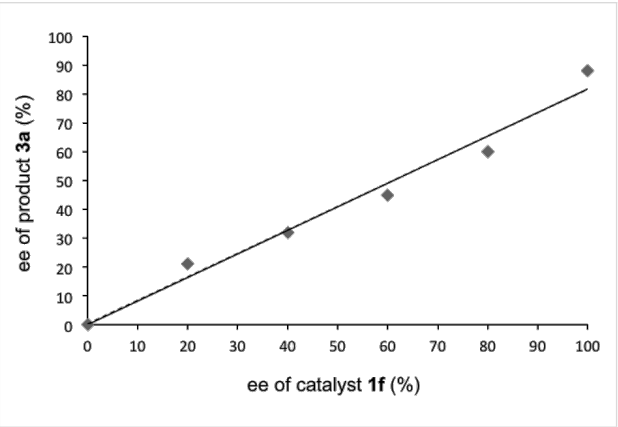


Figure 2: NLE study of α-amination.

Conclusion

In conclusion, we have developed an asymmetric α-amination of β-keto esters **4** by using guanidine–bisurea bifunctional organocatalyst **1f** in the presence of diethyl azodicarboxylate (DEAD). The α-amination of various indanone-derived β-keto esters proceeded in high yield (up to 99% yield) and with high enantioselectivity (up to 94% ee).

Supporting Information

Supporting Information File 1

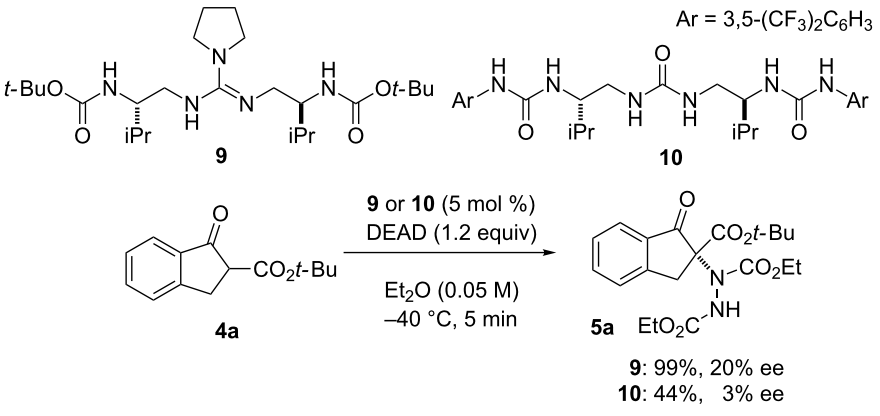
Experimental procedures, copies of NMR spectra and HPLC chromatograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-22-S1.pdf]

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Scheme 2: α-Amination of **4a** using **9** or **10** as catalyst.

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23. Guanidine–bisthiourea bifunctional organocatalyst was not suitable for the reaction. For details, see Tables S2 and S3 in Supporting Information File 1.
24. The absolute stereochemistry of **5a** was assigned by comparison with a known compound (ref. [17]).
25. Based on previously reported transition states (Figure 1a), we expected that the α-amination product would be the *S* conformer. However, the reaction afforded the *R* conformer. This result suggests that the reaction proceeds through a different transition state from previously reported reactions. Further investigation of the transition state is on-going.
26. The results of optimization of substituents on the aromatic ring are summarized in Table S1 in Supporting Information File 1.
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A quadruple cascade protocol for the one-pot synthesis of fully-substituted hexahydroisoindolinones from simple substrates

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Letter

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Abstract

A new and efficient synthetic method to obtain fully-substituted hexahydroisoindolinones was developed by using bifunctional tertiary amine-thioureas as powerful catalysts. As far as we know, there is no efficient synthetic method developed toward fully-substituted hexahydroisoindolinones. The products were obtained in good yield and diastereoselectivity. The one-pot cascade quadruple protocol features readily available starting materials, simple manipulation, mild conditions and good atom economy.

Introduction

Isoindolines and their congeners are one kind of the most widespread compounds in nature. They feature not only high biological activity, but also diverse chemical properties [1-16]. Therefore, it is highly desirable to develop efficient methods toward the synthesis of isoindoline derivatives, which is a frontier in organic synthesis.

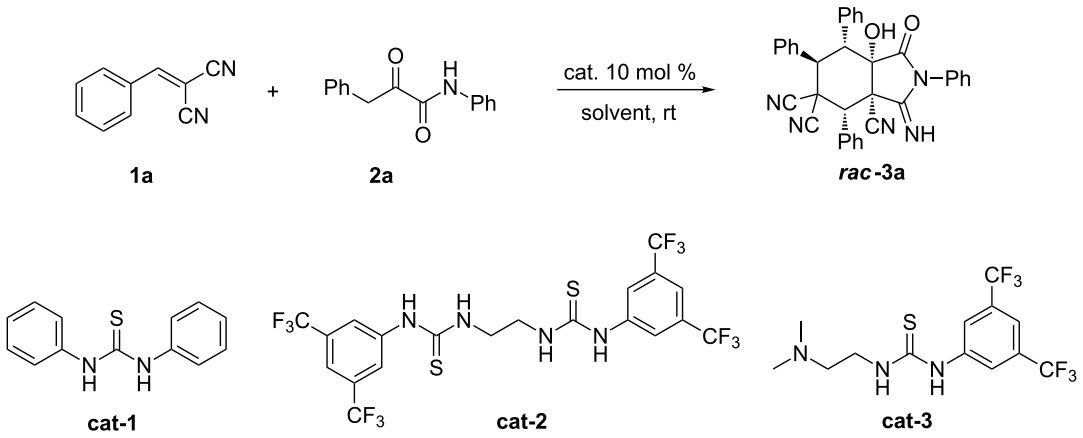
However, compared with the synthesis of their congeners, the synthesis of fully-substituted hexahydroisoindolinones is much more difficult due to the steric hindrance and the high strain of the molecular architectures [17]. Three methods to synthesize 3-substituted isoindolinones have been developed. The first method was the synthesis of 3-substituted isoindolinones from the corresponding *N*-methylmaleimides by the Diels–Alder reaction with 1,3-butadiene followed by hydrogenation. The second and the third methods employed the corresponding dicarboxylic acids and the carboxylic acid anhydrides, respectively [17]. To the best of our knowledge, no efficient method toward the synthesis of fully-substituted hexahydroisoindolinones has been developed so far.

The synthesis of complicated molecular structures can now be achieved by organocatalytic cascade reactions [18-33]. By simplifying the experimental procedures and reducing the usage of both solvents and reagents, one-pot reactions can improve the synthesis efficiency and both save time and reduce cost [34]. Although a few types of complicated molecules were generated through multicomponent quadruple cascade reactions, there is no report about the cascade synthesis of isoindolines in the past few decades [35-46], not mention the quadruple cascade synthesis of difficult fully-substituted hexahydroisoindolinones. Previously, we established organocatalytic domino reactions to construct very useful molecular architectures [47-60]. Based on this past experience, we decided to develop a one-pot quadruple protocol to construct this difficult molecular architecture using easily accessible substrates.

Results and Discussion

We initiated this study by using 2-benzylidenemalononitrile (**1a**) and 2-oxo-*N*,3-diphenylpropanamide (**2a**) [61-64] in 0.5 mL of CH_3CN in the presence of 10 mol % of DABCO. After 12 h at room temperature, the reaction afforded the expected product ***rac*-3a** in 59% yield (Table 1, entry 1). We then tested different catalysts to optimize the reaction. When Et_3N was used, the reaction afforded the product with 41% yield (Table 1, entry 2). However, a complex mixture was observed when DBU was used (Table 1, entry 3), while no reaction was observed when K_2CO_3 was used as the catalyst (Table 1, entry 4). When thioureas were used as the catalysts, we also did not get the expected product (Table 1, entries 5 and 6). Since bifunctional tertiary amine-thioureas have been proved as powerful catalysts that can catalyze a variety of organocascade

Table 1: Screening the reaction conditions.[a]



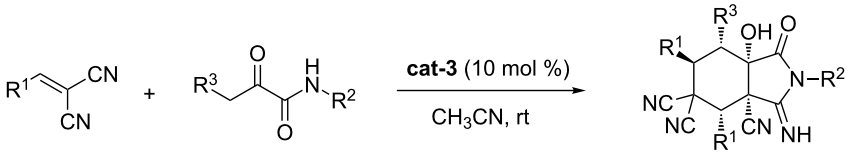
entry	cat.	solvent	dr[b]	yield [%][c]
1	DABCO	CH_3CN	4:1	59
2	Et_3N	CH_3CN	4:1	41
3	DBU	CH_3CN	n.d.	complex
4	K_2CO_3	CH_3CN	n.d.	n.r.
5	**cat-1**	CH_3CN	n.d.	n.r.
6	**cat-2**	CH_3CN	n.d.	n.r.
7	DABCO[d]	CH_3CN	4:1	62
8	Et_3N[d]	CH_3CN	5:1	52
9	**cat-3**	CH_3CN	9:1	87
10	**cat-3**	DCM	4:1	33
11	**cat-3**	THF	4:1	34
12	**cat-3**	toluene	n.d.	trace
13	**cat-3**	CH_3OH	n.d.	trace
14[e]	**cat-3**	CH_3CN	6:1	87

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.25 mmol, 38.5 mg), **2a** (0.1 mmol, 23.9 mg), catalyst (0.01 mmol, 10 mol %) in the indicated solvent (0.5 mL) at rt for 12 h. [b]Determined by ^{1}H NMR analysis of the crude products. [c]Column chromatography yields. [d]10 mol % **cat-2** was added. [e]The reaction was carried out at 35 °C.

reactions, we also tested thiourea catalysts, **cat-1** to **cat-3**. Interestingly, the thioureas **cat-1** and **cat-2** were able to promote the reaction (Table 1, entries 7 and 8), but we obtained an even better yield when the tertiary amine-thiourea **cat-3** was used as the catalyst (Table 1, entry 9). All products were racemic even when chiral catalysts were used (see Supporting Information File 1 for details). Next, we performed a solvent screening. As shown in Table 1, when DCM and THF were used as the solvent, the yield of the desired product was 33% and 34%, respectively (Table 1, entries 10 and 11). Only traces of the product were seen when toluene or methanol was used as the solvent (Table 1, entries 12 and 13). Furthermore, raising the reaction temperature was not beneficial for the diastereoselectivity of the reaction (Table 1, entry 14).

With the optimal conditions in hand, we next examined the reaction scope (Table 2). All reactions afforded the corresponding products **3a**–**t** with medium to good yield and diastereoselectivity using the simple protocol at room temperature. To our delight, with our optimized reaction system, various types of substrates **1** showed very good reaction activities. Different types of substrates **1**, bearing either electron withdrawing or donating groups in *para*-, *meta*- and *ortho*-positions, gave the desired products in good yield and diastereoselectivity (Table 2,

Table 2: Substrates scope.[a]



1 **2** ***rac*-3**

entry	R^1	R^2	R^3	dr[b]	yield [%][c]
1	C_6H_5	C_6H_5	C_6H_5	9:1	87 (**3a**)
2	2-MeC_6H_4	C_6H_5	C_6H_5	>20:1	89 (**3b**)
3	3-MeC_6H_4	C_6H_5	C_6H_5	10:1	69 (**3c**)
4	4-$OMeC_6H_4$	C_6H_5	C_6H_5	10:1	66 (**3d**)
5	2-BrC_6H_4	C_6H_5	C_6H_5	>20:1	84 (**3e**)
6	3-ClC_6H_4	C_6H_5	C_6H_5	4:1	72 (**3f**)
7	4-FC_6H_4	C_6H_5	C_6H_5	>20:1	82 (**3g**)
8	4-$CF_3C_6H_4$	C_6H_5	C_6H_5	>20:1	86 (**3h**)
9	2-$NO_2C_6H_4$	C_6H_5	C_6H_5	>20:1	89 (**3i**)
10	3-$NO_2C_6H_4$	C_6H_5	C_6H_5	>20:1	91 (**3j**)
11	4-$NO_2C_6H_4$	C_6H_5	C_6H_5	3:1	42 (**3k**)
12	2-naphthalene	C_6H_5	C_6H_5	>20:1	90 (**3l**)
13	2-thiophene	C_6H_5	C_6H_5	3:1	51 (**3m**)
14	3,4-diClC_6H_3	C_6H_5	C_6H_5	>20:1	84 (**3n**)
15	3,5-di$OMeC_6H_3$	C_6H_5	C_6H_5	15:1	55 (**3o**)
16	C_6H_5	4-$OMeC_6H_4$	C_6H_5	4:1	56 (**3p**)
17	C_6H_5	4-ClC_6H_4	C_6H_5	>20:1	89 (**3q**)
18	2-naphthalene	4-$OMeC_6H_4$	C_6H_5	14:1	88 (**3r**)
19	C_6H_5	C_6H_5	4-MeC_6H_4	8:1	61 (**3s**)
20	C_6H_5	C_6H_5	4-FC_6H_4	8:1	61 (**3t**)
21	$C_6H_5(CH_2)_2$	C_6H_5	C_6H_5	n.d.	n.r.
22	$CH_3(CH_2)_5$	C_6H_5	C_6H_5	n.d.	n.r.
23	C_6H_5	$CH_3(CH_2)_3$	C_6H_5	n.d.	n.r.
24	C_6H_5	CH_3CH_2	C_6H_5	n.d.	n.r.
25	C_6H_5	C_6H_5	H	n.d.	n.r.
26	C_6H_5	C_6H_5	CH_3	n.d.	n.r.

[a]Unless otherwise noted, the reactions were carried out with **1** (0.25 mmol), **2** (0.1 mmol), **cat-3** (3.6 mg, 0.01 mmol, 10 mol %) in CH_3CN (0.5 mL) at rt for 12 h. [b]Determined by ^1H NMR analysis of the crude products. [c]Column chromatography yields.

entries 1–10 and 12), although 4-$NO_2C_6H_4$ gave the product in medium yield due to its poor solubility (Table 2, entry 11). A heteroaromatic substrate such as thiophene could also be successfully employed to afford ***rac*-3** with medium yield and diastereoselectivity (Table 2, entry 13). 3,4-Dichloro-substituted and 3,5-dimethoxy-substituted substrates produced the desired products in 84% and 55% yield with 20:1 and 15:1 diastereoselectivity, respectively (Table 2, entries 14 and 15). When substrates with different R^2 and R^3 were used in this reaction, the corresponding products were obtained in medium yield and diastereoselectivity (Table 2, entries 16–20). The structure of **3p** was determined by X-ray analysis [65]. However, substrates with aliphatic R^1, R^2 or R^3 did not produce the desired products (Table 2, entries 21–26).

This bifunctional catalysis cascade reaction was also amenable to scale-up. When the reaction was carried out on a 3 mmol scale, the desired product was obtained in 84% yield. Therefore, this method is fast and easy to implement, and it is suitable for large-scale synthesis (Scheme 1).

Many isoindolinone skeletons show high biological potential as antihypertensives, anesthetics, etc. [66-68]. The useful hydrolyzed product ***rac*-4a** was obtained in 80% yield by treating ***rac*-3a** with trifluoroacetic anhydride in DCM (Scheme 2).

Finally, we propose a mechanism for the reaction. Initially, substrate **1** is activated by catalyst (**I**), which reacts with substrate **2** via two Michael addition reactions to sequentially produce **II** and **III**. Then, **IV** is generated from **III** by an aldol reaction. Finally, the product is produced after the nucleophilic reaction, and the catalyst is regenerated (Scheme 3).

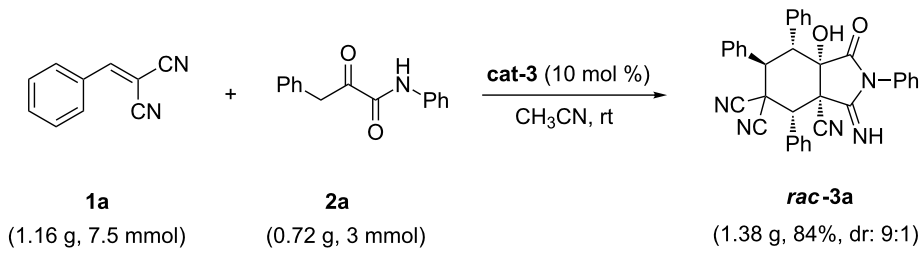
Conclusion

In summary, we have developed a one-pot quadruple cascade protocol to obtain fully-substituted hexahydroisoindolinones. This new, synthetic method is simple, efficient and atom-economic. This reaction can be widely used in organic synthesis due to its advantages such as simple operation, availability of raw materials, mild conditions and high efficiency.

Experimental

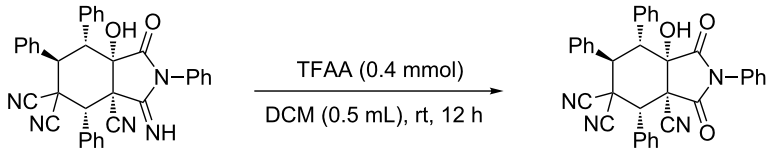
General procedure for the synthesis of fully-substituted hexahydroisoindolinones

Benzylidenemalononitrile (0.1 mmol), 2-oxo-*N*,3-diphenylpropanamide (0.25 mmol) and **cat-3** (0.01 mmol) were added to a test tube, then CH_3CN (0.5 mL) was added to the mixture. The reaction mixture was stirred at 300 rpm at 21 °C in a stoppered carousel tube for 12 h. The solvent was removed in vacuo and the product was purified by silica gel flash column chromatography to give the corresponding product **3**.



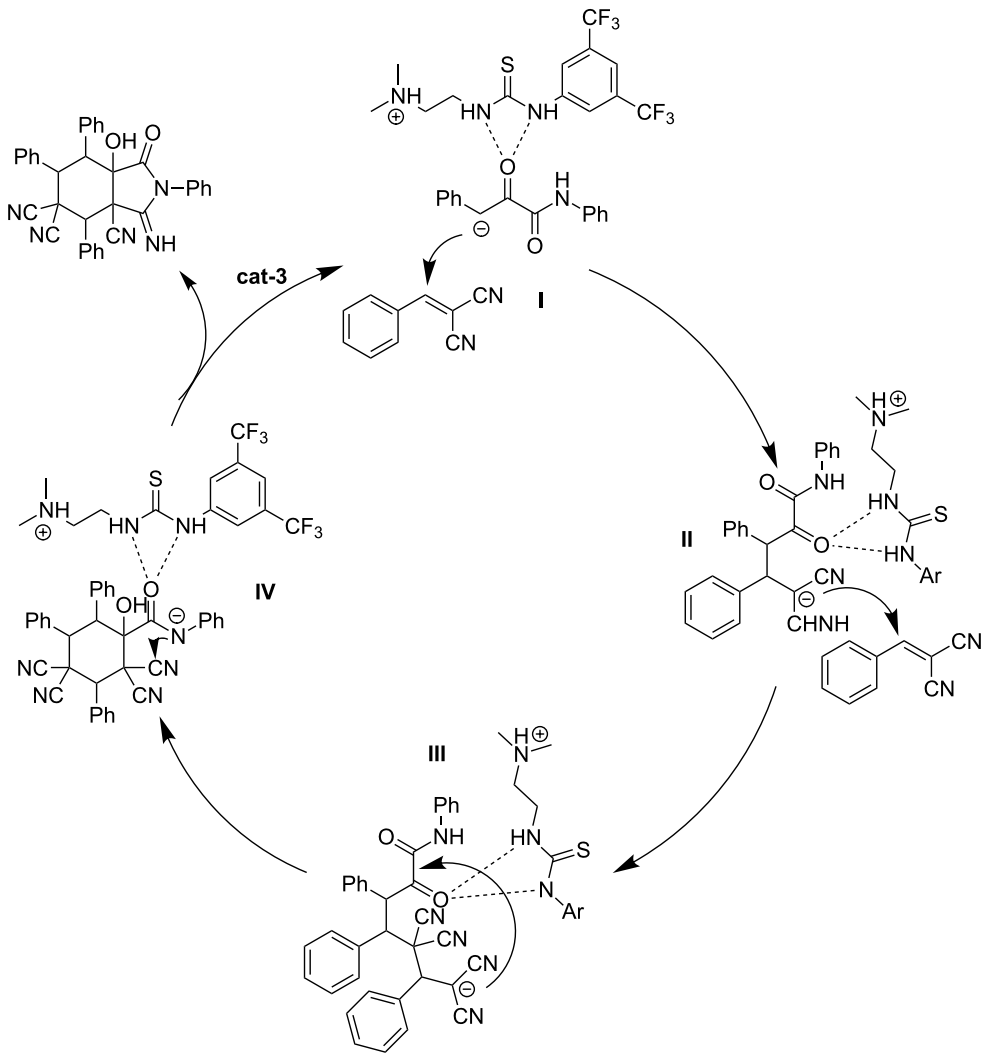
1a (1.16 g, 7.5 mmol) + **2a** (0.72 g, 3 mmol) → ***rac*-3a** (1.38 g, 84%, dr: 9:1)

Scheme 1: An example of scalable synthesis.



***rac*-3a** (0.109 g, 0.2 mmol, dr: 9:1) → ***rac*-4a** (0.088 g, 80%, dr: 9:1)

Scheme 2: Hydrolysis reaction to produce a useful product.



Scheme 3: Proposed mechanism.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data for all new compounds and X-ray analysis of compound **3**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-27-S1.pdf]

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Organocatalytic asymmetric Henry reaction of 1*H*-pyrrole-2,3-diones with bifunctional amine-thiourea catalysts bearing multiple hydrogen-bond donors

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Full Research Paper

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Abstract

For the first time, a catalytic asymmetric Henry reaction of 1*H*-pyrrole-2,3-diones was achieved with a chiral bifunctional amine-thiourea as a catalyst possessing multiple hydrogen-bond donors. With this developed method, a range of 3-hydroxy-3-nitromethyl-1*H*-pyrrol-2(3*H*)-ones bearing quaternary stereocenters were obtained in acceptable yield (up to 75%) and enantioselectivity (up to 73% ee).

Introduction

Asymmetric organocatalysis has been demonstrated to be an effective and versatile strategy in facilitating a variety of organic transformations over the past decade, and numerous catalytic asymmetric reactions have been developed with various activation modes [1-6]. In this realm, chiral bifunctional catalysts, possessing two active sites, have captured tremendous attention in particular due to their unique ability of the simultaneous activation of the nucleophile and the electrophile in the same transition state [7-11]. Among them, chiral bifunctional thioureas bearing multiple hydrogen-bond donors have been successfully used as chiral organocatalysts for the asymmetric Michael addition and Mannich reactions [12-14]. Meanwhile, the Henry reaction is one of the most important carbon–carbon bond-forming reactions that provides straightforward access to β-nitroalcohols, which can be further transformed into amino-alcohols, amino acids and carbonyl compounds [15]. Much attention has been devoted to the development of an efficient catalytic asymmetric version of this reaction from readily accessible nitroalkanes and carbonyl compounds [16], such as aldehydes [17-19], α-ketoesters [20],

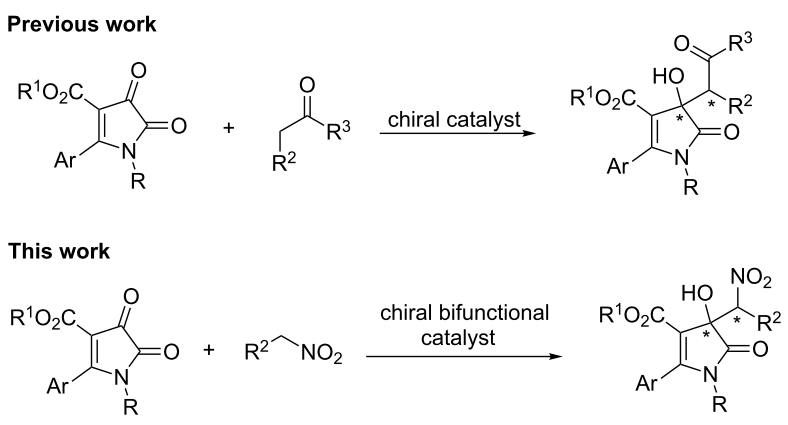
α-ketophosphonates [21,22], fluoromethyl ketones [23,24] and isatins [25,26]. Despite these significant advances described above, the use of more challenging ketones with heterocyclic structures as Henry acceptors has remained relatively less explored. In this context, developing a new Henry reaction for the construction of the useful and versatile β-nitroalcohol scaffolds is still desirable.

Pyrrole skeletons represent an important class of heterocycles and are frequently found in many biologically active molecules and natural products [27,28]. Particularly, 3-substituted-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives exhibit a wide spectrum of biological activities [29]. The reaction of 1*H*-pyrrole-2,3-diones with various nucleophiles should be a straightforward way to access diverse and interesting 3-substituted-3-hydroxy-1*H*-pyrrol-2(3*H*)-ones. A survey of the literature reveals that the study of 1*H*-pyrrole-2,3-diones is mainly focused on three-component spiro-heterocyclization reactions [30-32]. However, for the catalytic asymmetric transformation, only one example of an aldol reaction of 1*H*-pyrrole-2,3-diones with ketones has been reported so far (Scheme 1) [33]. Recently, our group developed a chiral bifunctional multiple hydrogen-bond amine-thiourea-catalyzed Michael reaction of acetyl phosphonates with nitroolefins, giving a series of β-substituted nitro compounds with excellent stereoselectivity [34]. Therefore, as part of our research program aimed at establishing new methods for the construction of quaternary stereocenters [35-37], we envisioned that the Henry reaction of nitroalkanes with 1*H*-pyrrole-2,3-diones should take place with a chiral bifunctional amine-thiourea catalyst, leading to 3-hydroxy-3-nitromethyl-1*H*-pyrrol-2(3*H*)-ones bearing quaternary stereocenters (Scheme 1) [14]. Notably, this work represents the first example of 1*H*-pyrrole-2,3-diones used as Henry acceptors for the asymmetric reaction. Herein, we report our preliminary results on this subject.

Results and Discussion

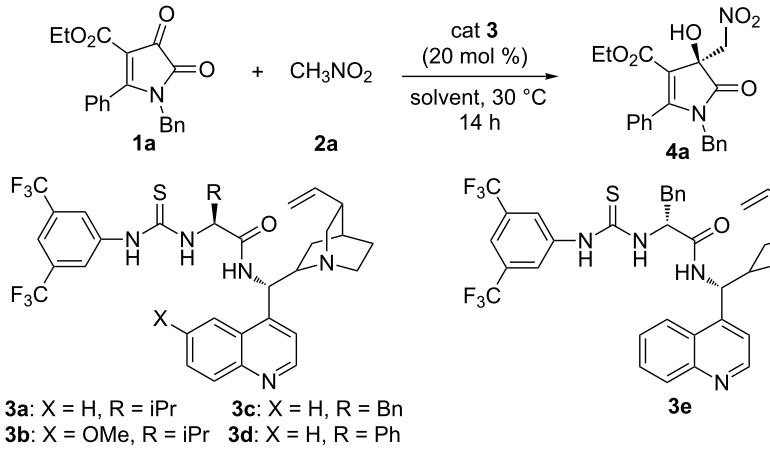
We started our studies with the reaction of ethyl 1-benzyl-4,5-dioxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**1a**) and nitromethane (**2a**) in the presence of various chiral bifunctional organocatalysts **3a**–**e** in dichloromethane (Table 1). As expected, the reaction proceeded and gave the desired product **4a** in 18% yield and 28% ee with cinchonidine and L-valine-based catalyst **3a** (Table 1, entry 1). The bifunctional, thiourea-tertiary amine catalyst **3b**, derived from quinine and L-valine, furnished a similar result to catalyst **3a** (Table 1, entry 2). Next, the reaction was attempted with catalyst **3c** derived from L-phenylalanine and catalyst **3d** derived from L-phenylglycine, and improvements in enantioselectivity were observed (Table 1, entries 3 and 4). Changing L-phenylalanine to D-phenylalanine furnished catalyst **3e**, and the enantioselectivity was improved to 61% ee (Table 1, entry 5). Having identified **3e** as the best catalyst, we undertook a solvent screening for this transformation with 20 mol % **3e** at 30 °C (Table 1, entries 6–12). Arenes such as toluene and mesitylene gave relatively lower ee values (Table 1, entries 6 and 7). In contrast, the reactions in ethers gave improved yield with slightly increased enantioselectivity (Table 1, entries 8–10). However, strong polar solvents such as acetonitrile and ethyl acetate proved inferior to this Henry reaction (Table 1, entries 11 and 12). The solvent survey revealed that THF was the suitable solvent in terms of the yield and enantioselectivity (Table 1, entry 8).

To further optimize the reaction conditions, the substituent at the nitrogen atom in 1*H*-pyrrole-2,3-diones **1** and the substrate concentration were investigated. The results are summarized in Table 2. It was found that an isopropyl group furnished a better yield and ee value than a benzyl group (Table 2, entry 2 vs entry 1). Changing the isopropyl group to a methyl group decreased the enantioselectivity (Table 2, entry 3). To enhance the reactivity of the substrate, we also tried to introduce some electron-



Scheme 1: The strategy to construct chiral 3-substituted-3-hydroxy-1*H*-pyrrol-2(3*H*)-ones.

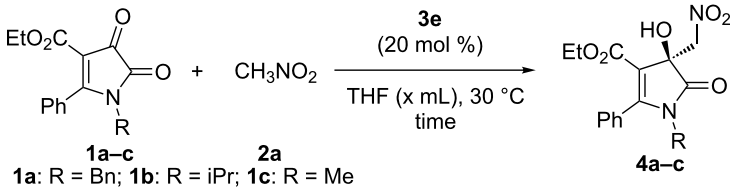
Table 1: Screening of the catalysts and solvents.[a]



Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**3a**	DCM	18	28
2	**3b**	DCM	25	27
3	**3c**	DCM	25	38
4	**3d**	DCM	29	41
5	**3e**	DCM	23	61
6	**3e**	toluene	24	46
7	**3e**	mesitylene	36	58
8	**3e**	THF	61	61
9	**3e**	dioxane	59	53
10	**3e**	Et_2O	48	62
11	**3e**	CH_3CN	14	40
12	**3e**	EtOAc	18	59

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol), **2a** (2.0 mmol), catalyst **3** (20 mol %) in solvent (2 mL) at 30 °C for 14 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Table 2: Further optimization of conditions.[a]



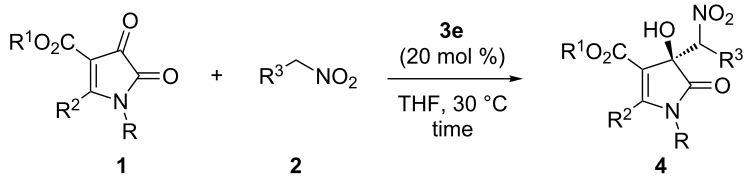
Entry	**1**	x	Time (h)	**4**	Yield (%)[b]	ee (%)[c]
1	**1a**	2	14	**4a**	61	61
2	**1b**	2	14	**4b**	64	71
3	**1c**	2	14	**4c**	19	57
4	**1b**	1	14	**4b**	69	71
5	**1b**	3	14	**4b**	60	70
6[d]	**1b**	1	14	**4b**	64	46
7[e]	**1b**	1	62	**4b**	trace	ND
8[f]	**1b**	1	14	**4b**	75	66

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.2 mmol), **2a** (2.0 mmol) and catalyst **3e** (20 mol %) in THF for the specified reaction time. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Run at 50 °C; [e]Run at 0 °C. [f]4 Å MS was added. ND, not determined.

withdrawing substituents on the nitrogen atom. However, we could not obtain the desired substrates. Afterwards, upon the investigation of substrate concentration (Table 2, entries 4 and 5), it was found that increasing the substrate concentration could slightly increase the yield with unchanged enantioselectivity (Table 2, entry 4). Ultimately, the effects of the reaction temperature and the additive were also examined and no improved results were obtained (Table 2, entries 6–8). Based on these observations, the most appropriate conditions for the Henry reaction could be established: 1 equiv of **1a** and 10 equiv of **2a** with 20 mol % catalyst **3e** in 1.0 mL THF at 30 °C (Table 2, entry 4).

Under the optimal reaction conditions, the substrate scope and the limitation of this organocatalytic Henry reaction were explored. The results are summarized in Table 3. First, we investigated the effects of the alkyl ester of 1*H*-pyrrole-2,3-diones **1**. The replacement of the ethyl group by either a methyl or a butyl group had only a slight effect on the ee value but an obvious effect on the yield (Table 3, entries 1 and 2 vs Table 2, entry 4). After introducing different substituent groups on the phenyl ring of substrate **1**, it was observed that the reactions take place, and the corresponding products in 44–73% yield with up to 73% ee were furnished. This was true regardless of the electronic nature and position of the substituents on the phenyl ring (Table 3, entries 3–10). When the substituent was in the ortho-position of the phenyl ring of the R^2 group, a diastereoselectivity was observed that may be due to the steric hindrance of ortho substituents led to the atropisomers (Table 3, entry 3). A similar result was observed for the bulky 1-naphthyl group (Table 3, entry 11). The reaction was also performed with a 2-thienyl residue and the desired product was obtained in 51% yield and 71% ee (Table 3, entry 10). In addition, substrate **1o** with no substituent on the nitrogen atom gave the desired product in 41% and 48% ee (Table 3, entry 12). The introduction of a phenyl group on the nitrogen atom had a negative effect on the reaction (Table 3, entry 13). Nitroethane was also used to react with 1*H*-pyrrole-2,3-dione **1b**, and a good diastereoselectivity was achieved with an unfavorable yield and ee value (Table 3, entry 14). For the substrates with methoxy groups on the phenyl rings, the reaction gave relatively better results

Table 3: Scope of the reaction.[a]



Entry	R/ R^1/R^2	2	Time (h)	4	Yield (%)[b]	ee (%)[c]
1	iPr/Me/Ph (**1d**)	**2a**	14	**4d**	55	65
2	iPr/*n*-Bu/Ph (**1e**)	**2a**	70	**4e**	52	70
3	iPr/Et/2-ClC_6H_4 (**1f**)	**2a**	62	**4f**	53	73[d]
4	iPr/Et/3-$MeOC_6H_4$ (**1g**)	**2a**	62	**4g**	73	71
5	iPr/Et/3-ClC_6H_4 (**1h**)	**2a**	120	**4h**	47	71
6	iPr/Et/3-BrC_6H_4 (**1i**)	**2a**	120	**4i**	44	70
7	iPr/Et/4-$MeOC_6H_4$ (**1j**)	**2a**	62	**4j**	61	72
8	iPr/Et/4-MeC_6H_4 (**1k**)	**2a**	48	**4k**	64	69
9	iPr/Et/4-FC_6H_4 (**1l**)	**2a**	62	**4l**	73	70
10	iPr/Et/2-thienyl (**1m**)	**2a**	120	**4m**	51	71
11	iPr/Et/1-naphthyl (**1n**)	**2a**	120	**4n**	75	51[e]
12	H/Me/Ph (**1o**)	**2a**	120	**4o**	41	48
13	Ph/Et/Ph (**1p**)	**2a**	120	**4p**	42	29
14	iPr/Et/Ph (**1b**)	**2b**	24	**4q**	23	22[f]
15	iPr/Me/4-$MeOC_6H_4$ (**1q**)	**2a**	84	**4r**	51	69
16	iPr/Me/3-$MeOC_6H_4$ (**1r**)	**2a**	120	**4s**	71	58

[a]Unless otherwise noted, the reactions were carried out with **1** (0.2 mmol), **2** (2.0 mmol). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]ee for the major isomer and ee of another isomer is 60%, and 54:46 dr was observed. [e]ee for the major isomer and ee of another isomer is 49%, and 53:47 dr was observed. [f]ee for the major isomer, and 94:6 dr was observed.

(Table 3, entries 4 and 7). We also tested the substrates **1q** and **1r** containing a methyl ester, and acceptable results were obtained (Table 3, entries 15 and 16). The absolute configuration of the major isomer **4i** was unambiguously determined to be *S* by single-crystal X-ray analysis (Figure 1) [38]. The configurations of the other products were assigned by analogy.

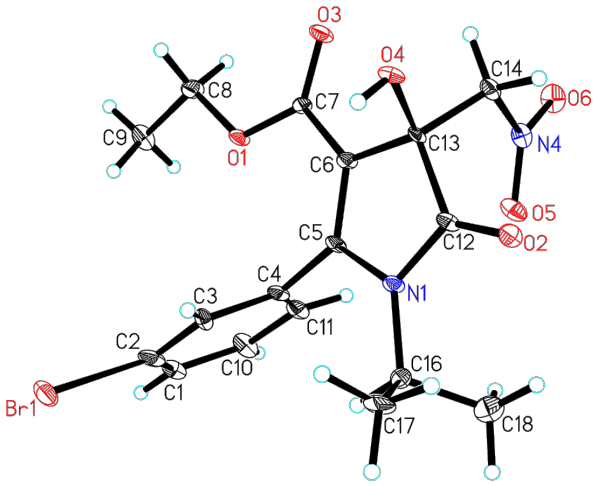


Figure 1: The X-ray structure of compound **4i**.

On the basis of our experimental results and the related reports about the bifunctional activation mode of nitromethane with different electrophiles [14,17,39], we propose a possible model to explain the stereochemistry of this transformation. As shown in Figure 2, nitromethane is activated by the tertiary amine to form the nitro enolate. Simultaneously, the 1*H*-pyrrole-2,3-diones **1** are orientated by the multiple hydrogen bonds of the catalyst. Thus, the nitro enolate attacks the keto carbonyl group of 1*H*-pyrrole-2,3-diones (to the *si*-face) to furnish the corresponding product with *S*-configuration (Figure 2).

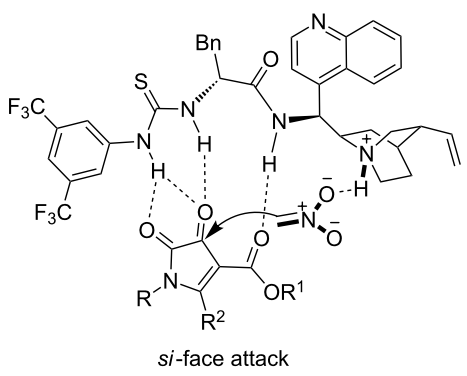


Figure 2: A proposed transition state for the asymmetric Henry reaction.

Conclusion

In conclusion, we have developed an asymmetric Henry reaction of 1*H*-pyrrole-2,3-diones with a chiral bifunctional amine-thiourea possessing multiple hydrogen-bond donors as the catalyst. With the developed protocol, a range of 3-hydroxy-3-nitromethyl-1*H*-pyrrol-2(3*H*)-ones bearing quaternary stereocenters were obtained in good yield (up to 75%) and with moderate to good enantioselectivity (up to 73% ee). A possible transition-state model, characterized by the bifunctional catalyst acting as a multiple hydrogen-bond donor, is also proposed. The application of 1*H*-pyrrole-2,3-diones in the catalytic asymmetric reactions for the preparation of biologically relevant compounds is currently underway.

Supporting Information

Supporting Information File 1

General procedure, analytical data and spectra of all compounds, methods for conversion.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-31-S1.pdf]

Supporting Information File 2

Single-crystal X-ray analysis of **4i**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-31-S2.cif]

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Application of 7-azaisatins in enantioselective Morita–Baylis–Hillman reaction

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Full Research Paper

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7-azaisatins; β-isocupreidine; bifunctional catalysis; maleimide; MBH reaction

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Abstract

7-Azaisatin and 7-azaoxindole skeletons are valuable building blocks in diverse biologically active substances. Here 7-azaisatins turned out to be more efficient electrophiles than the analogous isatins in the enantioselective Morita–Baylis–Hillman (MBH) reactions with maleimides using a bifunctional tertiary amine, β-isocupreidine (β-ICD), as the catalyst. This route allows a convenient approach to access multifunctional 3-hydroxy-7-aza-2-oxindoles with high enantiopurity (up to 94% ee). Other types of activated alkenes, such as acrylates and acrolein, could also be efficiently utilized.

Introduction

The asymmetric Morita–Baylis–Hillman (MBH) reaction is one of the most powerful synthetic methods in organic chemistry, as it directly constructs carbon–carbon bonds in an atom-economical manner and provides densely functionalized molecules [1-4]. In particular, the direct formation of stereogenic quaternary carbon centers by enantioselective MBH reactions has been a fascinating and challenging area, because the compatible electrophiles are always limited to aldehydes or derivatives thereof. Since the first elegant work on the enantioselective MBH reaction between isatins and acrolein catalyzed by β-isocupreidine (β-ICD) was reported by the Zhou group [5], isatin derivatives, as highly activated electrophiles, have been utilized by other groups for similar transformations with acrylates or acrylamides, affording the 3-hydroxyoxindole derivatives with moderate to excellent stereocontrol [6-12]. Maleimides are also good nucleophilic precursors in the MBH reactions and in 2013, Chimni developed an asymmetric MBH reaction of isatins and maleimides with excellent enantioselectivity [13]. Later, the same group expanded this strategy to isatin-derived ketimines under the identical catalytic conditions [14]. Remarkably, these reactions were usually promoted by bifunctional catalysts, such as β-ICD, whose C6'-OH group served as a H-bond donor to facilitate the proton-transfer step and to stabilize the transition state in MBH reactions [11-14]. Nevertheless, all these cases

suffered from low reactivity and long reaction times were always required (usually > 48 h) for better conversions.

7-Azaisatins bearing an additional nitrogen atom at the 7-position of the 2-oxindole scaffold might be better electrophiles than isatins owing to the electron-withdrawing effect of the pyridine motif. More importantly, a number of 7-azaisatins and 7-azaoxindoles were shown to exhibit significant anticancer or TrkA kinase inhibitory activities (Figure 1) [15-17]. This would render their derivatives as pharmaceutically interesting compounds with high potential. In addition, 7-azaisatins were also applied in asymmetric synthesis [18,19]. Therefore, with our continuing interest in the catalytic application of bifunctional β-ICD [20-23], herein we report the enantioselective MBH reaction of 7-azaisatins with maleimides. A series of 3-hydroxy-7-aza-2-oxindoles have been synthesized in good to excellent yields and with moderate to high enantioselectivity in a shorter time (for most cases, the reaction time is 24 h).

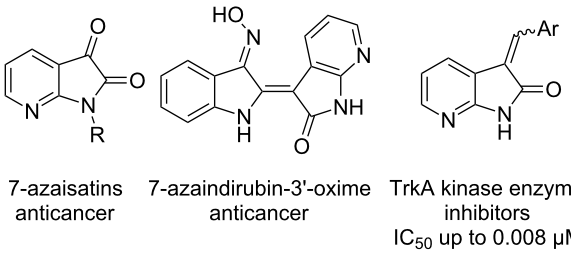
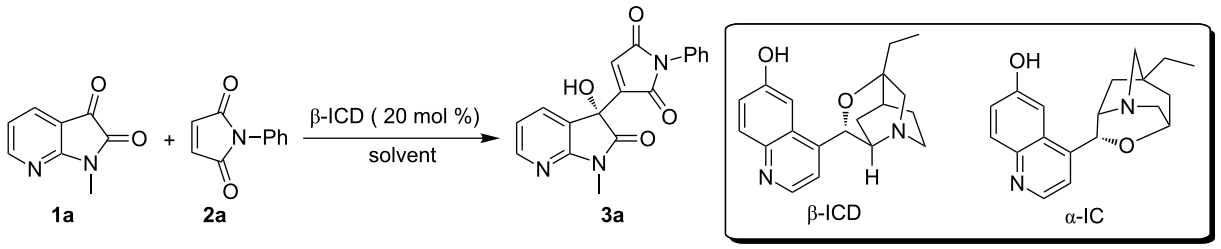


Figure 1: Bioactive 7-azaisatins and their derivatives.

Results and Discussion

The enantioselective MBH reaction was first investigated with *N*-methyl-7-azaisatin (**1a**) and *N*-phenylmaleimide (**2a**) in toluene catalyzed by β-ICD. To our delight, the desired product **3a** was obtained in 45% yield and with excellent enantioselectivity at 50 °C after 72 h (Table 1, entry 1). The reaction could be accelerated significantly by increasing the amounts of **2a** (Table 1, entries 2–5), and almost a quantitative yield could be obtained after 24 h by employing 6 equiv of **2a** (Table 1, entry 5). Other solvents, such as MeCN, THF and $CHCl_3$, were also tested but provided inferior results (Table 1, entries 6–8). The attempt to improve the enantioselectivity by lowering the temperature failed (Table 1, entry 9), and the enantiocontrol was diminished at 70 °C (Table 1, entry 10). On the other hand, when α-isocupreine (α-IC) [24,25] was employed as the catalyst instead of β-ICD, unfortunately no desired product was obtained even after 120 h (Table 1, entry 11). Finally, we com-

Table 1: Screening conditions of the enantioselective MBH reaction of **1a** and **2a**.



Entry[a]	**2a** (equiv)	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	1.5	toluene	50	72	45	91
2	3.0	toluene	50	72	66	92
3	4.0	toluene	50	48	83	92
4	5.0	toluene	50	48	89	91
5	6.0	toluene	50	24	98	94
6	6.0	MeCN	50	24	98	86
7	6.0	THF	50	24	98	88
8	6.0	$CHCl_3$	50	96	90	91
9	6.0	toluene	rt	48	91	91
10	6.0	toluene	70	24	85	88
11[d]	6.0	toluene	50	>120	–	–
12	2.0	$CHCl_3$	rt	72	90	95

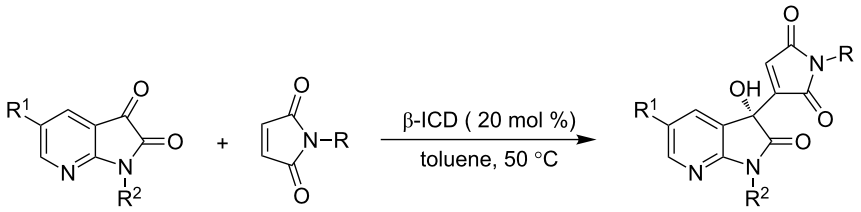
[a]Unless noted otherwise, reactions were performed with **1a** (0.05 mmol), **2a** and catalyst (0.01 mmol) in solvent (0.5 mL). [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]α-IC was used as the catalyst.

pared the reaction of 7-azaisatin **1a** and maleimide **2a** under the catalytic conditions developed by Chimni [13]. The reaction proceeded slowly, but a high yield with an outstanding ee value could be obtained after 72 h (Table 1, entry 12).

With the optimal conditions in hand, next, the substrate scope of the MBH reaction was studied under the catalysis of β-ICD (Table 2). At first, a variety of N-substituted maleimides **2** were explored in the reaction with 7-azaisatin **1a** in toluene. Maleimides bearing an electron-rich N-aryl ring generally afforded the corresponding 3-hydroxy-7-aza-2-oxindoles in high yields and with excellent enantioselectivity (Table 2, entries 2–4) while good results were obtained in a mixture of THF and DCM for a maleimide with an electron-deficient N-aryl group because of better solubility (Table 2, entry 5). In addition, N-alkylated maleimides provided the desired products in good yields (Table 2, entries 6–9), while only moderate enantioselectivity was observed for products **3h** and **3i** (Table 2, entries 8 and 9). 7-Azaisatins with different N-protecting groups were also applied to the MBH reaction with *N*-phenylmaleimide (**2a**), including methoxymethyl (MOM), benzyl (Bn) and 4-chlorophenyl substituents. All of them showed a lower reactivity and enantioselectivity than that of the methyl-substituted one, and better results were generally obtained in a mixture of THF and DCM (Table 2, entries 10–12). The C5-phenyl substituted or halogenated 7-azaisatins could be smoothly applied, although a longer reaction time was required for the halogenated substrates (Table 2, entries 13–15).

To further assess the high electrophilicity of 7-azaisatins in MBH reactions, more activated alkenes were explored with **1a**. Methyl and ethyl acrylates afforded products **3p** and **3q**, respectively, with comparable results to Wu's work [7], albeit in a shorter time (24 h vs 2–3 d). Notably, the MBH reaction of acrolein and 7-azaisatin **1a** was carried out under the same conditions as described in Zhou's work [5], providing the highly enantio-enriched product **3r** in an excellent yield after 1.5 h. The reaction with **1a** was much more efficient, as it took 4 d to afford the product **5** in a high yield by using *N*-methylisatin (**4**) as the substrate (Scheme 1).

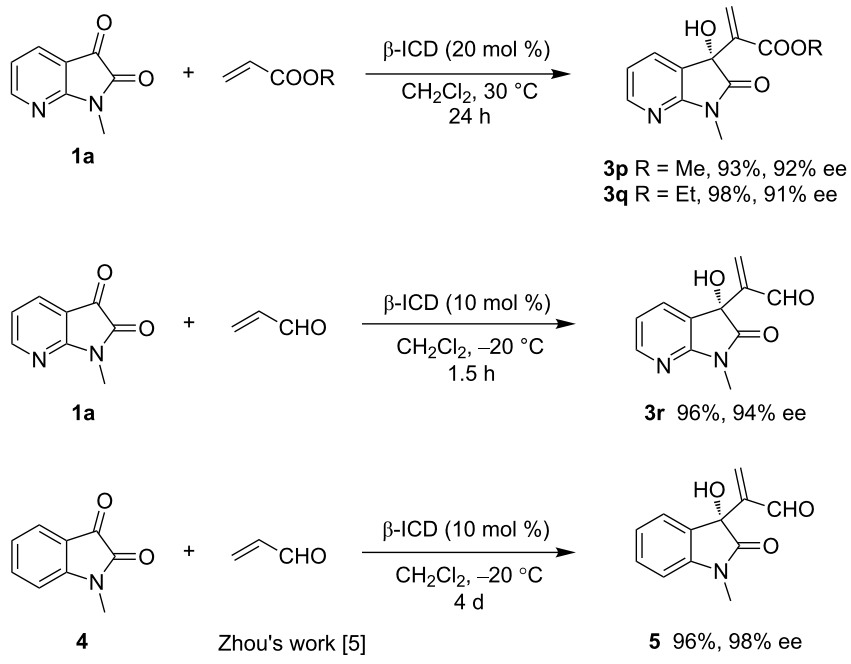
Table 2: Substrate scope of the enantioselective MBH reaction.



1a–g **2a–i** **3a–o**

Entry[a]	R^1	R^2	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	H	**1a**, Me	**2a**, Ph	24	**3a**, 98	94
2	H	**1a**,Me	**2b**, 4-MePh	24	**3b**, 87	90
3	H	**1a**, Me	**2c**, 4-MeOPh	24	**3c**, 88	92
4	H	**1a**, Me	**2e**, 2,4,6-MePh	24	**3e**, 90	79
5[d]	H	**1a**, Me	**2d**, 4-ClPh	24	**3d**, 87	92
6	H	**1a**, Me	**2f**, Me	24	**3f**, 84	89
7	H	**1a**, Me	**2g**, Bn	24	**3g**, 86	89
8	H	**1a**, Me	**2h**, *n*-Bu	24	**3h**, 86	66
9	H	**1a**, Me	**2i**, cyclohexyl	24	**3i**, 84	61
10[d]	H	**1b**, MOM	**2a**, Ph	24	**3j**, 92	91
11[d]	H	**1c**, Bn	**2a**, Ph	48	**3k**, 93	87
12[d]	H	**1d**, 4-ClPh	**2a**, Ph	96	**3l**, 37	71
13[d]	Ph	**1e**, Me	**2a**, Ph	24	**3m**, 88	92
14	Cl	**1f**, Me	**2a**, Ph	48	**3n**, 81	85
15	Br	**1g**, Me	**2a**, Ph	48	**3o**, 82	88

[a]Unless otherwise noted, all reactions were performed with **1** (0.1 mmol), **2** (0.6 mmol) and β-ICD (0.02 mmol) in toluene (1.0 mL) at 50 °C. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. The absolute configuration of the chiral products was assigned by analogy to Chimni's work [13]. [d]In a mixture of THF and DCM (0.5/0.5 mL).



Scheme 1: Further exploration with 7-azaisatin **1a** and comparison with the previous work by Zhou [5].

Conclusion

In summary, we have developed an efficient and enantioselective Morita–Baylis–Hillman reaction between 7-azaisatins and maleimides and other activated alkenes in the presence of the bifunctional catalyst β-ICD. 7-Azaisatins were proven to be better electrophiles than the analogous isatins, and furnished a convenient protocol to enantio-enriched multifunctional 3-hydroxy-7-aza-2-oxindoles. Such substances might be further applied in organic synthesis for potential biological and pharmaceutical studies in the future.

Experimental

General procedure for the synthesis of 3-hydroxy-7-aza-2-oxindoles: A solution of N-protected 7-azaisatin **1** (0.1 mmol), N-substituted maleimide **2** (0.6 mmol) and β-ICD (20 mol %) was stirred in dry toluene (1.0 mL) at 50 °C. The progress of the reaction was monitored by TLC. After completion, the MBH reaction product **3** was purified by flash chromatography on silica gel using petroleum ether/EtOAc 6:1–3:1 as the eluent.

Supporting Information

Supporting Information File 1

Detailed experimental procedures and analytical data for the compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-33-S1.pdf]

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Enantioselective [3 + 2] annulation of α-substituted allenoates with β,γ-unsaturated *N*-sulfonylimines catalyzed by a bifunctional dipeptide phosphine

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Full Research Paper

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Abstract

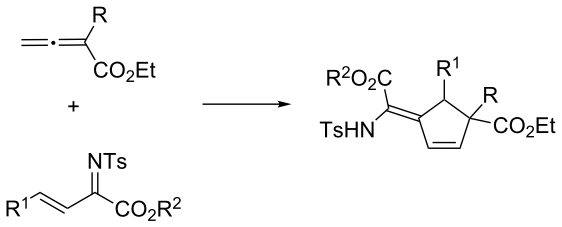
The first enantioselective [3 + 2] annulation of α-substituted allenoates with β,γ-unsaturated *N*-sulfonylimines is described. In the presence of a dipeptide phosphine catalyst, a wide range of highly functionalized cyclopentenes bearing an all-carbon quaternary center were obtained in moderate to good yields and with good to excellent enantioselectivities.

Introduction

Over the past decade, chiral phosphine catalysts have been utilized extensively for the construction of a broad range of synthetically useful molecular structures [1-13]. Since the initial discovery of phosphine-catalyzed [3 + 2] annulation of allenoates and activated alkenes by Lu in 1995, this type of annulation reaction has received considerable attention due to its high efficiency and versatility in creating five-membered ring systems [14-33]. However, most of the earlier examples make use of allenoates without an α-substitution. As demonstrated by Yu, Kwon and their co-workers [34-36], this is due to the requirement of a hydrogen atom at the α-position for a proton shift during the reaction cycle. Instead, α-substituted allenoates were shown to interact with phosphine in different reaction modes and undergo [4 + 2] annulations with suitable reaction partners to afford six-membered ring structures [37-47]. Recently, He and co-workers disclosed that the reaction between α-substituted allenoates and β,γ-unsaturated *N*-sulfonylimines proceeded in an unexpected [3 + 2] annulation mode to afford a cyclopentene ring with an all-carbon quaternary center (Scheme 1) [48]. In recent years our group has developed a family of amino acid-derived bifunctional phosphines and has intensively investigated related asymmetric transformations [49-63]. We became interested in developing an asymmetric variant of the above transformation by utilizing our amino acid-derived bifunctional phosphine catalysts.

Results and Discussion

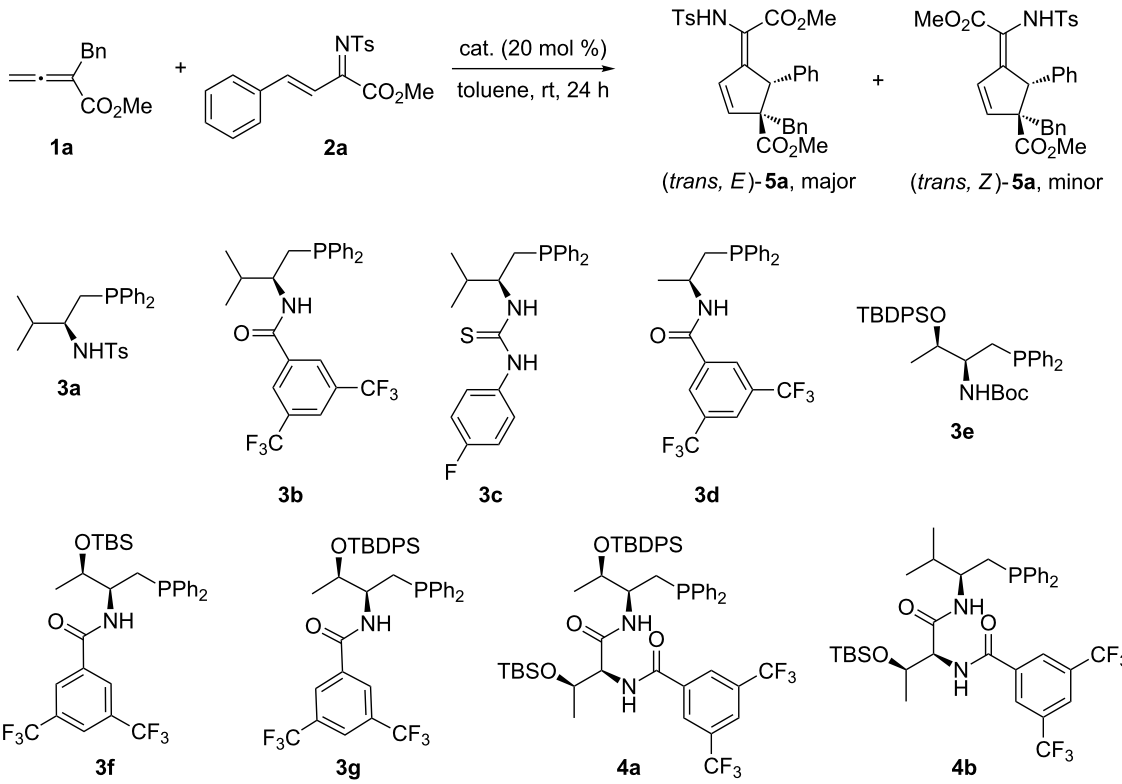
We chose the [3 + 2] annulation between α-benzyl-substituted allenoate **1a** and β,γ-unsaturated *N*-sulfonylimine **2a** as a model reaction and evaluated a number of amino acid based bifunc-



Scheme 1: The [3 + 2] annulation of α-substituted allenoates reported by He.

tional phosphines as catalyst. As shown in Table 1, simple L-valine-derived phosphines **3a**–**c** were found to be effective in promoting the reaction, and products were obtained in moderate to good yields and with good *E*/*Z* ratios, and amide–phosphine **3b** worked best (Table 1, entries 2–4). L-Alanine-based phosphine **3d** and L-threonine-derived catalysts **3e** and **3f** did not provide better results (Table 1, entries 5–7). By employing L-threonine-derived catalyst **3g**, the enantioselectivity of the reaction was improved to 68%. To further improve the reaction results, we next utilized dipeptide phosphine catalysts, which are more structurally diverse and tunable. The L-thr-L-thr-

Table 1: Screening of different amino acid-based bifunctional phosphine catalysts.



Entry	Catalyst	*E*/*Z* ratio[a]	Yield (%)[b]	ee (%)[c]
1	$MePPh_2$	85:15	67	–
2	**3a**	83:17	60	10
3	**3b**	88:12	70	48
4	**3c**	80:20	65	32
5	**3d**	89:11	72	35
6	**3e**	87:13	64	36
7	**3f**	85:15	73	47
8	**3g**	88:12	74	68
9	**4a**	86:14	71	60
10	**4b**	89:11	72	76

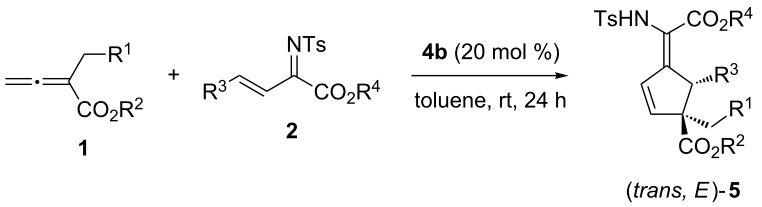
[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of the *E*-isomers. [c]Determined by HPLC analysis on a chiral stationary phase.

derived catalyst **4a** was a poor catalyst, on the other hand, L-val-L-thr-derived catalyst **4b** led to adequately improved enantioselectivity of the reaction and was chosen for further investigations.

With the optimized conditions established, the substrate scope of this [3 + 2] annulation was explored by varying α-substituted allenoates **1** and imines **2** (Table 2). Firstly, different ester groups at the allenoates were examined (Table 2, entries 1–3). An allenoate bearing a *tert*-butyl ester group (**1b**) was found to be the best substrate, and the annulation products were obtained in good *E*/*Z* ratio, high yield and an ee of 84% (Table 2, entry 2). Allenoate substrates having different substitutions at the α-position were well tolerated, and the employment of various α-benzyl allenoates led to the formation of the products in consistently high *E*/*Z* ratios and enantioselectivities (Table 2, entries 4–6). It seemed that the presence of the *ortho* substituent in allenoates led to better enantioselectivity and decreased chemical yield (Table 2, entry 6). The utilization of 1-naphthyl substituted allenoate **1g** resulted in poor yield but excellent enantioselectivity (Table 2, entry 7). Notably, the electronic properties of the benzyl groups in allenoates did not have much effect on the reaction outcome (Table 2, entries 8 and 9). Furthermore, methoxycarbonylmethyl-substituted allenoate **1j** also proved to be a suitable substrate (Table 2, entry 10). The scope of β,γ-unsaturated *N*-sulfonylimines was subsequently examined by employing a number of differently substituted imines (Table 2, entries 11–15). In general, all the reactions worked well and afforded the annulation products in good *E*/*Z* ratios, moderate to good yields, and high enantioselectivities. Notably, imine **2e** bearing an electron rich aryl substituent was found to be a superior substrate; higher yield and ee value were attainable (Table 2, entry 14).

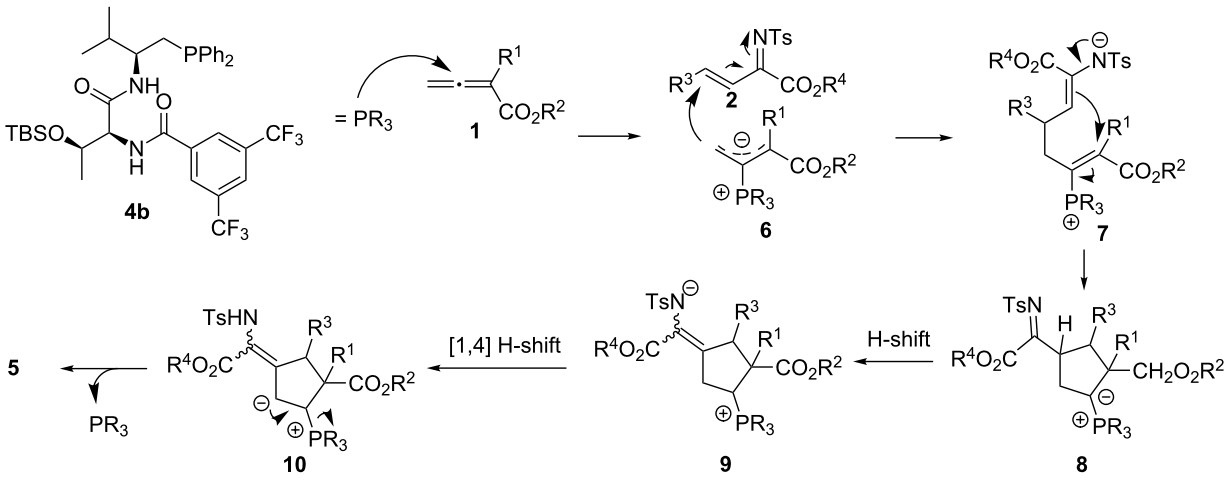
A possible reaction mechanism rationalizing the formation of the [3 + 2] annulation product is shown in Scheme 2 [34-36,48]. The reaction is initiated by the activation of the allenoate through a nucleophilic attack of the phosphine, generating zwitterionic intermediate **6**, which undergoes a [3 + 2] annulation with imine **2** to furnish intermediate **8**. Due to the lack of a hydrogen atom at the α-position, the normal proton shift in a typical [3 + 2] annulation cannot occur. Instead, this intermediate undergoes a proton shift to generate intermediate **9**, where a [1,4]-proton shift can occur to yield intermediate **10**. Lastly,

Table 2: Enantioselective [3 + 2] annulation of α-substituted allenoates with β,γ-unsaturated *N*-sulfonylimines catalyzed by dipeptide catalyst **4b**.[a]



Entry	**1** (R^1/R^2)	**2** (R^3/R^4)	**5**	*E*/*Z*[b]	Yield (%)[c]	ee (%)[d]
1	**1a** (Ph/Me)	**2a** (Ph/Me)	**5a**	89:11	76	76
2	**1b** (Ph/*t*-Bu)	**2a** (Ph/Me)	**5b**	83:17	70	84
3	**1c** (Ph/Bn)	**2a** (Ph/Me)	**5c**	85:15	72	78
4	**1d** (4-ClPh/*t*-Bu)	**2a** (Ph/Me)	**5d**	80:20	69	86
5	**1e** (3-ClPh/*t*-Bu)	**2a** (Ph/Me)	**5e**	81:19	60	89
6	**1f** (2-ClPh/*t*-Bu)	**2a** (Ph/Me)	**5f**	78:22	45	94
7	**1g** (1-naphthyl/*t*-Bu)	**2a** (Ph/Me)	**5g**	80:20	43	93
8	**1h** (4-MePh/*t*-Bu)	**2a** (Ph/Me)	**5h**	83:17	65	86
9	**1i** (4-NO_2Ph/*t*-Bu)	**2a** (Ph/Me)	**5i**	81:19	73	92
10	**1j** (CO_2Me/Bn)	**2a** (Ph/Me)	**5j**	90:10	72	82
11	**1b** (Ph/*t*-Bu)	**2b** (Ph/Et)	**5k**	80:20	68	85
12	**1b** (Ph/*t*-Bu)	**2c** (4-FPh/Et)	**5l**	83:17	55	86
13	**1b** (Ph/*t*-Bu)	**2d** (4-ClPh/Et)	**5m**	78:22	58	82
14	**1b** (Ph/*t*-Bu)	**2e** (4-MeOPh/Et)	**5n**	88:12	70	90
15	**1b** (Ph/*t*-Bu)	**2f** (2-Thienyl/Et)	**5o**	80:20	67	86

[a]Reactions were performed with **1** (0.15 mmol), **2** (0.1 mmol) and **4b** (0.02 mmol) in toluene (0.5 mL) at room temperature. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Yield of isolated product. [d]Determined by HPLC analysis on a chiral stationary phase.



Scheme 2: Possible reaction mechanism.

elimination of the phosphine catalyst furnishes the final [3 + 2] annulation product **5**.

Conclusion

In conclusion, we have described the first enantioselective [3 + 2] cycloaddition of α-substituted allenoates with β,γ-unsaturated *N*-sulfonylimines, catalyzed by amino acid-derived bifunctional phosphines. The [3 + 2] annulation reactions yielded highly functionalized cyclopentenes with an all-carbon quaternary center in moderate to good yields and good to excellent enantioselectivities. Further extension of the reaction reported herein and mechanistic studies are ongoing in our laboratory.

Experimental

General procedure for the [3 + 2] annulation

Into a flame-dried round bottle flask with a magnetic stirring bar under N_2 at room temperature were added allenoate **1** (0.15 mmol) and β,γ-unsaturated *N*-sulfonylimine **2** (0.1 mmol), followed by the addition of anhydrous toluene (0.5 mL). Catalyst **4b** (0.02 mmol, 14.5 mg) was then introduced, and the reaction mixture was stirred at room temperature for 24 h. After complete consumption of the β,γ-unsaturated *N*-sulfonylimine, monitored by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford annulation adducts **5**.

Supporting Information

Supporting Information File 1

Additional material.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-37-S1.pdf]

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Cupreines and cupreidines: an established class of bifunctional cinchona organocatalysts

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Review

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Abstract

Cinchona alkaloids with a free 6'-OH functionality are being increasingly used within asymmetric organocatalysis. This fascinating class of bifunctional catalyst offers a genuine alternative to the more commonly used thiourea systems and because of the different spacing between the functional groups, can control enantioselectivity where other organocatalysts have failed. In the main, this review covers the highlights from the last five years and attempts to show the diversity of reactions that these systems can control. It is hoped that chemists developing asymmetric methodologies will see the value in adding these easily accessible, but underused organocatalysts to their screens.

Introduction

The cinchona alkaloids, comprising quinine (**QN**), quinidine (**QD**), cinchonidine (**CD**), cinchonine (**CN**, Figure 1), and their derivatives have revolutionized asymmetric catalysis owing to their privileged structures. The functional groups within these catalysts are highly pre-organized [1,2] and can both coordinate to, and activate the components of a reaction in a well-defined manner, thus facilitating a stereocontrolled process. The ability to easily derivatise these catalyst systems in a bespoke fashion in order to optimize their stereoselective behaviour has seen their utility burgeon dramatically over the last decade. Of particular note is the use of these cinchona systems within bifunctional thiourea catalysis [3-12].

Cupreine (**CPN**) and cupreidine (**CPD**), the non-natural demethylated structures of quinine and quinidine, respectively, have also found extensive utility, but not to the same extent, which is surprising given the broad range of chemistries that they have been shown to facilitate, and which are the subject of this review.

Herein, we describe the highlights of **CPN**, **CPD** and their derivatives in asymmetric organocatalysis over the last five years or so [13,14]. The review is organized by reaction type, beginning with the Morita–Baylis–Hillman process – one of the first reactions to utilize 6'-OH-cinchona alkaloid derivatives in

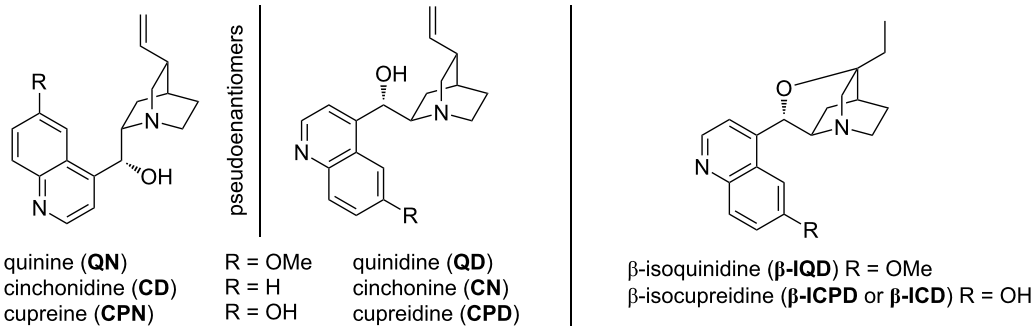


Figure 1: The structural diversity of the cinchona alkaloids, along with cupreine, cupreidine, β-isoquinidine and β-isocupreidine derivatives.

asymmetric organocatalysis. The focus will then turn to asymmetric 1,2-additions followed by conjugate additions, a cyclopropanation, (ep)oxidations, α-functionalisation processes, cycloadditions, domino processes and finally miscellaneous reactions. We ultimately aim to demonstrate through this plethora of diverse processes, that the 6'-OH cinchona class of alkaloids are a dynamic and versatile type of organocatalyst that should be included in the screening libraries of chemists seeking to develop asymmetric methodologies.

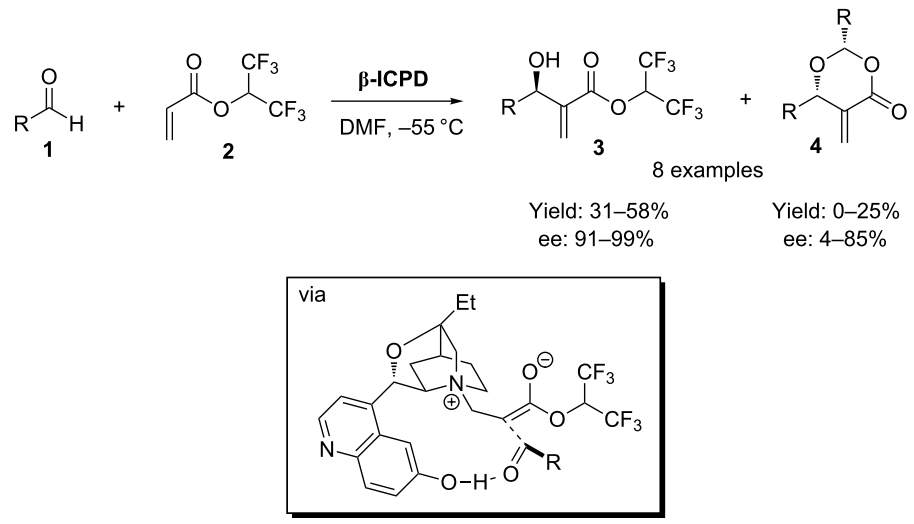
Review

Morita–Baylis–Hillman (MBH) and MBH-carbonate reactions

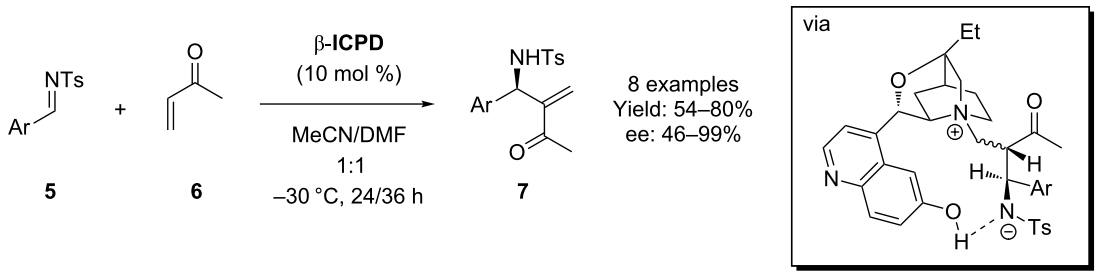
The first reports of an asymmetric reaction catalyzed by a cinchona organocatalyst with a 6'-OH functionality came from Hatakeyama and co-workers in 1999 who demonstrated the use of **β-ICPD** in an asymmetric Morita–Baylis–Hillman (MBH) reaction [15-18] what is essentially an asymmetric C3-substituted ammonium enolate reaction (Scheme 1) [19,20]. In this classic process, it was hypothesized that the 6'-OH group was critical in directing the incoming aldehyde electrophile (see Scheme 1 box).

Soon after, Shi and co-worker demonstrated the use of **β-ICPD** in the reaction of imines **5** with methyl vinyl ketone (MVK, **6**) using the same catalyst (Scheme 2) [21]. The same study investigated methylacrylate and acrylonitrile as the conjugated partner, but these were less successful. Shi proposed a similar reaction mechanism for this process, whereby the 6'-OH functionality is critical in the control of stereoselectivity.

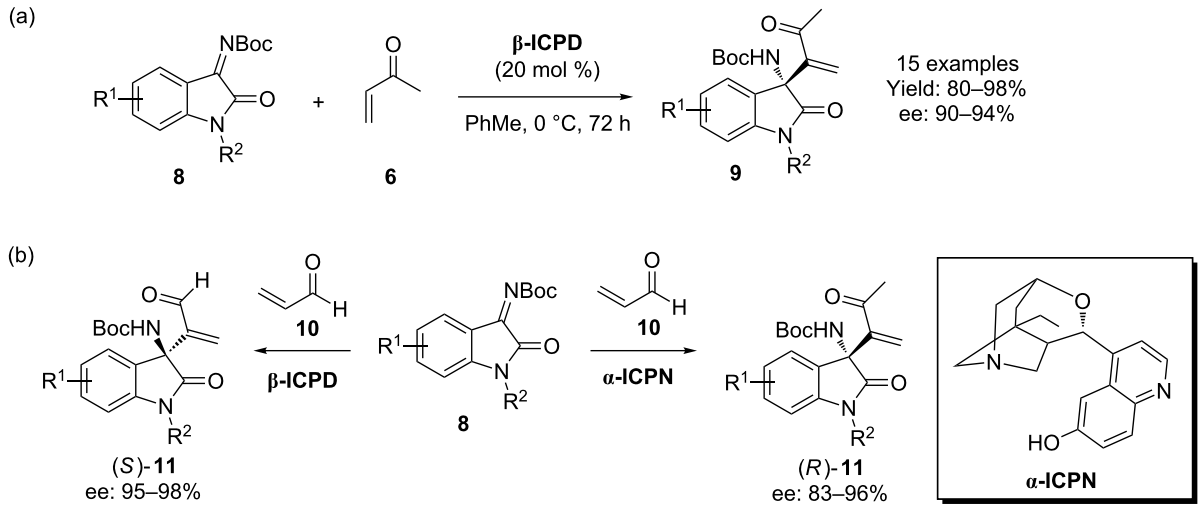
In a more recent extension of this work, Shi, Li and co-workers partnered the isatin derived *N*-Boc ketimines **8** with MVK (**6**, Scheme 3a) to obtain the corresponding adducts **9** with very



Scheme 1: The original 6'-OH cinchona alkaloid organocatalytic MBH process, showing how the free 6'-OH is essential for coordination to the substrate.



Scheme 2: Use of **β-ICPD** in an aza-MBH reaction.



Scheme 3: (a) The isatin motif is a common feature for MBH processes catalyzed by **β-ICPD**, as demonstrated by Shi and Li and co-workers. (b) Takizawa and co-workers demonstrated similar chemistry, but also utilized the catalyst **α-ICPN** (inset).

good selectivity [22]. Interestingly, replacing the Boc group with an ethyl carbamate decreased the yield and enantioselectivity dramatically, as did having a substituent at the 4-position of the ketimine. In a related study, Takizawa and co-workers demonstrated that the quinine derived organocatalyst, **α-ICPN** [23] produced the enantiomeric product in a similar process using acrolein **10** as the conjugate partner (Scheme 3b) [24].

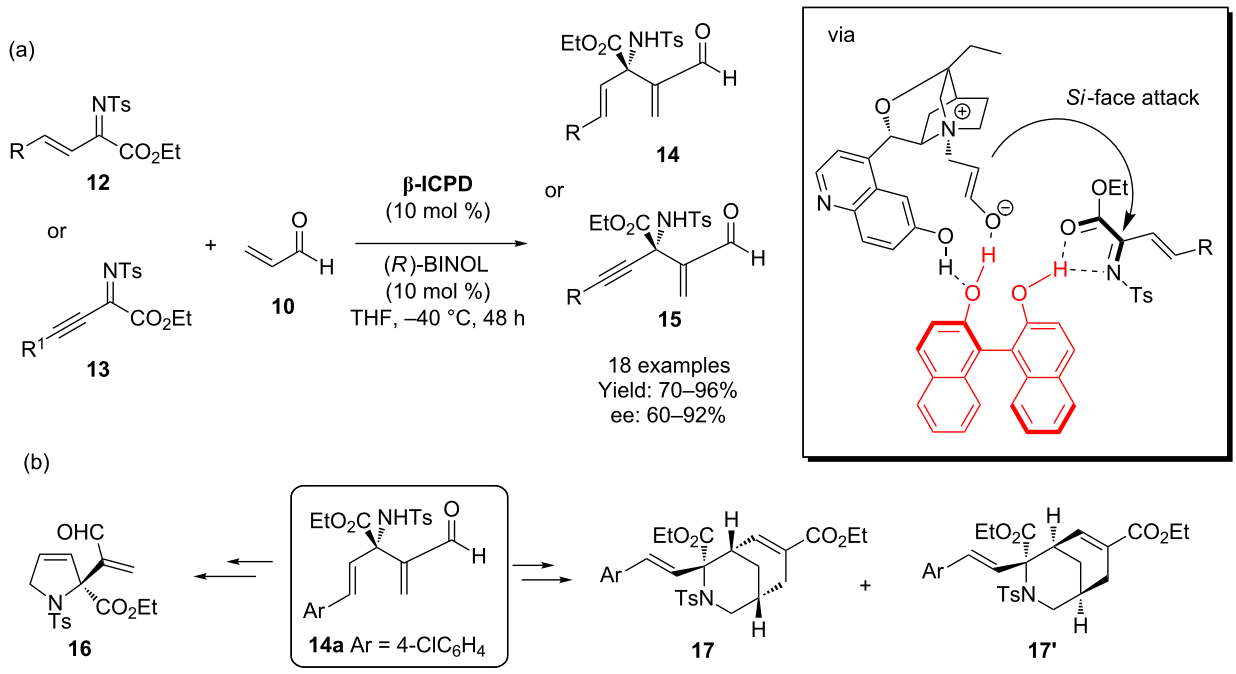
Chen and co-workers developed an aza-MBH process using **β-ICPD** in the reaction between *N*-sulfonyl-1-aza-1,3-butadienes and activated alkenes (Scheme 4) [25]. In this report, optimal selectivity required (*R*)-BINOL as a co-catalyst (see inset for proposed catalytic transition state – (*R*)-BINOL shown in red). Furthermore, the utility of the adducts obtained was demonstrated through their conversion to a number of useful constructs (e.g., **16** and **17**).

In reactions very much related to the MBH process, isatin derivatives have also proven to be particularly suited to the reaction of MBH-like products [26-28]. In these processes, the tertiary amine adds into the conjugate ester as with the MBH reaction, but instead of the resulting C3-ammonium enolate reacting with an electrophile, an E1cB elimination of the carbonate occurs to generate another conjugated system. This can then undergo an attack by a Michael donor; elimination of the catalyst then generates the *exo*-methylene adduct. For example, Lu and co-workers have used **β-ICPD** to react isatin-derived MBH carbonates **18** with nitroalkanes **19** [29]. The resulting adducts **20** could be converted to the corresponding spiroxindole **21** via a Zn/HOAc mediated reduction of the nitro functionality (Scheme 5).

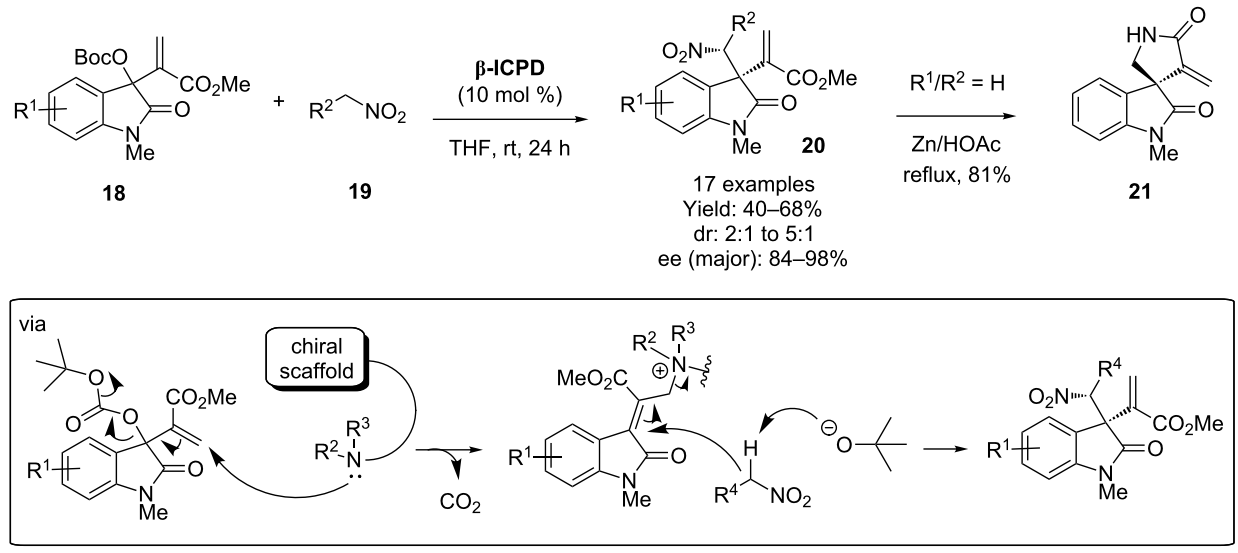
Similarly, Kesavan and co-workers reacted 3-*O*-Boc-oxindoles **23** with MBH carbonates **22** to generate a range of spirocyclic scaffolds containing α-*exo*-methylene-γ-butyrolactone **24** – again using **β-ICPD** (Scheme 6) [30].

Nazarov cyclization

An asymmetric Nazarov cyclization has been developed by Frontier and co-worker using **β-ICPD** through a mechanism



Scheme 4: (a) Chen's asymmetric MBH reaction. Good selectivity was dependent upon the presence of (*R*)-BINOL (shown in red) as well as **β-ICPD**. (b) Diverse structures were obtained from the MBH adduct **14a**.



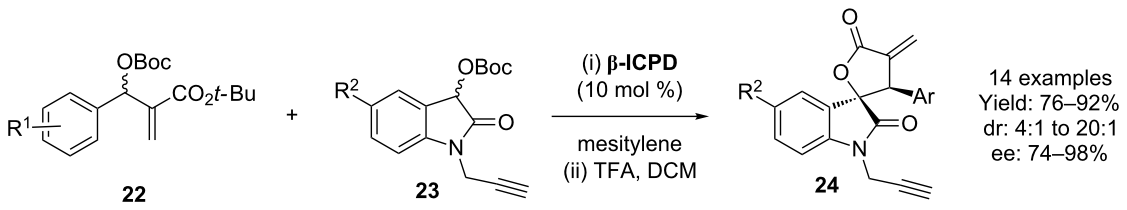
Scheme 5: Lu and co-workers synthesis of a spiroxindole.

that is reminiscent of the MBH reaction (Scheme 7) [31]. In this process however, the tertiary amine adds to the conjugated system **25** in a 1,6-fashion to generate intermediate enolate **26**. This undergoes a single bond rotation to set up a 4π-electrocyclization, generating second intermediate **27**. Elimination of the tertiary amine then gives γ-methylene cyclopentenone **28**.

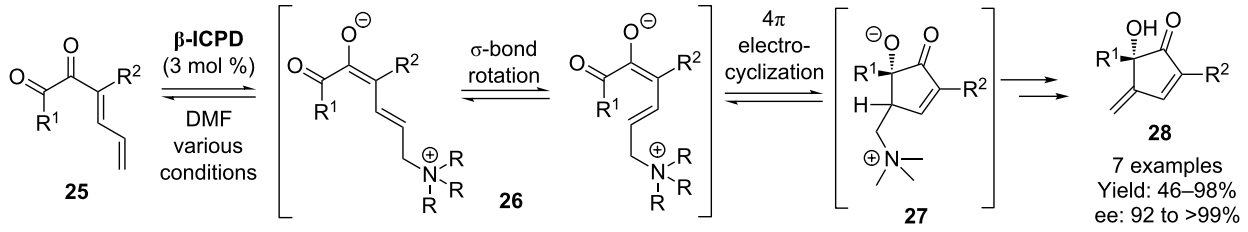
1,2-Addition reactions

Henry reaction

The use of cupreine and cupreidine derivatives in the addition of nitroalkanes to carbonyl compounds was first demonstrated by Deng and co-workers [32-34]. In this excellent study, catalysts substituted with benzyl at the 9-OH position gave the best



Scheme 6: Kesavan and co-workers' synthesis of spiroxindoles.



Scheme 7: Frontier's Nazarov cyclization catalyzed by **β-ICPD**.

results (**CPD-30**, Scheme 8). This report also demonstrated that the enantiomer of β-nitroester **31** could be obtained using the corresponding pseudoenantiomeric organocatalyst with comparable results.

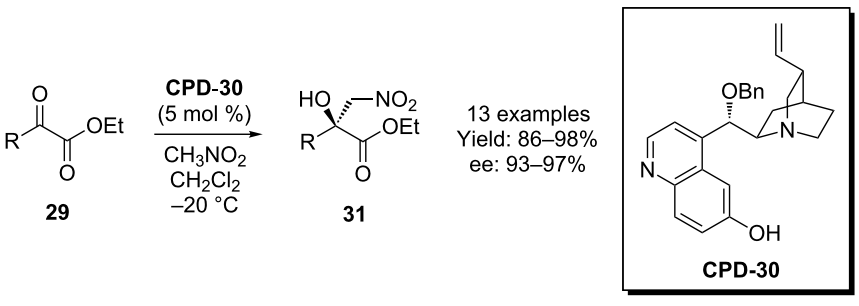
More recently, Johnson and co-worker used the *o*-toluoyl derived organocatalyst **CPD-33** to effect a dynamic kinetic asymmetric transformation of racemic β-bromo-α-keto esters **32** (Scheme 9a) [35]. The mechanism, deduced from deuterium labeling studies, proposes that one of the two enantiomers of **32** will react more rapidly with nitromethane in the presence of the cupreidine catalyst **CPD-33**. As these enantiomers equilibrate via **35** in the presence of the catalyst, a dynamic kinetic asymmetric reaction occurs (Scheme 9b).

Friedel–Crafts reaction

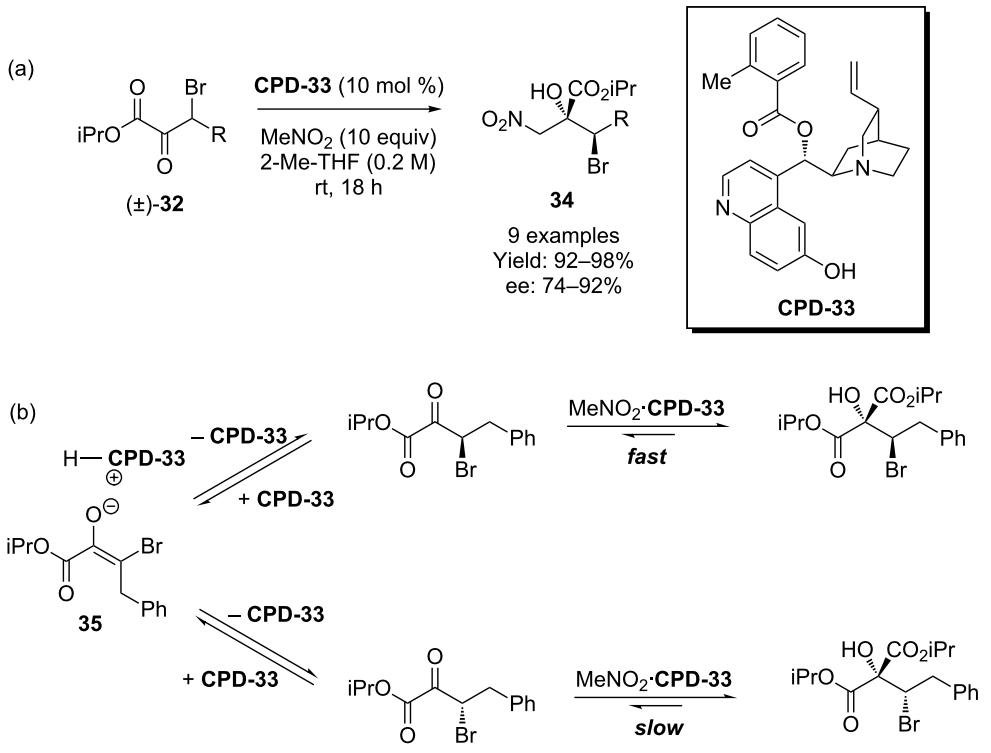
Pedro and co-workers have utilized a 9-OH benzoyl derivatised cupreine **CPN-38** to effect a Friedel-Crafts reaction of 2-naphthols **36** with benzoxathiazine 2,2-dioxides **37** (Scheme 10). These cyclic imides, derived from salicylic aldehydes, have a rigid structure which prevents *E*/*Z*-isomerization, allowing for greater control over the stereochemical outcome of the reaction [36]. This work was based on a related scheme from Chimni and co-worker, who used **CPN** derivatised at the 9-OH with 1-naphthoyl in the addition of sesamol to a range of *N*-sulfonylimines [37].

1,4-Conjugate additions

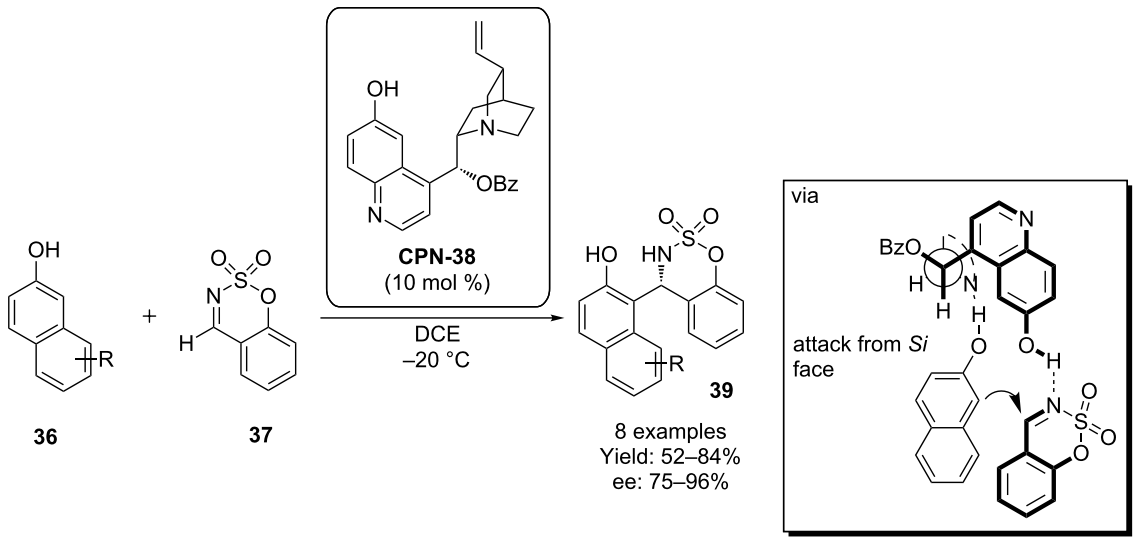
Deng and co-workers have contributed many examples of 1,4-additions that have been facilitated by **CPD** and **CPN** derived catalysts. For example, and amongst the earliest examples in the field, underivatized **CPD** or **CPN** were used in the addition of dimethyl malonate (**40**) to a range of nitrostyrenes **41**, giving the resulting adducts with excellent enantioselectivity (Scheme 11a) [38]. Subsequent reports by Deng and co-workers include, amongst many varieties of Michael acceptor and donor



Scheme 8: The first asymmetric nitroaldol process catalyzed by a 6'-OH cinchona alkaloid.

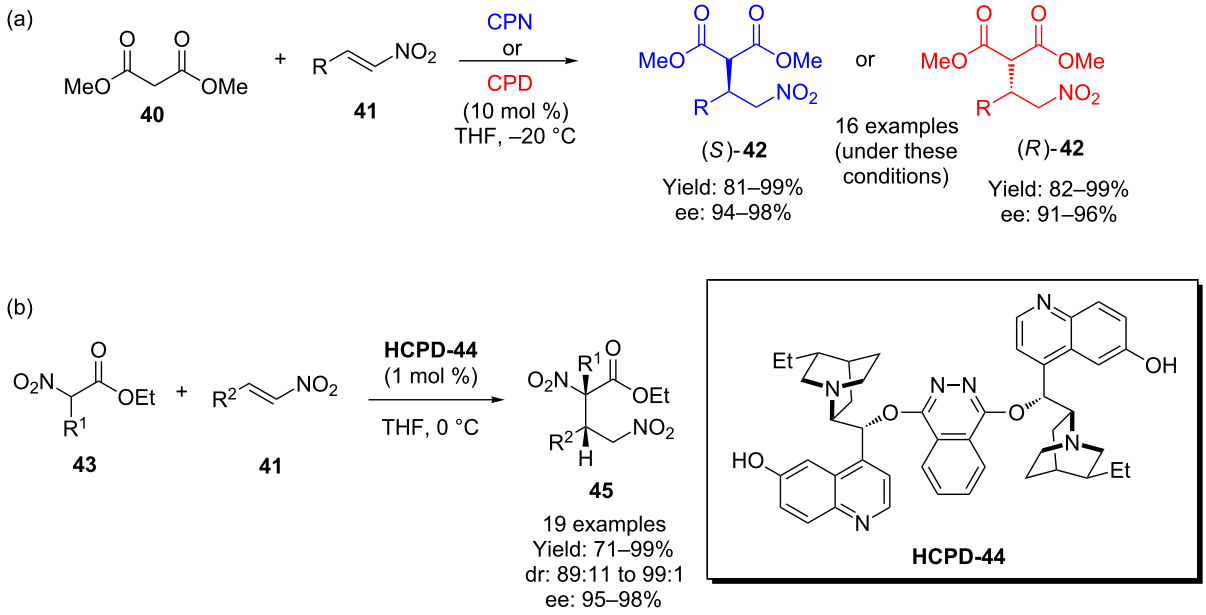


Scheme 9: A cupreidine derived catalyst induces a dynamic kinetic asymmetric transformation.



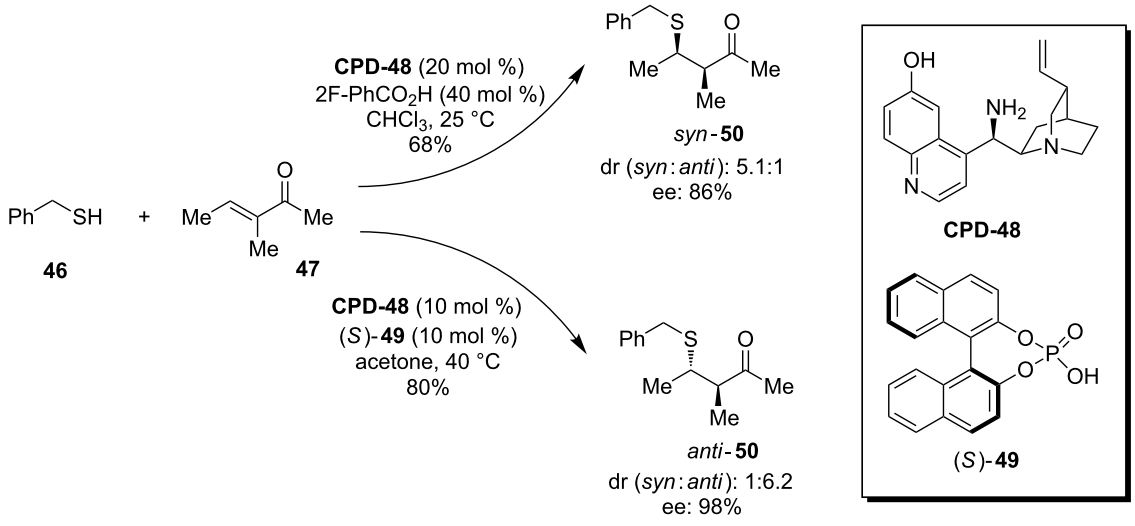
Scheme 10: Cupreine derivative **38** has been used in an organocatalytic asymmetric Friedel–Crafts reaction.

with various **CPN**/**CPD** derivatives [39-41], an example where β-ketoesters are used as the nucleophilic component [42]. It is on the basis of this work that Lin and co-workers were recently inspired to use the (*de*-Me-DHQ)$_2$PHAL catalyst **HCPD-44** in the addition of α-substituted nitro acetates **43** also into nitroolefins **41** (Scheme 11b) [43-46].



Scheme 11: Examples of 6'-OH cinchona alkaloid catalyzed processes include: (a) Deng's addition of dimethyl malonate into nitroolefins, and (b) Lin's similar process with α-nitroesters using the symmetric hydrocupreidine system **HCPD-44**.

In a fascinating report, Melchiorre and co-workers use the 9-amino-CPD system **CPD-48** to control the Michael addition of thiols **46** into α-branched enones **47** via iminium ion catalysis (Scheme 12) [47]. This study found that the catalytic function could be modulated to induce diastereodivergent pathways by applying an external chemical stimulus (Scheme 12). Several conclusions were made from this study, one of which was that the hydrogen-bonding moiety of the 6'-OH in the catalyst is essential in directing the reaction towards the *anti*-diastereoselective pathway. Secondly, the solvent was critical in the diastereocontrol of the reaction. This is put down to the fact that the solvent can have an important influence on the conformation of the flexible cinchona framework, which has a knock-on effect on the catalytic outcome. Interestingly, the chiral nature of the binol phosphoric acid catalyst (*S*)-**49** in the *anti*-selective process was not thought to be hugely influential upon the stereochemical outcome. Indeed replacing it with diphenyl hydrogen phosphate (DPP) gave comparable results, ultimately



Scheme 12: A diastereodivergent sulfa-Michael addition developed by Melchiorre and co-workers.

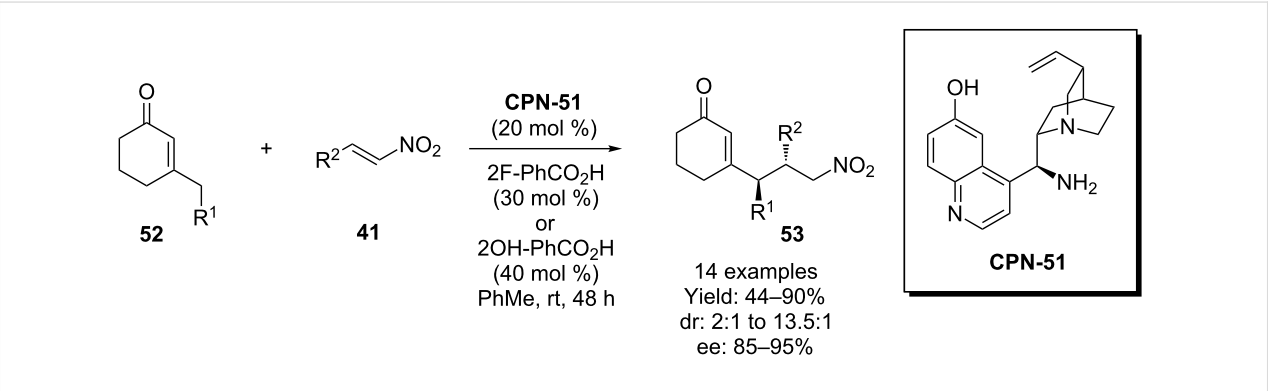
leading to a third conclusion – that the strong hydrogen-bonding ability of the phosphate anion will favour the *anti*-selective pathway.

Melchiorre and co-workers have also succeeded in using the related cupreine organocatalyst **CPN-51** in a direct vinylogous Michael addition reaction [48]. In this process, cyclic enones **52** are added to nitroalkenes **41** using dienamine catalysis (Scheme 13). Although no model is suggested with respect to how the 6'-OH is involved, it is clearly of importance as the analogous 6'-OMe derived cupreine catalyst gives significantly lower conversions and selectivities.

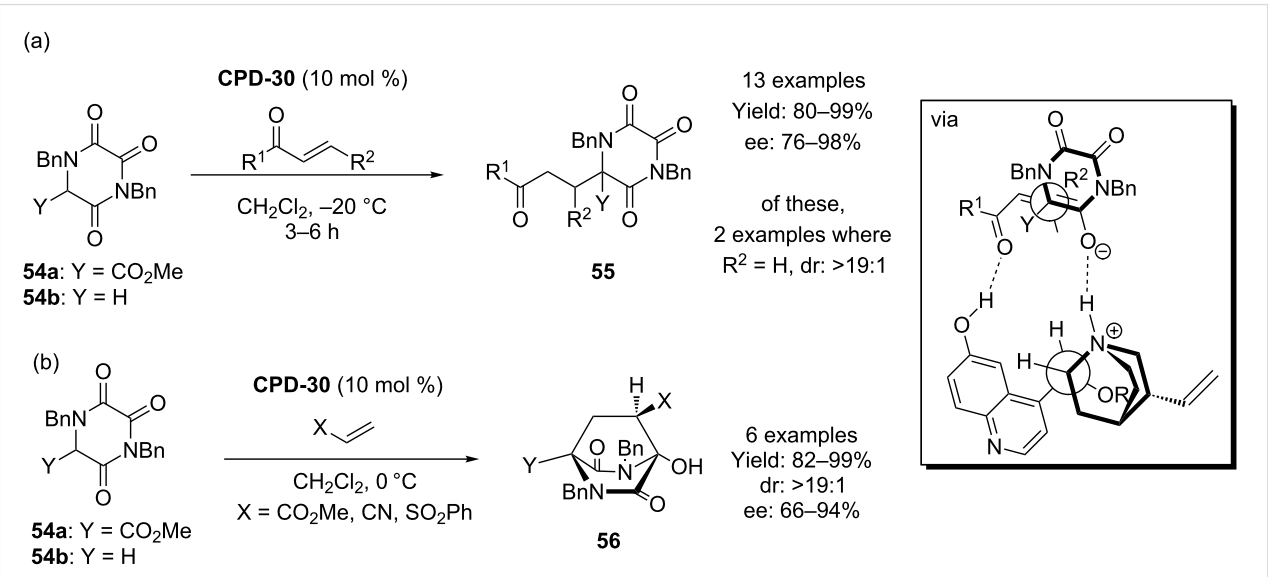
Simpkins and co-workers have used **CPD-30** in the reaction of triketopiperidines (TKPs) **54** with a variety of enones with very good selectivity (Scheme 14a) [49]. Interestingly, with different types of acceptor, a cyclization event occurred leading to the bicyclic hydroxydiketopiperizine system **56** with very high diasterecontrol. Once again, the authors invoke a critical role for the 6'-OH group in the co-ordination and activation of the electrophile in these processes.

Cyclopropanations

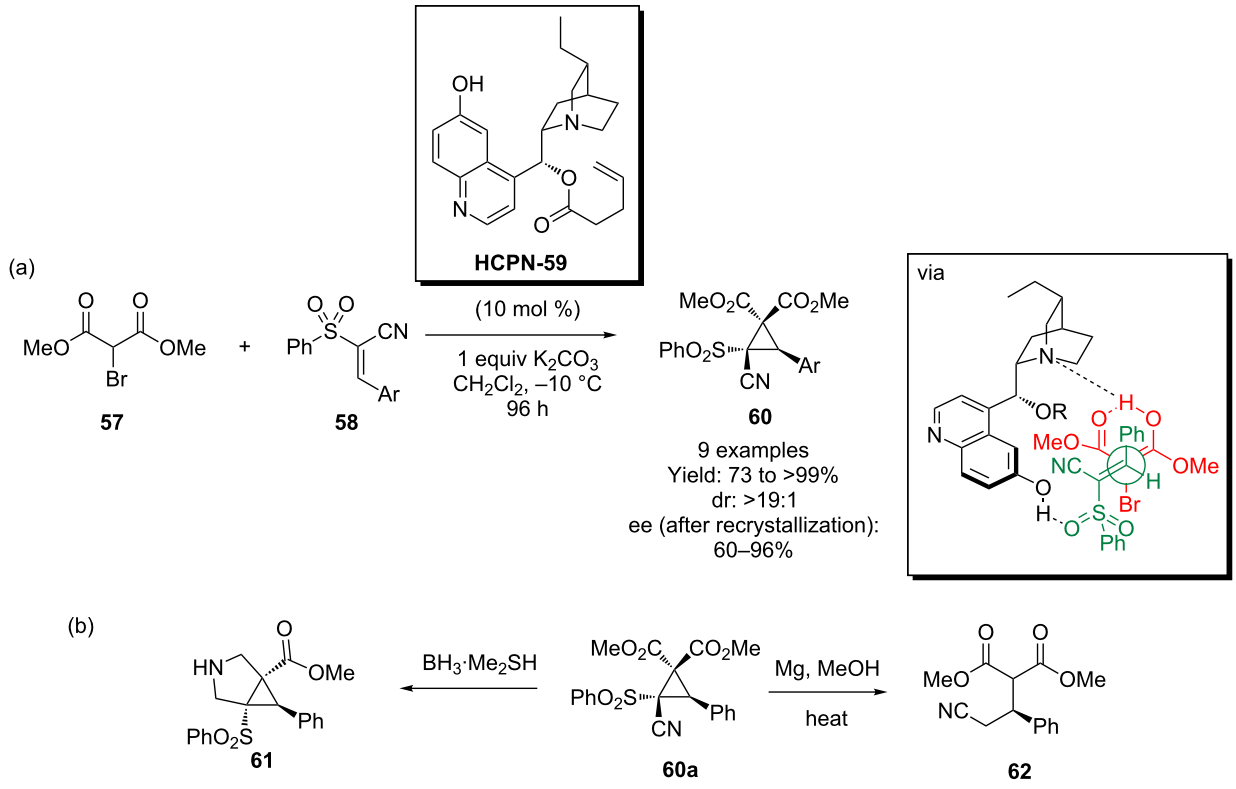
Not unrelated to the Michael addition in a mechanistic sense, is the asymmetric cyclopropanation using dimethyl bromomalonate (**57**) and some form of Michael acceptor. In this process, the enolate resulting from the initital conjugate addition attacks the C–Br bond to form a three-membered ring. In our work in this area, we designed a new cupreine derived catalyst **HCPN-59** to add dimethyl bromomalonate (**57**) to a conjugated cyanosulfone **58** (Scheme 15). Our expectations were that the highly functionalized adduct **60** that resulted would be able to undergo a variety of chemistries, allowing access to a number of diverse scaffolds. This was demonstrated through the synthe-



Scheme 13: Melchiorre's vinylogous Michael addition.



Scheme 14: Simpkins's TKP conjugate addition reactions.



Scheme 15: Hydrocupreine catalyst **HCPN-59** can be used in an asymmetric cyclopropanation.

sis of the corresponding 3-azabicyclo[3.1.0]hexane system **61** and the δ^3-amino acid precursor **62** [50].

Epoxidations and oxaziridinations

A variety of cinchona-derived phase transfer catalysts have been employed in the asymmetric epoxidation [51,52], but only one utilizes the free 6'-OH. In this report by Berkessel and co-workers, cupreine and cupreidine PTCs **HCPN-65** and **HCPD-67** were used in the epoxidation of the *cis*-α,β-unsaturated ketone **63** with sodium hypochlorite [53,54]. Interestingly, the use of these pseudoenantiomers did not lead to similar magnitudes of stereoselection in the opposite enantiomers of epoxide **64** that they produced, as is often the case with cinchona alkaloid catalyzed processes. However, the role of the 6'-OH was clearly important when directly compared with the equivalent 6'-OiPr catalysts **66** and **68** (Scheme 16).

Jørgensen and co-workers have used another anthracenyl-modified hydrocupreidine **HCPD-70** in an enantioselective oxaziridination using mCPBA as the oxidant (Scheme 17) [55]. The authors propose that the quinuclidine nitrogen is protonated by the peracid, giving rise to a tight ion pair, whilst the 6'-OH coordinates to the sulfonyl group oxygen, thus bringing the reactants together. Subsequent reaction then leads to an intermediate α-aminoperoxy structure, which quickly collapses to the oxaziridine **71**.

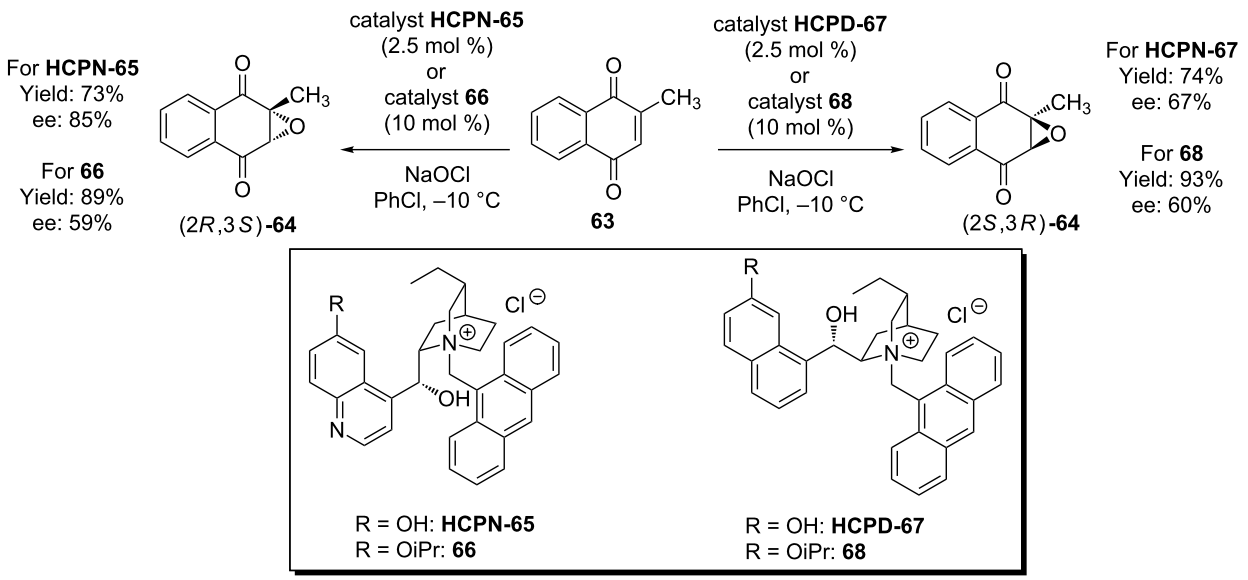
Formation of C–X bonds α-functionalisation

In two separate reports, Zhou and co-workers demonstrate the use of di-*tert*-butyl azodicarboxylate **72** (DBAD) in the direct amination of several different substrates using β-isocupreidine (**β-ICPD**). In the first of these, α-substituted nitoacetates **73** are used [56], and in the second 3-thiooxindoles **75** are employed (Scheme 18) [57]. Unfortunately, in neither of these papers is the absolute stereochemistry elucidated.

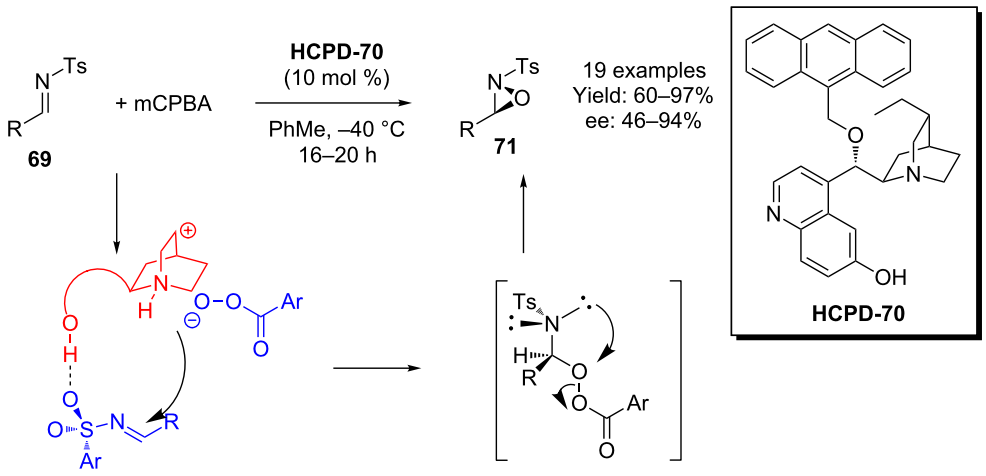
Finally, Meng and co-workers used cupreidine (**CPD**) in the α-hydroxylation of indenones (where $n = 1$ in **77**) using cumyl hydroperoxide (Scheme 19) [58]. Interestingly, the 3,4-dihydronaphthalen-1(2*H*)-one derivative (where $n = 2$ in **77**) did not afford any detectable product.

Transamination

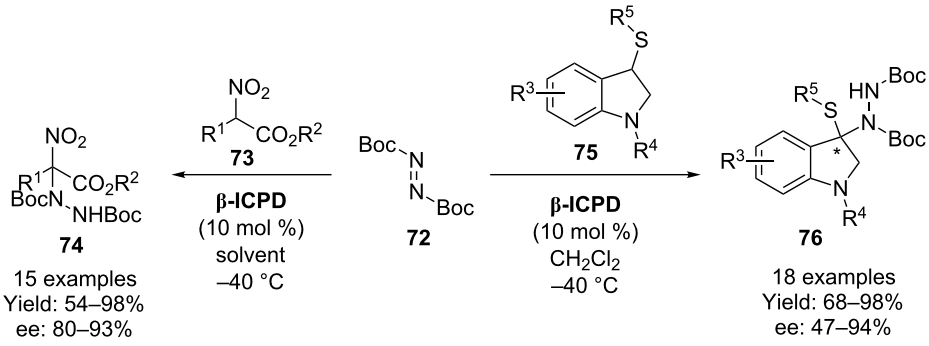
A range of α-amino acid derivatives have been accessed by Shi and co-workers who developed an organocatalytic transamination process using the cupreine catalyst **CPN-81**, which is substituted with *n*-butyl at the 9-OH position [59]. In this report, the α-ketoester **79** was reacted with the primary amine



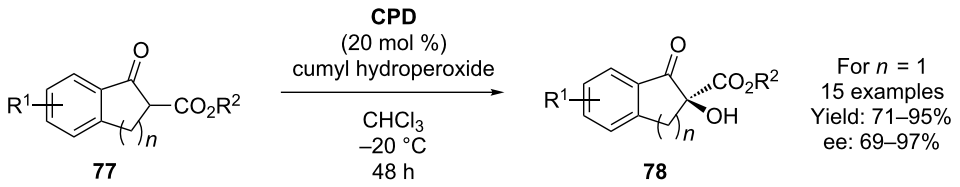
Scheme 16: The hydrocupreine and hydrocupreidine-based catalysts **HCPN-65** and **HCPD-67** demonstrate the potential for phase transfer catalyst derivatives of the 6'-OH cinchona alkaloids to be used in asymmetric synthesis.



Scheme 17: Jørgensen's oxaziridination.



Scheme 18: Zhou's α-amination using **β-ICPD**.



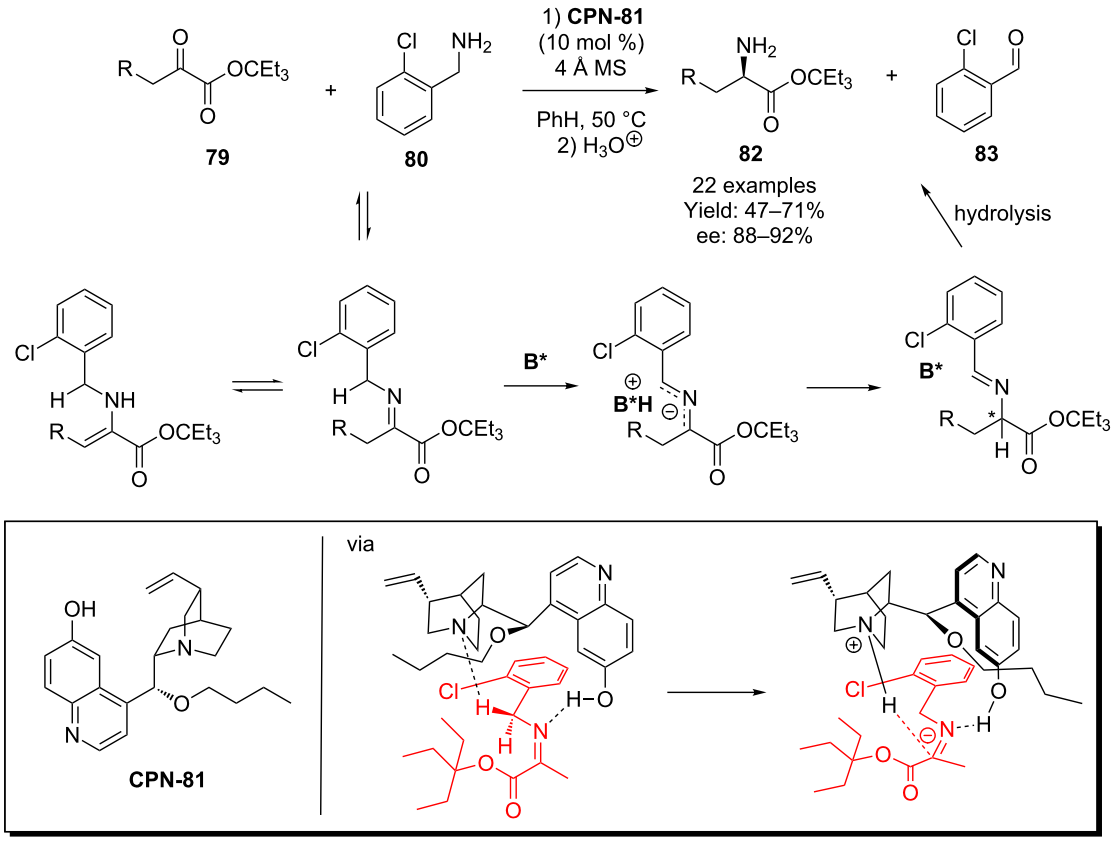
Scheme 19: Meng's cupreidine catalyzed α-hydroxylation.

o-$ClC_6H_4CH_2NH_2$ **80** in the presence of the catalyst. Once again, the role of the 6'-OH functionality is shown to be critical in the orchestration of the reaction process, as depicted in the proposed transition state model (Scheme 20).

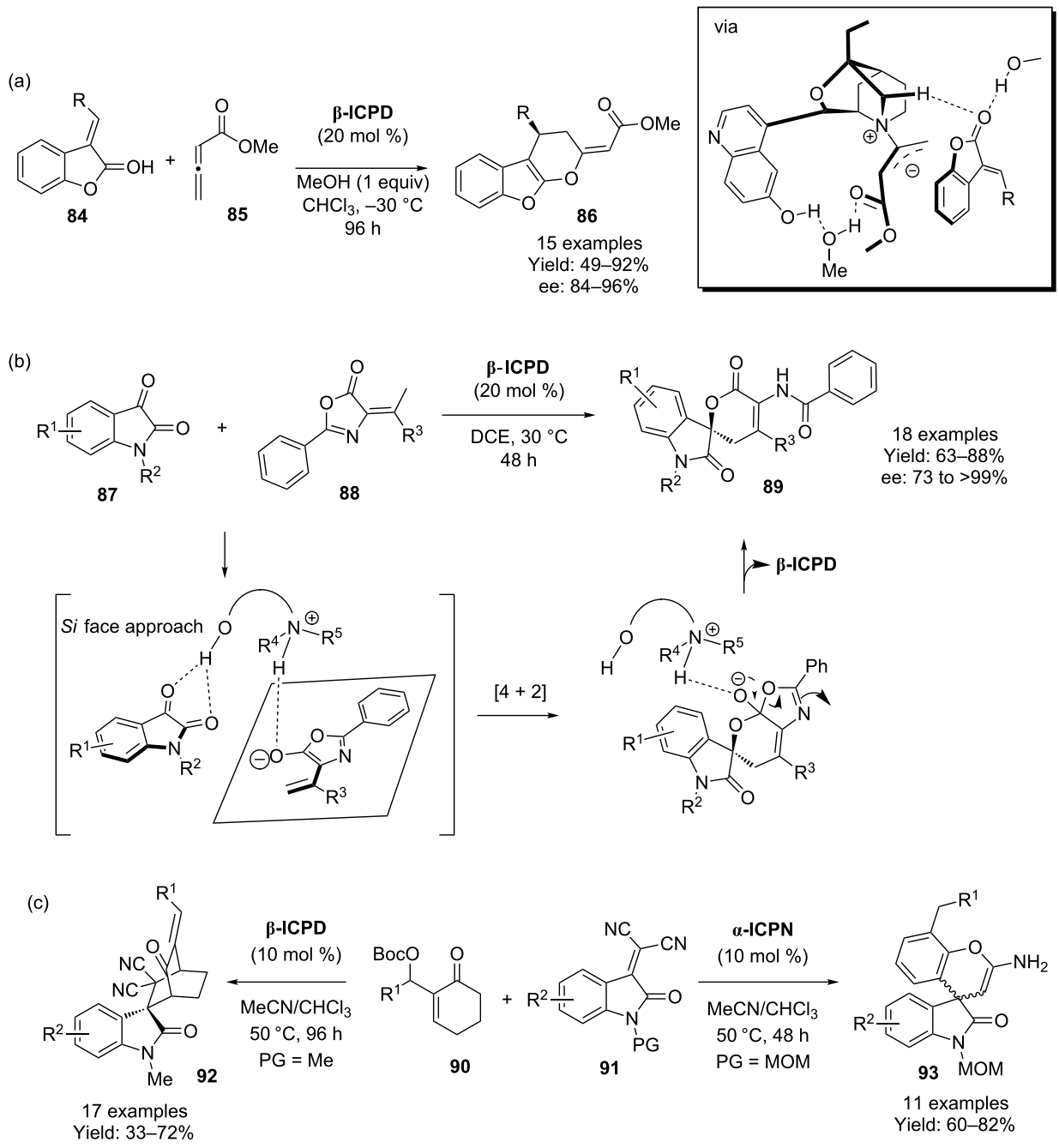
Cycloadditions

The [4 + 2] cycloaddition of benzofuran-2(3*H*)-one derivatives **84** with methyl allenoate **85** to give the corresponding dihydropyran fused benzofuran precursors **86** using **β-ICPD** has been achieved by Li and Cheng and co-workers (Scheme 21a) [60-63]. A large number of computational studies were conducted to explain the enantioselection of the process, resulting in the transition state shown which depicts a critical methanol bridge, explaining the need for this as an additive within the reaction to give optimal stereoselectivities. Similarly, Xu and co-workers have used **β-ICPD** in the cycloaddition between isatin framework **87** and olefinic azlactones **88** to give adduct **89** (Scheme 21b) [64].

Finally, in a remarkable demonstration of diversity-oriented synthesis, Chen and co-workers have shown that simply by switching the type of 6'-OH cinchona-derived catalyst used, two different products can be obtained in their reaction between the 2-cyclohexenone MBH derivative **90** and isatylidene malontirile **91**, one of which is the [4 + 2] adduct **92**, albeit achieved in a step-wise manner (Scheme 21c) [65]. Disappoint-



Scheme 20: Shi's biomimetic transamination process for the synthesis of α-amino acids.



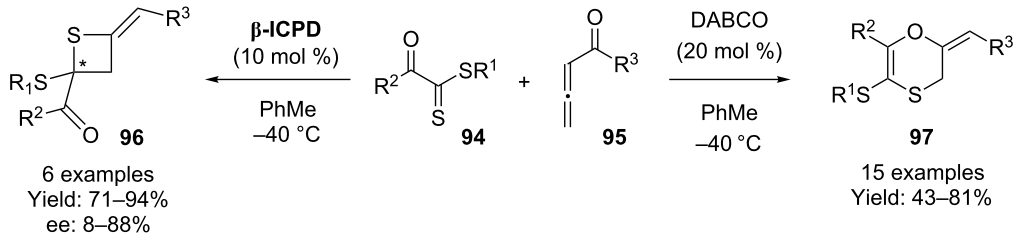
Scheme 21: β-Isocupreidine catalyzed [4 + 2] cycloadditions.

ingly, though not uninteresting, is the fact that there is no enantioinduction for either of these processes.

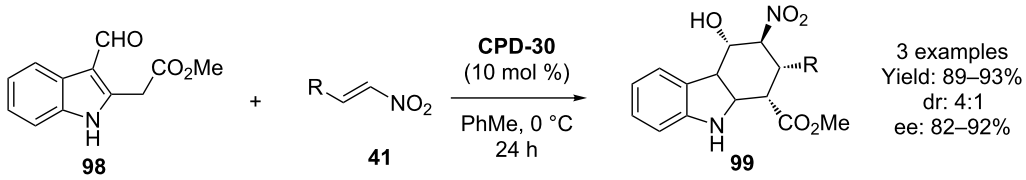
β-Isocupredeine has also been used in the [2 + 2]-addition between 2-thioxoacetates **94** and allenoates **95** to give the corresponding thietanes **96**. In another example of how a different catalyst can lead to a different product, the authors demonstrated that the use of DABCO led instead to the [4 + 2] adduct (Scheme 22) [66].

Domino reaction

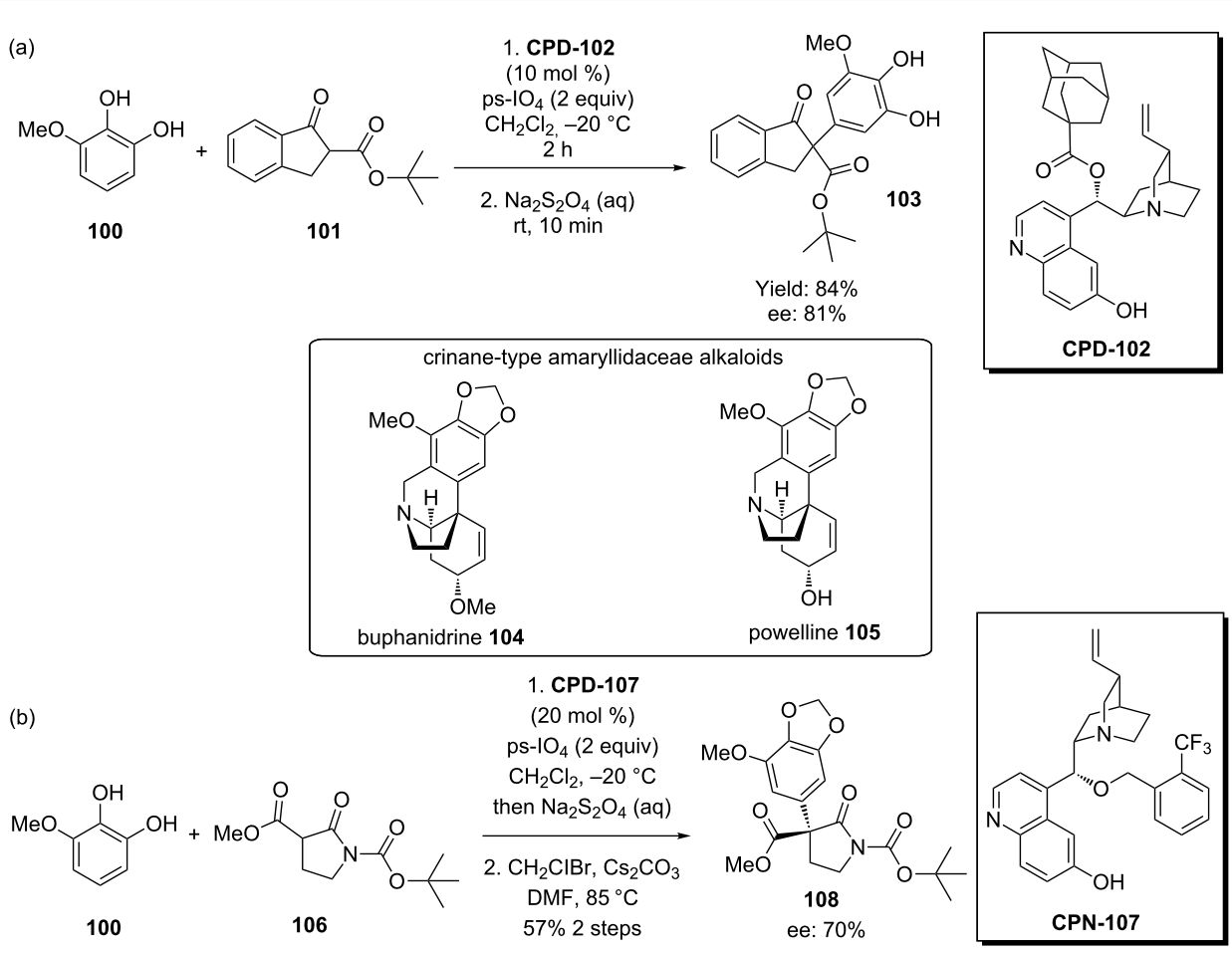
Although it could be argued that some of the reactions within this review are already domino reactions (e.g., MBH, and the cyclopropanation), a recent and clearer example of the use of a 6'-OH cinchona derived catalyst in such a process comes from the laboratory of Samanta and co-workers [67,68]. They have demonstrated an enantioselective domino reaction between 3-formylindoles **98** and nitroolefins **41** to generate the corresponding tricyclic adducts **99** using cupreidine derivative **CPD-**



Scheme 22: β-Isocupreidine catalyzed [2+2] cycloaddition.



Scheme 23: A domino reaction catalyst by cupreidine catalyst **CPD-30**.



Scheme 24: (a) Dixon's 6'-OH cinchona alkaloid catalyzed oxidative coupling. (b) An asymmetric oxidative coupling en route to the attempted total synthesis of some amaryllidaceae alkaloids.

30 (Scheme 23). Although the substrate scope for the enantioselective reaction is limited, the diastereoselectivities are reasonable, and the enantioselectivities are excellent.

Other processes

Asymmetric oxidative coupling

All carbon quaternary centers are prevalent in both natural and pharmaceutical compounds, but rank amongst the hardest to synthesize in a stereoselective manner. Dixon and co-workers have addressed this through the development of an asymmetric organocatalytic oxidative coupling – initially between 3-methoxycatechol (**100**) and *tert*-butyl 1-oxoindan-2-carboxylate (**101**) using an adamantane derivative of cupreidine **CPD-102** to give the corresponding adduct **103** in 84% yield and 81% ee (Scheme 24a) [69]. An attempt to develop this methodology towards an asymmetric total synthesis of buphanidrine (**104**) and powelline (**105**) led to the bespoke development of another cupreidine catalyst **CPN-107**. Unfortunately, although the resulting adduct **108** (after alkylation of the catechol) was produced in a 70% enantiomeric excess (Scheme 24b), subsequent steps that had worked with the racemic synthesis severely deteriorated this, preventing completion of the total synthesis [70,71].

Conclusion

Cupreine and cupreidine and their derivatives have been demonstrated to be suited to a wide range of reaction processes, often with very good enantioinduction. In most cases these catalysts are easy to make from the corresponding cinchona alkaloids, making them attractive compounds for methodologists to have within their catalyst arsenal. They seem particularly suited to catalysis with systems that have an aromatic ring next to a five-membered ring – e.g., indoles, indenones, isatin etc. – especially when it comes to the Morita–Baylis–Hillman reaction, although they are in no way limited to these, and one can only expect the prevalence of these remarkable bifunctional catalysts within the literature to increase over the coming years.

Acknowledgements

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(Thio)urea-mediated synthesis of functionalized six-membered rings with multiple chiral centers

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Review

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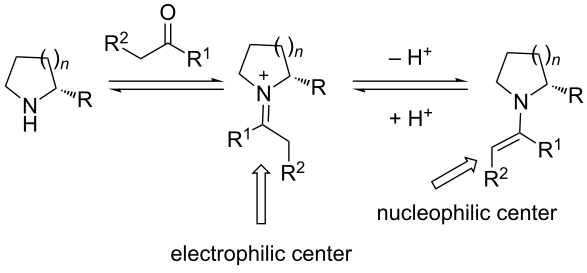
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Abstract

Organocatalysis, now running its second decade of life, is being considered one of the main tools a synthetic chemist has to perform asymmetric catalysis. In this review the synthesis of six-membered rings, that contain multiple chiral centers, either by a ring closing process or by a functionalization reaction on an already existing six-membered ring, utilizing bifunctional (thio)ureas will be summarized. Initially, the use of primary amine-thioureas as organocatalysts for the above transformation is being discussed, followed by the examples employing secondary amine-thioureas. Finally, the use of tertiary amine-thioureas and miscellaneous examples are presented.

Introduction

During the last 15 years, organocatalysis has flourished and has been established as one of the three major pillars of asymmetric synthesis [1-3]. Among the modes of activation of organic molecules that have been designed and developed, the functionalization of carbonyl compounds via enamine and iminium ion intermediates are the most common [4,5] (Scheme 1).

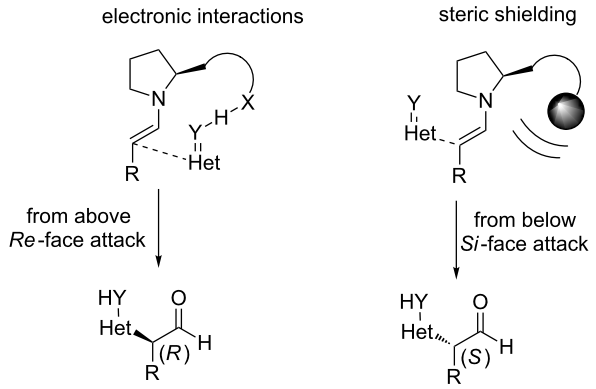


Scheme 1: Activation of carbonyl compounds via enamine and iminium intermediates [2].

The carbonyl compound condenses with the amino catalyst, to form an iminium ion, subsequent deprotonation leads to the highly nucleophilic enamine. This kind of intermediates have been proposed to be the reactive intermediates in many reactions such as aldol, Michael, Mannich, and α-functionalization

(α-chlorination, α-amination, α-fluorination) reactions. Proline-type organocatalysts are considered priviliged, because their corresponding enamines exist mainly in the *s-trans* conformation, that factor is crucial since complete prediction of the stereochemical outcome of the reaction is possible.

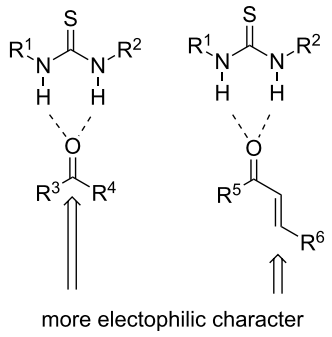
Generally, the enamines formed can interact with the substrates in two ways, via electronic or steric interactions (Scheme 2). The electronic interaction depicted in the left, in Scheme 2, seems to be operative, when the R group of the organocatalyst possesses a moiety, that is able to form hydrogen bonds, being the hydrogen bond donor. Employing this logic, many organocatalysts have been developed, possessing various groups, that are able to form hydrogen bonds, such as carboxylic acids, tetrazoles, thioureas, etc. The selectivity observed, when steric shielding interaction is employed, is due to the bulky group of the catalyst. This group shields one face of the enamine to provide the selectivity.



Scheme 2: Electronic and steric interactions present in enamine activation mode [2].

The third most valuable and studied mode of activation involves hydrogen bonding, which is also postulated to be present in enzymatic reactions. (Thio)urea moieties have been employed in order to activate electrophiles and in order to allign them, in a specific manner, so as to react with nucleophiles (Scheme 3) [6,7]. In addition, many bifunctional (thio)ureas have been synthesized in order to utilize both hydrogen bonding interactions and enamine formation. In the last 10 years the field has witnessed the development of some new activation modes, such as SOMO catalysis [8] and photoredox organocatalysis [9].

Six-membered rings are found in many natural products, pharmaceuticals and agrochemicals, thus, a lot of effort has been put by the synthetic community to provide mild, reliable, robust and operationally simple methods to construct them. Of the vast variety of six-membered rings, those with multiple chiral



Scheme 3: Electrophilic activation of carbonyl compounds by a thiourea moiety.

centers pose the most difficult synthetic challenge, because not only the regiochemical outcome, but also the stereochemical outcome of the reaction must be carefully controlled. Since its rebirth, organocatalysis has made many contributions in the synthesis of six-membered rings with multiple chiral centers, this area has been reviewed in the past [10-14]. This review will focus on (thio)urea organocatalysts, including primary, secondary and tertiary amine groups. Miscellaneous catalysts will be also presented. Thus, it will provide an exhaustive overview of this area, rather than providing a few examples of each class of organocatalysts.

Review

Primary amine-thioureas as organocatalysts promoting asymmetric transformations that lead to a six-membered ring

As discussed earlier, except from the activation of the substrates with the formation of the corresponding enamines or iminium ions, the synthesis of enantiopure products can be also achieved organocatalytically with hydrogen bonding. Organocatalysts that contribute to hydrogen bond formation bear usually a urea or thiourea moiety and they mostly interact with carbonyl groups, nitro moieties or even imines that exist to the substrates, leading to increased electrophilicity; urea and thiourea moieties have also been proposed to interact with nucleophiles. Besides the fact that hydrogen bond donors increase the electrophilicity of the substrates, they mostly coordinate the transition state of the reaction, controlling this way the stereoselectivity of the products. It has been postulated that as the acidity of component HX is increased, the stronger the resulting hydrogen-bonding interaction Y···H–X is [15]. As a logical conclusion, it seems that multiple hydrogen-bonding interactions will provide a more defined conformation to the transition state, thus the catalysts, which contain urea or thiourea moieties are more efficient. If someone combines the ability of amines, to form the corresponding enamines with a carbonyl compound

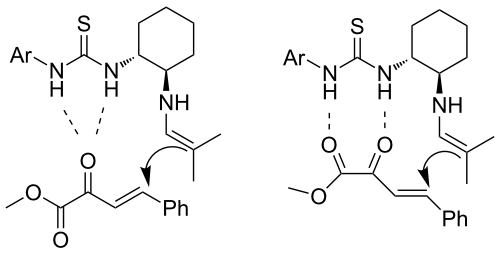
and the ability of ureas or thioureas to define a specific conformation in the transition state of the reaction, then, one can take advantage of a bifunctional catalyst. The first family of these bifunctional catalysts, that are going to be discussed, are the "primary amine-thioureas".

Initially, catalyst **4** was studied as an organocatalyst in the addition of isobutyraldehyde (**1**) to *(E)*-methyl 2-oxo-4-phenylbut-3-enoate (**2**) for the formation of substituted dihydro-*2H*-pyran-6-carboxylate **3** (Scheme 4) [16]. It was observed, that by employing PhCOOH as an additive, the yield (%) and the ee (%) increased, in comparison to the use of 4-dimethylaminopyridine (DMAP). A single example was shown leading to 82% yield and an enantiomeric excess of 71%. The suggested mechanism for this catalytic reaction involves a bifunctional activation.

Utilizing the primary amino group, the authors proposed that the catalyst condenses to form an imine, which is in equilibrium with the corresponding enamine of isobutyraldehyde, while the two hydrogens of the thiourea group interact with one or two carbonyl groups of phenylbutenoate **2** (Scheme 5).

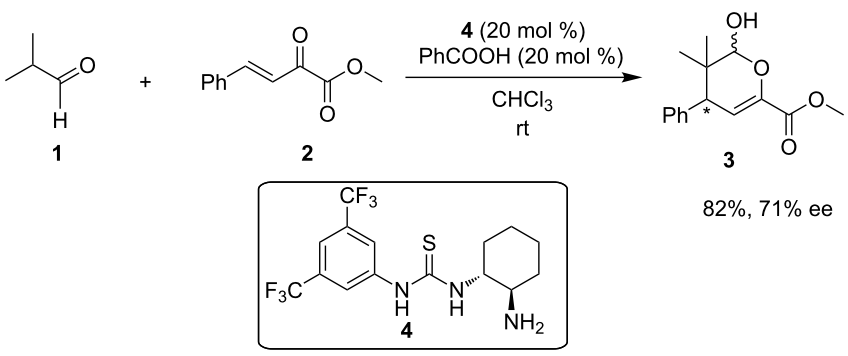
Another catalytic reaction catalyzed by a primary amine-thiourea that leads to multiple chiral centers is the asymmetric desymmetrization of 4,4-disubstituted cyclohexadienones **5**, using the Michael addition of malonates **6**, to obtain 3,4,4-trisubstituted cyclohexanones **7** [17]. It is noted that the organocatalyst employed is the same with the previous example, catalyst **4**. Furthermore, this reaction is taking place in the presence of PPY and high pressure was utilized. The authors proposed that PPY deprotonates the ethyl malonate, producing the active nucleophile, while the thiourea group activates the electrophile (Scheme 6). The above catalytic reaction provided products with yields up to 99%, dr up to 93:7 and ee up to 93%.

Carter and co-worker utilized a similar primary amine-thiourea, organocatalyst **11**, in an enantioselective synthesis of α,α-disubstituted cycloalkanones **10**. Starting from α-substituted cycloalkanones **8** and alkenes **9**, containing an electron withdrawing group, α,α-disubstituted cycloalkanones were obtained (Scheme 7) [18]. The reaction described above provided products with yields up to 96%, ee up to 98% and complete regiocontrol. The authors proposed that the primary amino group of the organocatalyst condenses with the ketone, to form the corresponding enamine, which in turn reacts with the electrophilic alkene **9**.

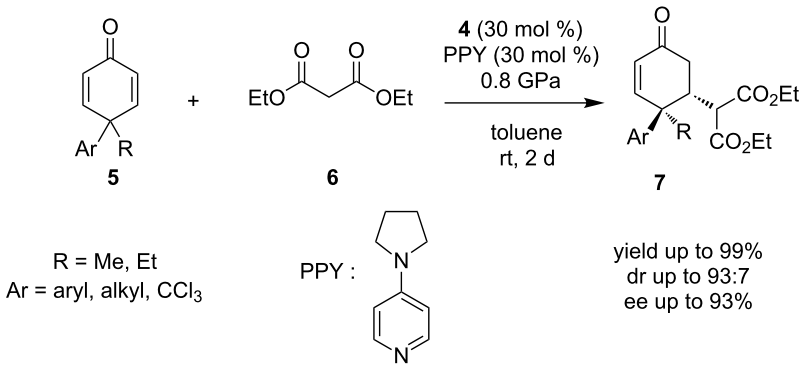


Scheme 5: Possible hydrogen-bonding for the reaction of *(E)*-methyl 2-oxo-4-phenylbut-3-enoate [16].

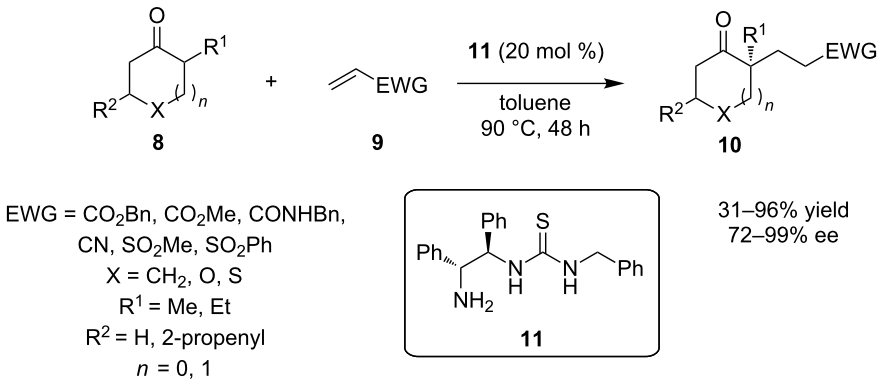
Jacobsen and co-workers have introduced a number of (thio)ureas as organocatalysts for a variety of transformations. Utilizing the primary amine-thiourea **18**, an enantioselective formal aza-Diels–Alder reaction of enones **12** and **13** was reported. In this reaction the enamine is formed from the side of the methyl ketone, which is conjugated with the pre-existing double bond, providing the electron-rich diene, which reacts with substituted dihydroisoquinoline **14** and dihydro-β-carboline **15**, so that cyclohexanone derivatives **16** and **17** will be produced, respectively (Scheme 8) [19]. Also, a cyclic derivative of **13** was utilized (not shown). This aza-Diels–Alder reaction provides products with yields up to 99% and up to 99% ee. This constitutes an excellent addition in a synthetic chemist's arsenal for the synthesis of polycyclic heterocycles.



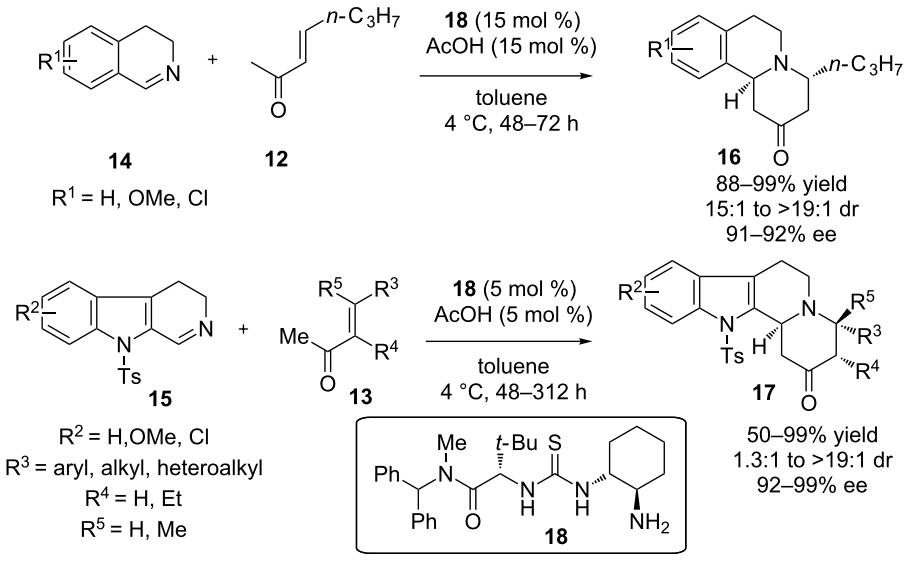
Scheme 4: Asymmetric synthesis of dihydro-*2H*-pyran-6-carboxylate **3** using organocatalyst **4** [16].



Scheme 6: Asymmetric desymmetrization of 4,4-cyclohexadienones using the Michael addition reaction with malonates [17].



Scheme 7: The enantioselective synthesis of α,α-disubstituted cycloalkanones using catalyst **11** [18].



Scheme 8: The enantioselective synthesis of indolo- and benzoquinolidine compounds through aza-Diels–Alder reaction of enones with cyclic imines [19].

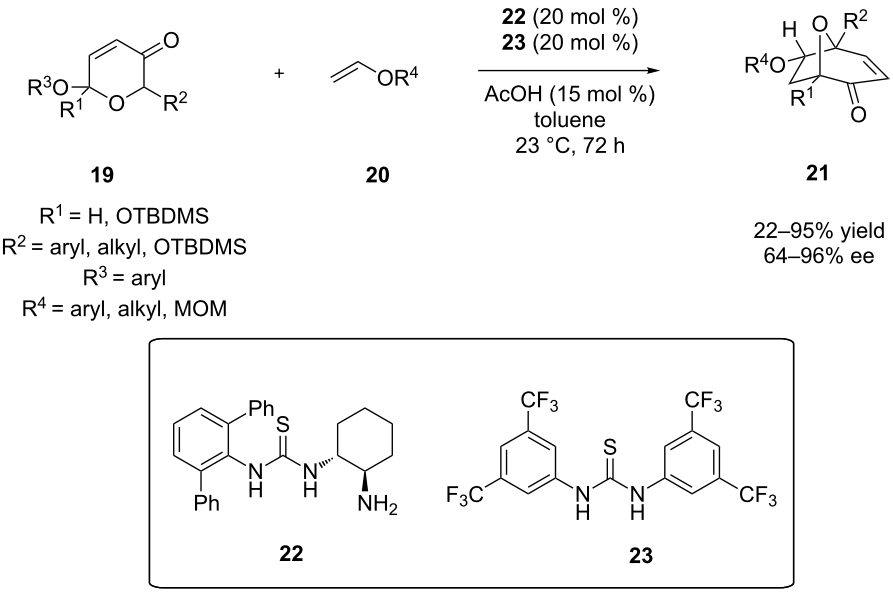
Along the same lines of cycloadditions, Jacobsen and co-workers reported the combination of a primary amine-thiourea **22** and an achiral thiourea catalyst, organocatalyst **23**. More specifically, the reaction is a catalytic asymmetric synthesis of 8-oxabicyclooctanes via an intermolecular [5 + 2] pyrylium cycloaddition (Scheme 9) [20]. This novel [5 + 2] cycloaddition describes the coupling of a pyrylium ylide **19** with dipolarophile **20**, in order to give access to the 8-oxabicyclo[3.2.1]octane **21** framework. In this reaction, the main factor of achieving high yields or enantioselectivities, is how electron-rich or electron-poor, the dienophile is. Electron-rich olefins, like the benzyl vinyl ether and ethyl vinyl ether, reacted with success providing high yields and high enantiomeric excess. It has been observed that a nucleophilic 2π-reactant is needed for the successful conversion of the reactants into the desired products, following a mechanism which involves a cationic, electron-poor amino-pyrylium intermediate. In addition, for the achievement of high ee values the nature of R^3 is very important. The better the leaving group R^3 is, the higher the values of the ee. It is mentioned that the ee in this reaction is up to 96%, and the recommended R^3 group to be used is 3,4,5-trifluorobenzyl.

The use of the bifunctional amine-thiourea catalyst **27**, into a reaction providing oxazine derivatives **26**, was reported by Ye and co-workers (Scheme 10) [21]. In this reaction, nucleophile **24** is coupled to arylenone **25** to give the desired product. Initially a Michael reaction is taking place, followed by cyclization. After screening of various acids, hydrobromic acid was found to be the optimum acid for the second step of the reaction. Products were obtained in good to excellent yields (64–99%), with >20:1 diastereoselectivity and excellent values of up to 98% ee.

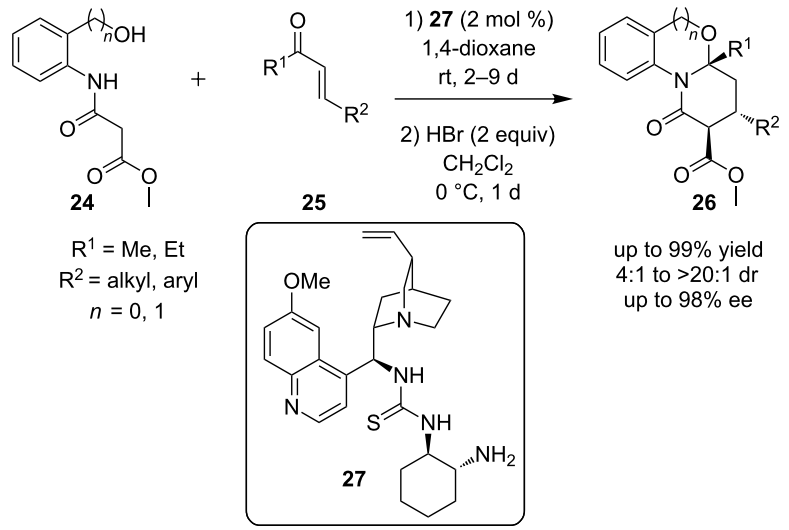
Employing the same catalyst as before, organocatalyst **27**, another synthesis of the bridged core **30** and specifically the bicyclo[3.3.1]nonadienone of (−)-huperzine was reported (Scheme 11) [22]. The reagents were the analogue of pyridine **28** and an α,β-unsaturated aldehyde **29**. In order to obtain the desired products, an α-substituted α,β-unsaturated aldehyde must be used. In this particular reaction, the product was obtained in 78–90% yield and 15–92% ee. Finally, β-substituted α,β-unsaturated aldehydes were completely unreactive.

In 2012, a proposed inverse electron-demand Diels–Alder reaction was reported by Wang and co-workers, obtaining enantiopure products **33**, starting from diene **31** and dienophile **32**, using compound **34** as the catalyst (Scheme 12) [23]. This reaction provided products in 84–99% yield and with a diastereoselectivity of up to >20:1 and excellent enantioselectivity (88–99% ee).

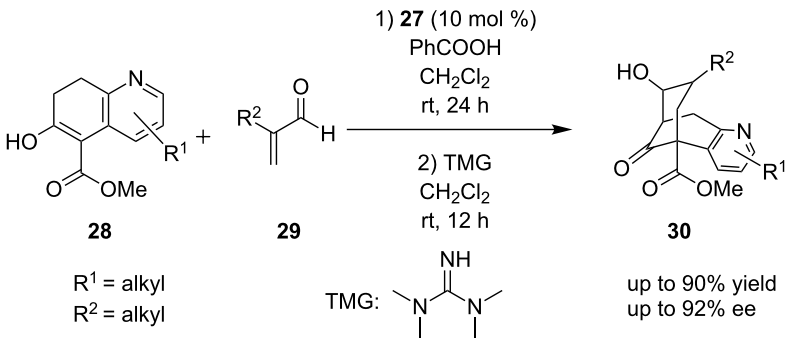
In 2015, Dixon, Paton and co-workers demonstrated an elegant route to morphan skeletons, utilizing prochiral ketones **35** or **36**, catalyzed by a primary amine-thiourea **37** developed by Jacobsen. The proposed pathway is based on desymmetrization of **35** or **36** by an intramolecular Michael addition of the corresponding enamines to an α,β-unsaturated ester, to yield bicyclic



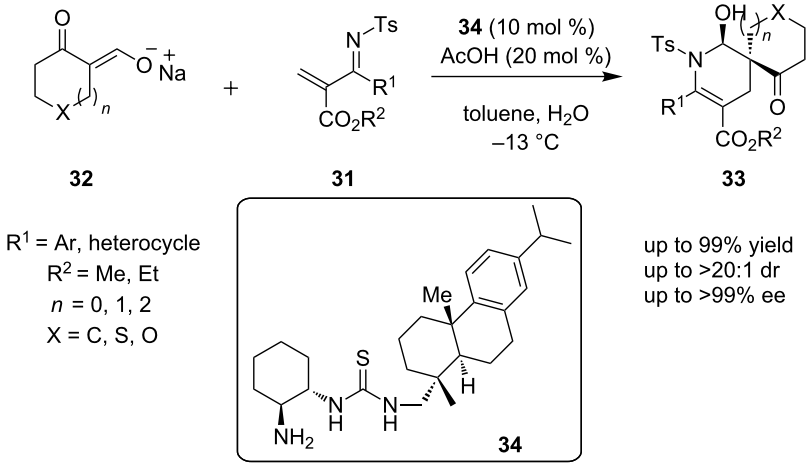
Scheme 9: Enantioselective [5 + 2] cycloaddition [20].



Scheme 10: Asymmetric synthesis of oxazine derivatives **26** [21].



Scheme 11: Asymmetric synthesis of bicyclo[3.3.1]nonadienone, core **30** present in (−)-huperzine [22].

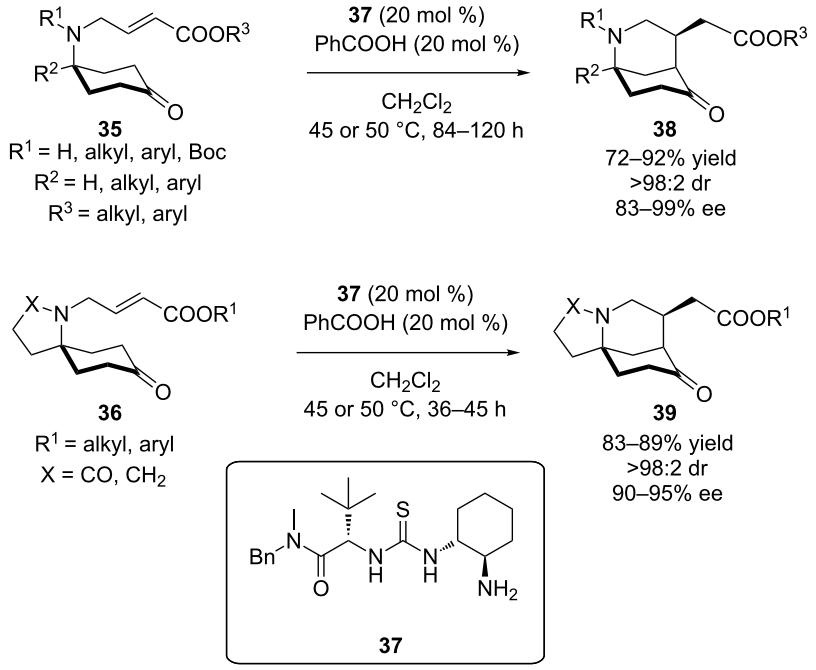


Scheme 12: Asymmetric inverse electron-demand Diels-Alder reaction catalyzed by amine-thiourea **34** [23].

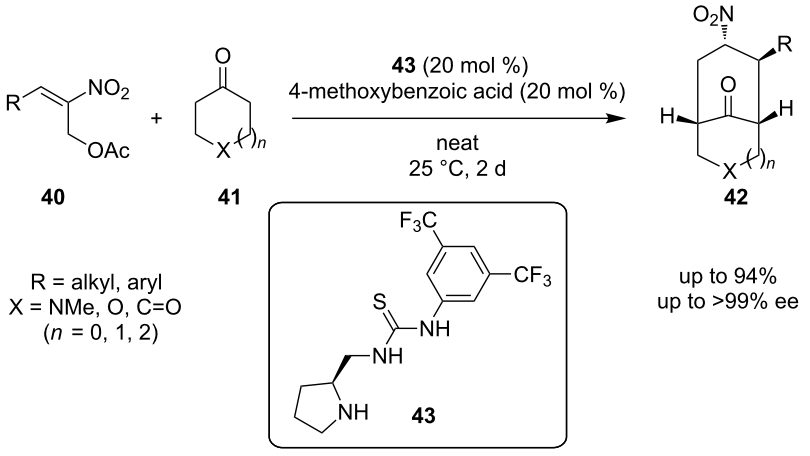
or spiro-bicyclic products **38** and **39**, respectively, in excellent yields and stereoselectivities (Scheme 13) [24]. Computational studies were employed, in order to support the mechanistic pathway and the origins of stereocontrol.

Secondary amino-thioureas as organocatalysts promoting asymmetric transformations that lead to a six-membered ring

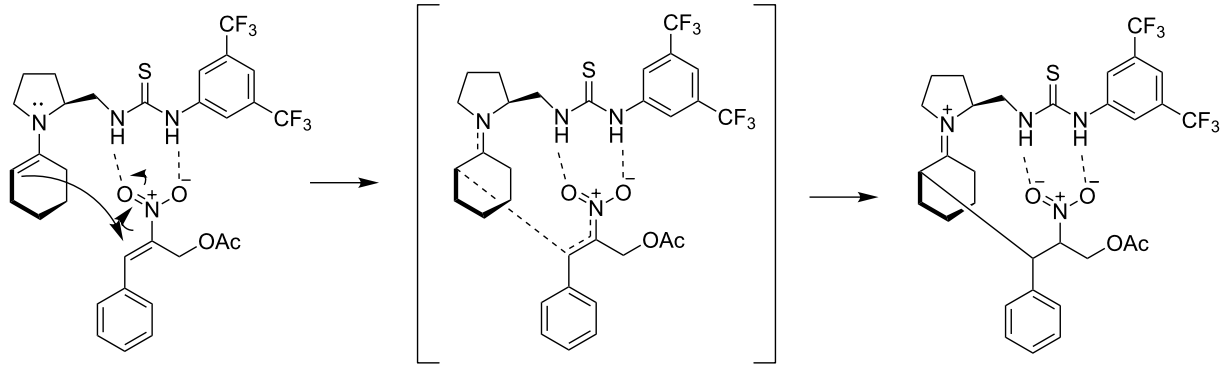
In 2009, the first asymmetric tandem reaction for the construction of bicyclic skeletons utilizing a secondary amine-thiourea was reported (Scheme 14) [25]. In this reaction, *(E)*-2-nitroallyl acetates **40** were used, that could serve as reagents, which can install a nitro group into the final product. After screening of various catalysts, organocatalyst **43** and 4-methoxybenzoic acid as a cocatalyst, was identified as the optimum for the reaction of *(E)*-2-nitroallyl acetate **40** with cyclohexanone **41** to provide nitrobicyclo[3.3.1]nonan-9-one **42**, in solvent-free conditions. This reaction provides products with yields up to 94% and enantiomeric excess up to >99%. A proposed mechanism for this reaction is shown below, where the formation of the *s-trans*-enamine occurs and then attacks the electrophilic double bond of the nitroallyl acetate (Scheme 15).



Scheme 13: Asymmetric entry to morphan skeletons, catalyzed by amine-thiourea **37** [24].



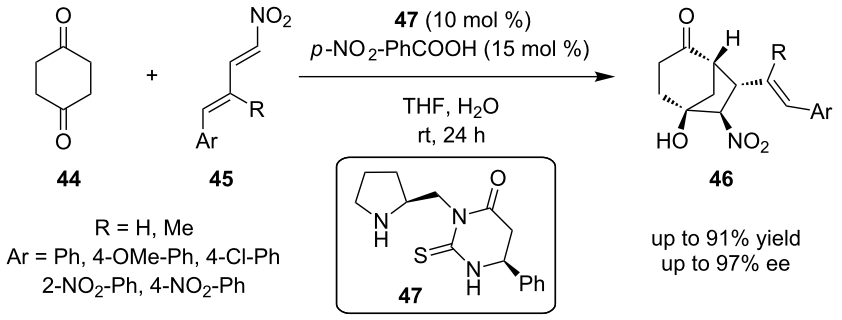
Scheme 14: Asymmetric transformation of *(E)*-2-nitroallyl acetate [25].



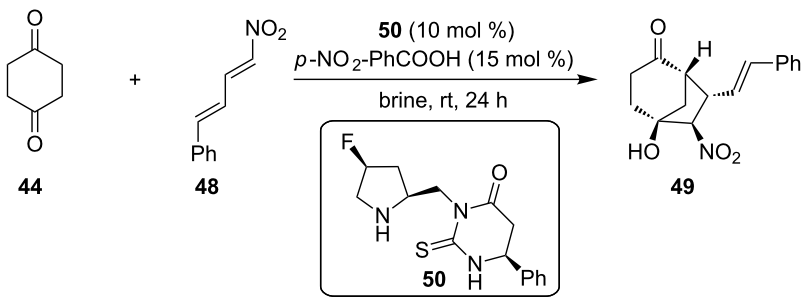
Scheme 15: Proposed way of activation.

Among the same lines, Tsakos and Kokotos reported an enantioselective domino-Michael–Henry reaction catalyzed by a secondary amine-thiourea between cyclohexa-1,4-dienone (**44**) and a γ,δ-alkyl-aryl-disubstituted nitrodiene **45**, providing bicyclo-[3.2.1]octan-2-one **46** (Scheme 16) [26]. The organocatalyst used in this reaction is the cyclic thiourea **47**. It is noted, that organocatalyst **47** affords products only in organic solvents and more specifically in THF. This tandem Michael–Henry reaction provided the product in an excellent yield of 91%, excellent enantiomeric excess of 96% and complete diastereocontrol.

Trying to provide a greener alternative, Kokotos and co-workers, catalyzed the same tandem Michael–Henry reaction between cyclohexa-1,4-dienone (**44**) and nitrodiene **48** by employing the secondary amine-thiourea **50**, which contains a fluorine on its skeleton and 4-nitrobenzoic acid as a cocatalyst, to provide the substituted bicyclo[3.2.1]octan-2-one **49** (Scheme 17) [27]. It is highly noted that the difference to the moiety at the 4-position of the pyrrolidine ring, where a fluorine atom exists, gives to the organocatalyst **50** the ability to catalyze this tandem Michael–Henry reaction in brine, giving



Scheme 16: Asymmetric synthesis of nitrobicyclo[3.2.1]octan-2-one derivatives [26].



Scheme 17: Asymmetric tandem Michael–Henry reaction catalyzed by **50** [27].

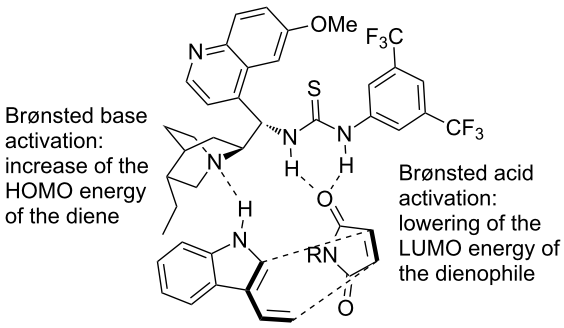
excellent diastereoselectivity and enantiomeric excess, unlike the previously employed catalyst **47**, which worked only in organic solvent. The key component for the achievement of catalyst's **50** catalytic ability is the known "gauche effect" of fluorine in the pyrrolidine ring, where σ*(C–F) and σ(C–H) vicinal orbitals tend to overlap [28]. For a more efficient overlap of these two orbitals the ring has a certain bent conformation, which presumably makes the formed enamine more planar and a better nucleophile to attack the nitrodiene. This tandem Michael–Henry reaction provided the product in a medium yield 48%, excellent enantiomeric excess 97% and excellent diastereoselectivity >99:1.

Tertiary amine-(thio)ureas as organocatalysts promoting asymmetric transformations that lead to a six-membered ring

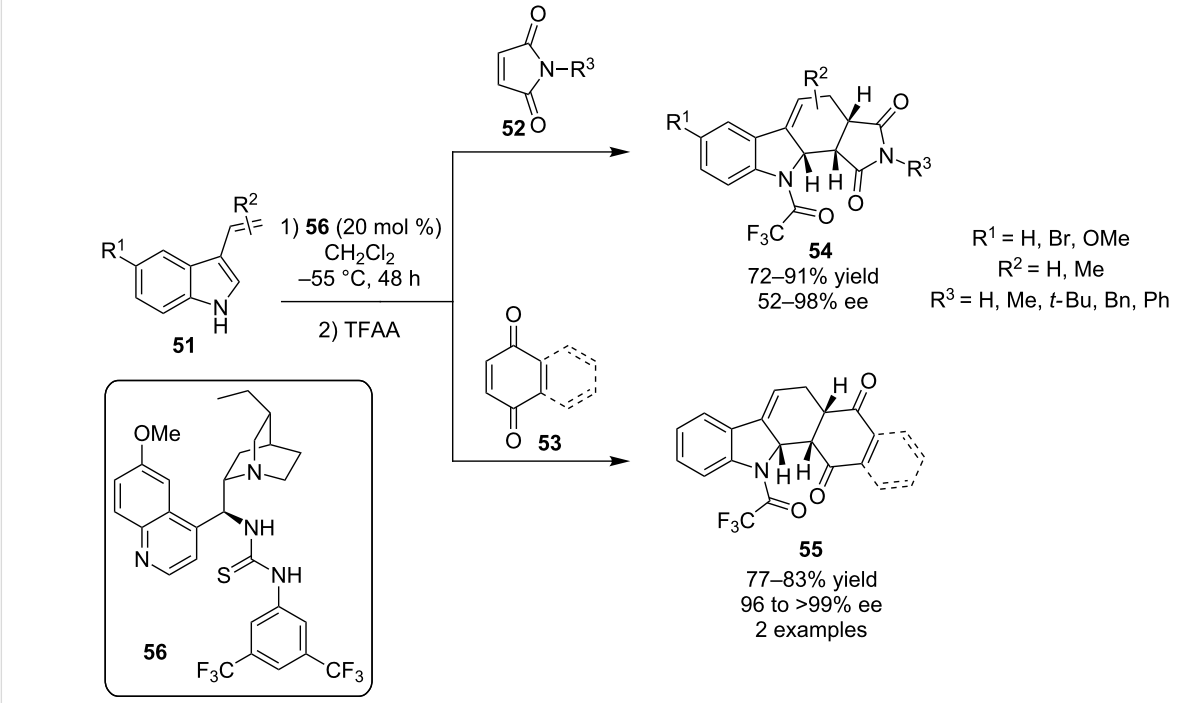
One-step reactions producing six-membered rings

In 2008, the first example of a single reaction producing a six-membered ring with multiple stereocenters catalyzed by a tertiary amine-thiourea **56** was reported by Bernardi, Ricci and co-workers for the Diels–Alder reaction of 3-vinylindoles **51** (Scheme 18) [29]. The authors utilized either maleimides **52** or quinones **53** as the dienophile, affording the products **54** and **55** in excellent yields and enantioselectivities, after trapping of the adducts with trifluoroacetic anhydride (TFAA), in order to make the products more stable. As expected the *endo*-adduct was the sole product observed.

For this transformation, quinine-derived bifunctional organocatalyst **56** was utilized. The authors proposed that the catalyst raises the HOMO of the nucleophile, making the diene more nucleophilic, and lowers the LUMO of the electrophile, making the dienophile more electrophilic (Scheme 19), thus the catalyst acts via a bifunctional mode. All these interactions are developed in the transition state through hydrogen-bonding, which controls the stereochemical outcome of the reaction.

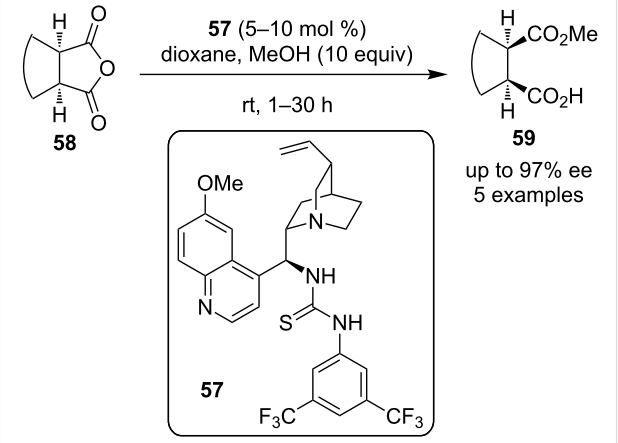


Scheme 19: Proposed transition state and activation mode of the asymmetric Diels–Alder reactions of 3-vinylindoles **51** [29].

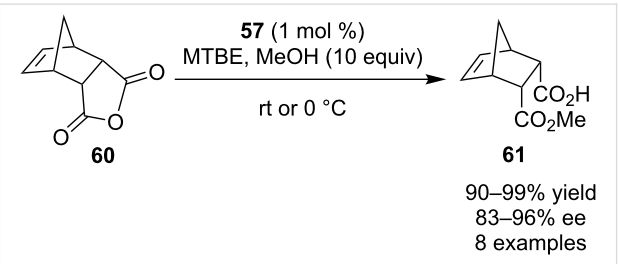


Scheme 18: Asymmetric Diels–Alder reactions of 3-vinylindoles **51** [29].

The same year, two different groups utilized thiourea catalyst **57** to catalyze the desymmetrization of *meso* anhydrides **58** and **59** through a methanolysis reaction (Scheme 20 and Scheme 21).



Scheme 20: Desymmetrization of *meso*-anhydrides by Chin, Song and co-workers [30].

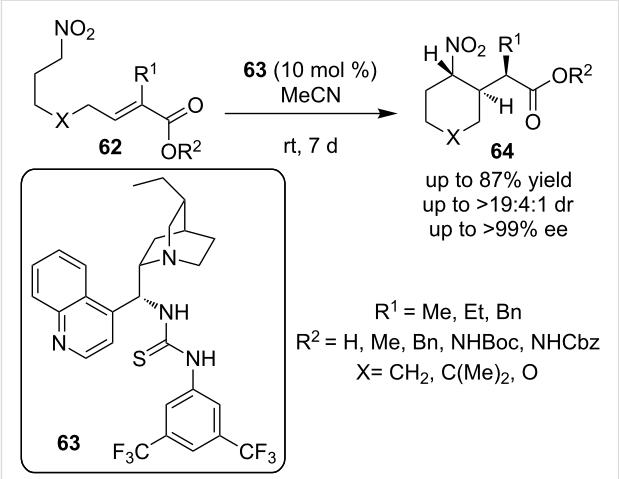


Scheme 21: Desymmetrization of *meso*-anhydrides by Connon and co-workers [31].

Chin, Song and co-workers utilized the catalyst in 5–10 mol % catalyst loading and dioxane as solvent, producing the desired products **59** in excellent enantioselectivities [30].

Connon and co-workers, on the other hand, changed slightly the catalytic system, using only 1 mol % catalyst loading and MTBE as solvent to afford products **61** in excellent yields (90–99%) and good to excellent enantioselectivities (83–96% ee) [31].

In 2009, Cobb and co-workers disclosed the asymmetric intramolecular Michael addition of nitronates **62** onto conjugated esters utilizing the cinchona-derived thiourea **63** (Scheme 22) [32]. The reaction proceeded with excellent selectivity and afforded products **64** in good yield. The substrate scope of this reaction was thoroughly studied and the products of the transformation were exploited to generate a variety of γ-amino acids, including examples containing three contiguous stereocenters.



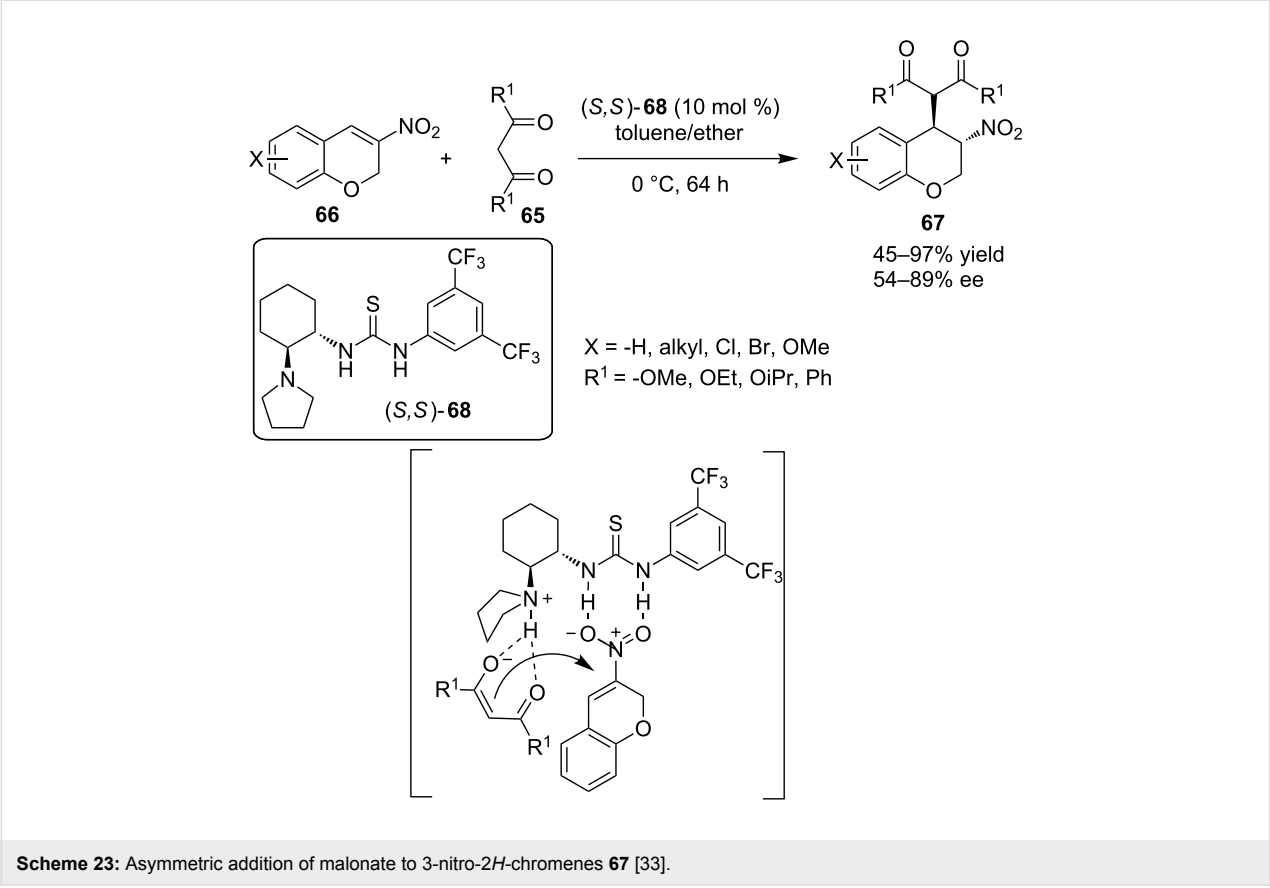
Scheme 22: Asymmetric intramolecular Michael reaction [32].

In 2010, Yan and co-workers described the Michael addition of malonates **65** to 3-nitro-2*H*-chromenes **66**, which provided the substituted chromanes **67** in moderate to excellent yields and good enantioselectivities (Scheme 23) [33]. Catalyst (*S,S*)-**68** is postulated to catalyze the reaction in a bifunctional manner: the tertiary amine deprotonates the malonate and the resulting enolate is directed to the upper face of the 3-nitro-2*H*-chromene due to hydrogen bonding of the enolate with the ammonium cation. The thiourea moiety, firstly activates the 3-nitro-2*H*-chromene through two hydrogen bonds, making it more electrophilic (LUMO lowering effect) and secondly it orients it near the enolate.

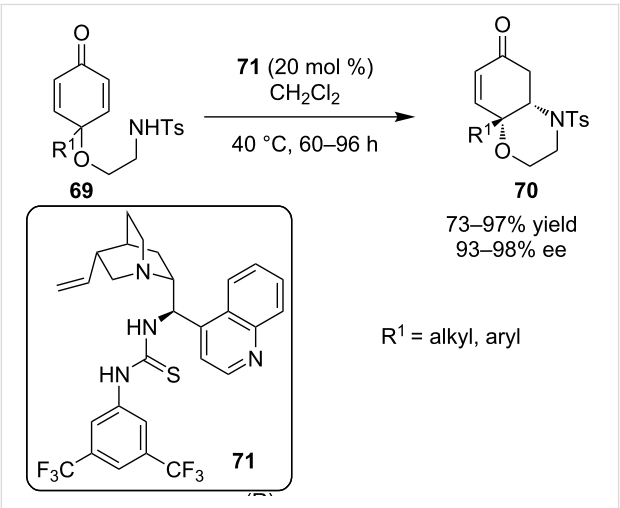
In 2011, You and co-workers described the intramolecular desymmetrization of cyclohexadienones **69** catalyzed by thiourea **71**, derived from cinchonine to give a bicyclic system **70** containing two chiral centers, utilizing an aza-Michael reaction (Scheme 24) [34]. The reaction proceeded in good to excellent yield and excellent enantioselectivity for almost all of the substrates that were tested.

This methodology was further extended in the total synthesis of (−)-mesembrine. This natural product contains a sterically hindered and arylated quaternary carbon center, which was constructed via a desymmetrization aza-Michael reaction. That key intermediate **72** was afforded in 91% yield and 97% ee. (Scheme 25).

In 2012, Cobb and co-workers developed a novel asymmetric Michael–Michael reaction between nitrohex-4-enoates **73** and nitroolefins **74** to construct a cyclohexene moiety, bearing multiple contiguous stereocenters, including one quaternary center [35]. The reaction proceeded smoothly and a wide range of products **75** were obtained in good yields and moderate to



Scheme 23: Asymmetric addition of malonate to 3-nitro-2*H*-chromenes **67** [33].



Scheme 24: Intramolecular desymmetrization through an intramolecular aza-Michael reaction [34].

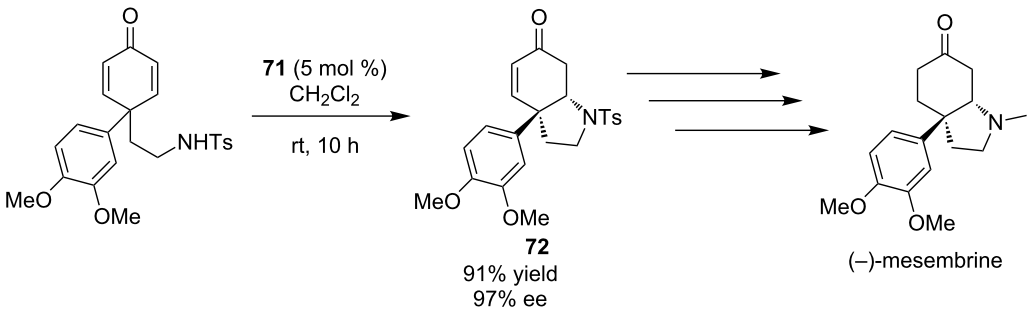
excellent stereoselectivity (Scheme 26). The authors proposed that the organocatalyst deprotonates substrate **73** to produce a nitronate, which reacts with the electrophilic nitroolefin via a Michael addition. The resulting nitro compound is again deprotonated by the organocatalyst and reacts with the α,β-unsaturated ester to yield the desired product.

Cascade/domino/tandem reactions producing six-membered rings

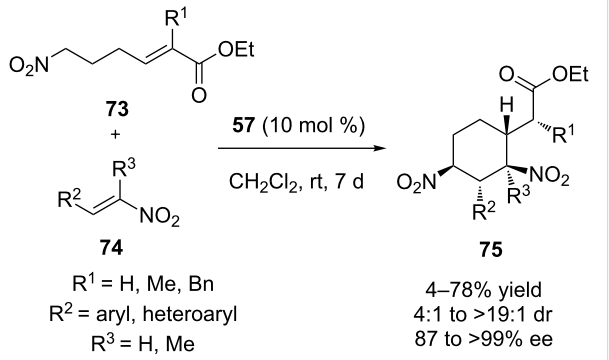
Cascade and tandem reactions always seemed very appealing to the synthetic community, not only because of their elegance, but also for their efficiency [36-42]. Cascade and tandem reactions have been proven extremely efficient because in only one synthetic operation, many bond-forming steps are achieved. Organocatalysis has made many contributions in cascade and tandem processes [43-45], due to the mild conditions required for the organocatalysts to operate, many distinct reactions can be conducted in one-pot fashion.

Cascade/domino/tandem reactions producing six-membered rings initiated by Michael addition

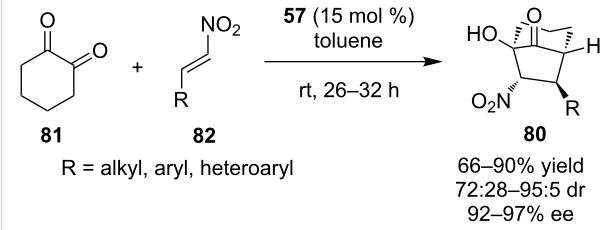
Bonne, Constantieux, Rodriguez and co-workers reported an enantioselective three-component Michael–Michael–Henry reaction to access a highly substituted cyclohexane **76** with excellent selectivity over three steps (>95:5 dr, 98% ee) using Takemoto's catalyst **77** (Scheme 27) [46]. The cascade starts with a Michael addition of the enol of the α-keto-amide **78** to nitroalkene **79**, subsequent Michael addition of nitronates to the second equivalent of nitroalkene **79** and finally a Henry-type reaction between nitronate and the highly electrophilic carbonyl of the α-keto-amide, resulting in the final product **76**.



Scheme 25: Enantioselective synthesis of (−)-mesembrine [34].

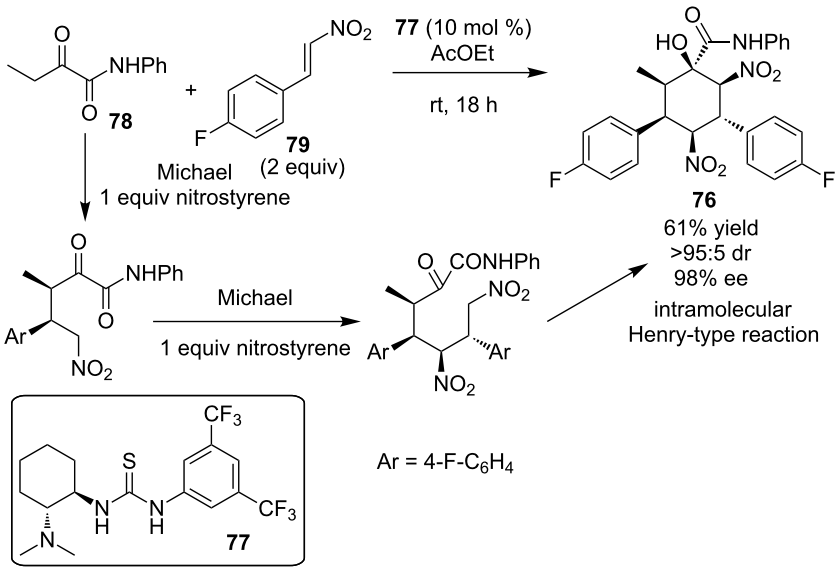


Scheme 26: A novel asymmetric Michael–Michael reaction [35].



Scheme 28: Asymmetric domino Michael–Henry reaction [47].

In 2010, Zhao and his group demonstrated the synthesis of bicyclo[3.2.1]octan-8-ones **80**, via a domino Michael–Henry reaction using quinine-derived catalyst **57** (Scheme 28) [47]. The nucleophile in this process is cyclohexane-1,2-dione (**81**) and the Michael acceptor is nitroolefin **82**. A wide range of substrates were tested and the products were isolated in good yields, moderate diasteroselectivities and excellent enantioselectivities. To expand the utility of the developed process, Zhao and co-workers performed the reaction with *trans*-β-nitrostyrene in gram scale isolating the desired product in 74% yield, 88:12 dr and 96% ee.



Scheme 27: Asymmetric three-component reaction catalyzed by Takemoto's catalyst **77** [46].

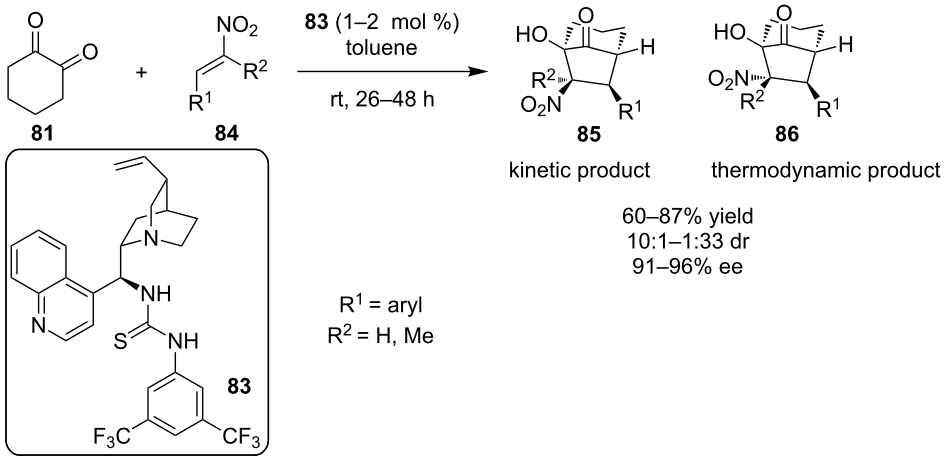
The same year, Rueping and co-workers utilized the cinchonidine-based thiourea catalyst **83** in much lower catalyst loading, in order to catalyze the same reaction producing the product in high yields and good selectivity (Scheme 29) [48]. In addition, they proposed an explanation for the low diastereoselectivity of the reaction: the kinetic product is slowly interconverting into the thermodynamic product by two pathways: the first one is deprotonation of the α-H to the nitro group and subsequent protonation, and the second pathway is by a retro-Henry process.

Employing the same nucleophile **81**, Wang and his group combined it with β,γ-unsaturated α-ketoesters **87**, as the electrophile, catalyzed by bifunctional indane-derived thiourea **88**, to produce derivatives of 3,4-dihydro-*2H*-pyran **89** (Scheme 30) [49]. This reaction sequence involved a Michael reaction, followed by a hemiacetalization reaction.

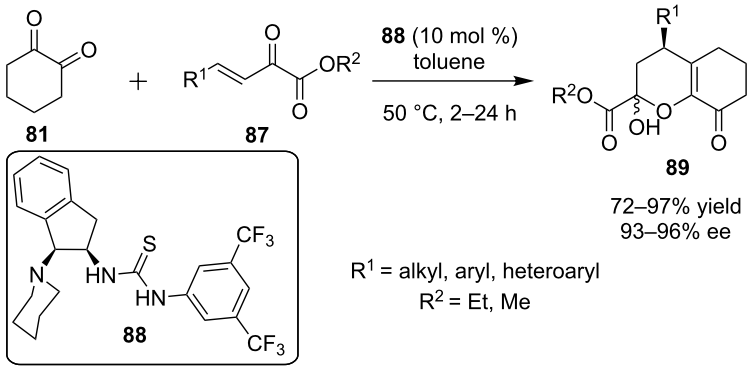
The reaction proceeded smoothly for a wide range of substrates to afford the desired products in good to excellent yields (72–97%) and excellent enantioselectivities (93–96% ee). Unfortunately, the product epimerized in the reaction medium, and the resulting product is a mixture of the two anomers.

In 2012, Xie and his group envisioned the use of α,α-dicyano olefins **90**, as a vinylogous Michael donor in an asymmetric Michael addition to substituted 3-nitro-2*H*-chromenes **91** catalyzed by bifunctional thiourea catalyst **92** (Scheme 31) [50]. When R^2 is an alkyl group the reaction resulted in the production of **93** and **94** in moderate to excellent enantioselectivities, considering the high molecular complexity achieved in only one step.

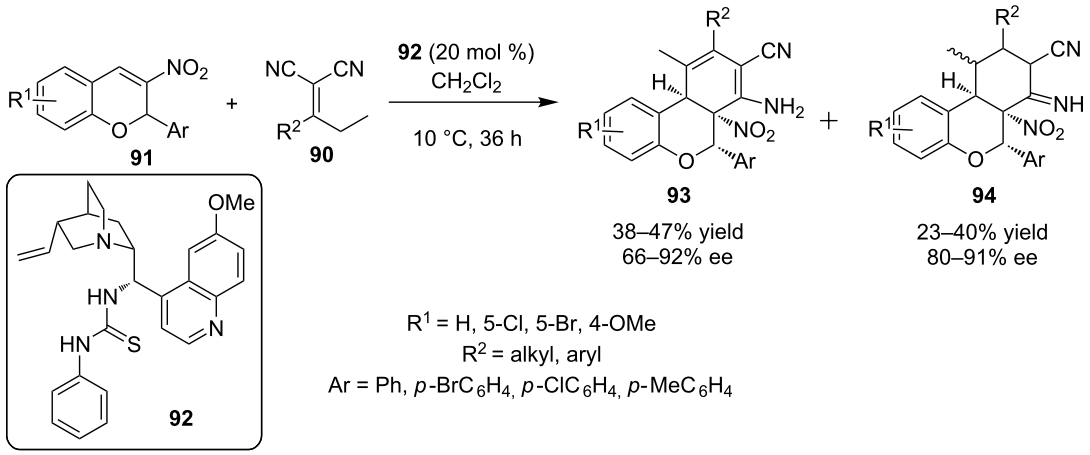
Recently, Bugaut, Constantieux and co-workers described the enantioselective organocatalytic multicomponent synthesis of 2,6-diazabicyclo[2.2.2]octanones **95**, utilizing Takemoto's catalyst **77** (Scheme 32) [51]. The reaction was carried out in dry toluene in the presence of molecular sieves at −10 °C, to afford the highly substituted product, containing a 2,6-diazabicyclo[2.2.2] unit and multiple stereocenters, of which two are contiguous and tetrasubstituted, in good yields and selectivities.



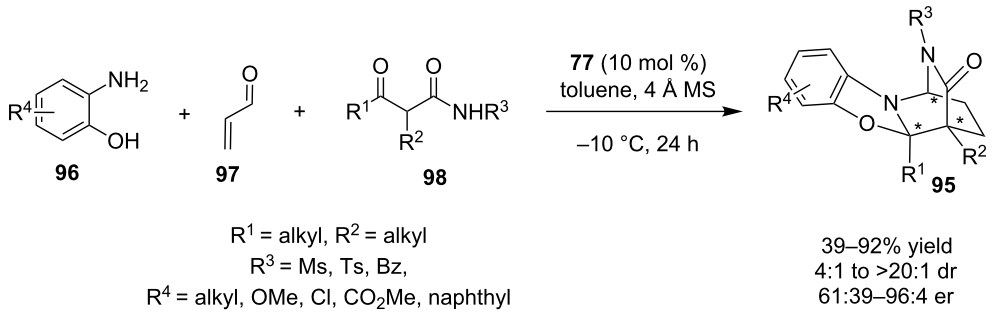
Scheme 29: Asymmetric domino Michael–Henry reaction [48].



Scheme 30: Enantioselective synthesis of derivatives of 3,4-dihydro-2*H*-pyran **89** [49].



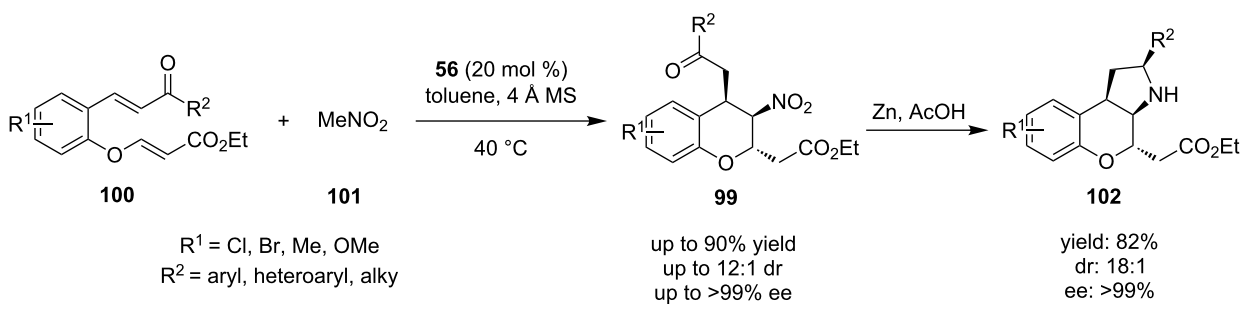
Scheme 31: Asymmetric addition of α,α-dicyano olefins **90** to 3-nitro-2*H*-chromenes **91** [50].



Scheme 32: Asymmetric three-component reaction producing 2,6-diazabicyclo[2.2.2]octanones **95** [51].

In 2013, Luo, Xu and co-workers demonstrated an easy method for the synthesis of enantiomerically pure polysubstituted chromans **99**, via the reaction of chalcone enolates **100** and nitromethane (**101**), catalyzed by quinine-derived thiourea **56** (Scheme 33) [52]. Initially nitromethane adds to the chalcone moiety, followed by a nitronate addition to the α,β-unsaturated ester. The substrate scope was widely expanded, including the aromatic moieties containing halogens, alkyl and alkoxy groups. Also, ketones bearing aryl, heteroaryl and alkyl groups, provided the desired products in excellent yields and selectivities. In order to broaden the utility of this methodology, the authors reduced the nitro group to an amine. The product was in situ transformed to the tricyclic product **102**, through a diastereoselective reductive amination, that controlled the stereochemistry of the carbon bearing the R^2 group.

Very recently, Wang and co-workers used a cinchona alkaloid-based bifunctional thiourea **103** as the catalyst of choice to an



Scheme 33: Asymmetric double Michael reaction producing substituted chromans **99** [52].

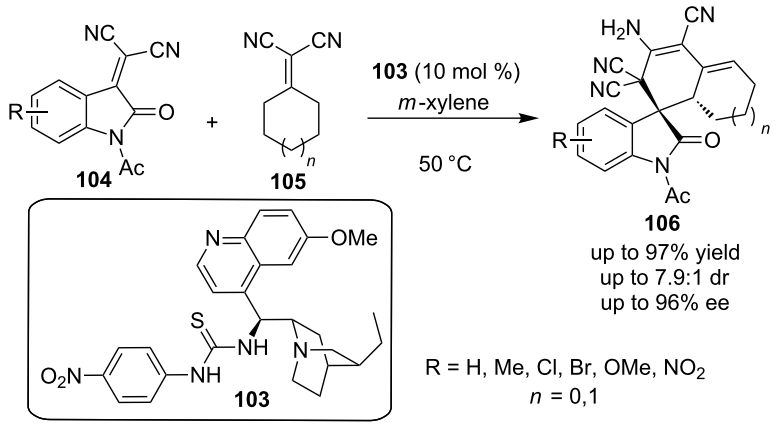
organocatalytic domino process. This domino reaction involded a Michael cyclization–tautomerization reaction sequence between isatylidene malononitriles **104** and α,α-dicyanoalkenes **105**. The process yielded highly functionalized spiro-oxindole dienes **106**. The products were obtained in good to excellent yields (up to 97%) and enantioselectivities (up to 96%), but the diastereoselectivities were moderate (up to 7.9:1) (Scheme 34) [53].

In 2015, Soós and co-workers disclosed an elegant synthesis of polysubstituted cyclohexanes, utilizing the chiral adduct **107** of the Michael reaction of chalcone **109** catalyzed by a bifunctional thiourea **56** [54]. The authors used a range of different adducts, as well as monosubstituted and disubstituted α,β-unsaturated aldehydes **108**, affording the desired products **110** in moderate to good yields and good to excellent stereoselectivities (Scheme 35).

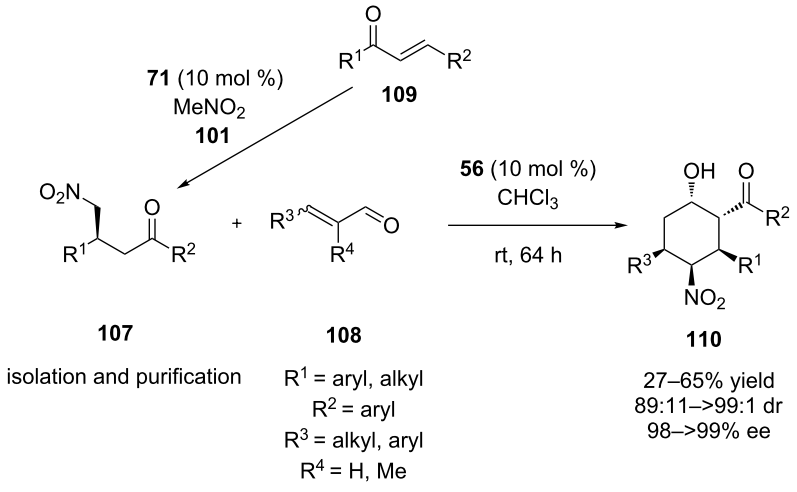
Recently, Wang and co-workers disclosed an asymmetric synthesis of dihydrocoumarins **113** containing adjacent stereogenic centers, utilizing the cinchona-derived bifunctional thiourea **57** [55]. A wide range of azlactones **112** were tested, as well as a plethora of *o*-hydroxychalcone derivatives **111**, providing the products in good to excellent yield and good to excellent stereoselectivity (Scheme 36). The authors proposed that azlactones are deprotonated by the tertiary amine of the organocatalyst to provide an enolate, which in turn reacts with the Michael acceptor **111**.

Cascade/domino/tandem reactions producing six-membered rings initiated by Michael addition of activated methylenes and derivatives

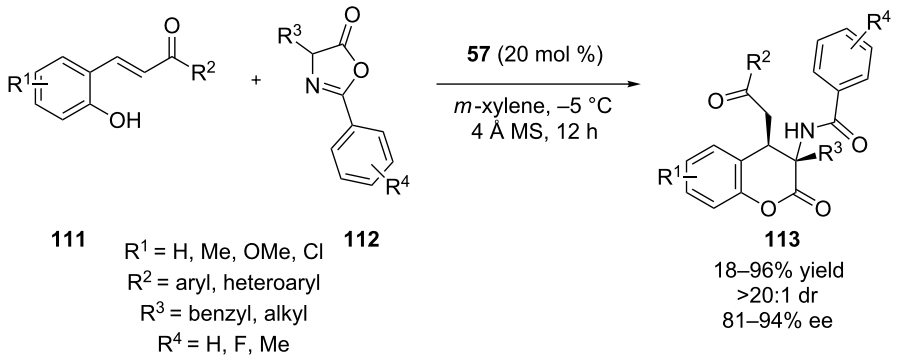
In 2004, Takemoto and co-workers demonstrated the enantioselective tandem Michael addition of γ,δ-unsaturated-β-ketoesters **114** to *trans*-β-nitrostyrene **115** which produced tetrasubstitut-



Scheme 34: Enantioselective synthesis of multi-functionalized spiro oxindole dienes **106** [53].



Scheme 35: Organocatalyzed Michael aldol cyclization [54].

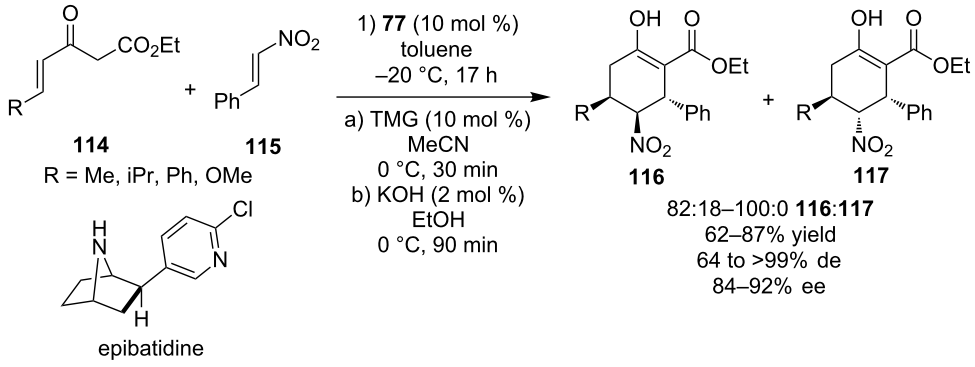


Scheme 36: Asymmetric synthesis of dihydrocoumarins [55].

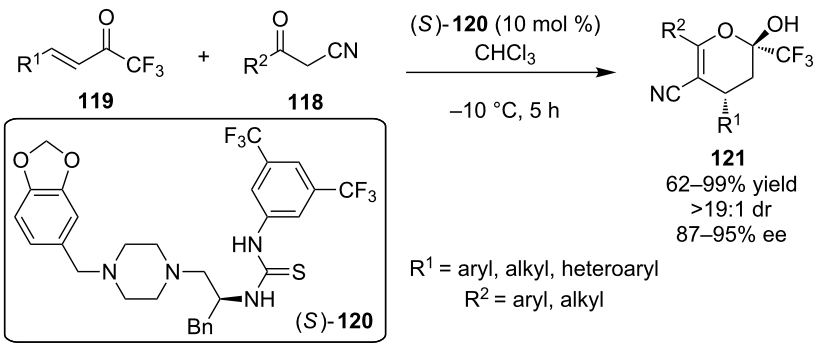
ed cyclohexenols **116** and **117** utilizing Takemoto's catalyst **77** (Scheme 37) [56].

In a paper that described in more detail the transformation, the authors showed that the substitution of the olefin **114** is crucial, in order to proceed the reaction smoothly [57]. The products were isolated in moderate to good yields, excellent diasteroselectivities and good enantioselectivities. With this methodology in hand, the natural product (–)-epibatidine was synthesized.

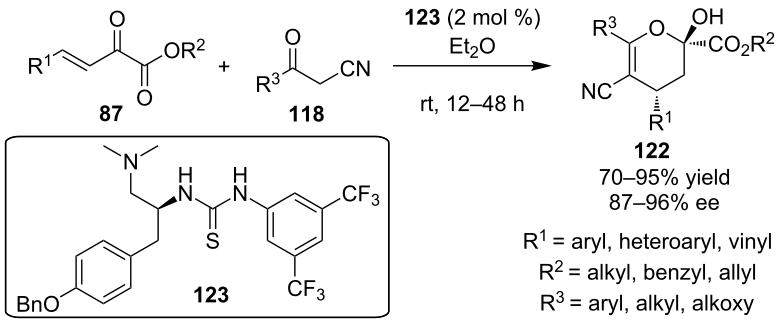
In 2009, Zhao, Zhu and co-workers disclosed the first enantioselective reaction of α-cyanoketones **118** to α,β-unsaturated trifluoromethyl ketones **119**, utilizing a novel organocatalyst that they developed containing a piperazine moiety (*S*)-**120** (Scheme 38) [58]. The reaction proceeded through a Michael addition to the unsaturated ketone, subsequent hemiacetalization and finally elimination to result in the α-trifluoromethyl-dihydropyrans **121**. The products were isolated in moderate to excellent yields and selectivities.



Scheme 37: Asymmetric double Michael reaction en route to tetrasubstituted cyclohexenols [56].

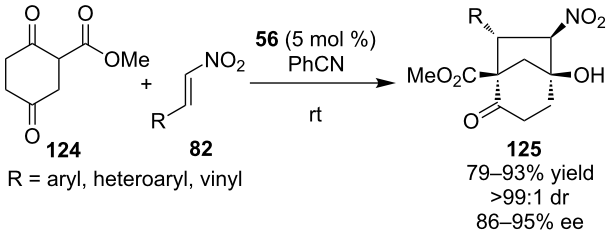


Scheme 38: Asymmetric synthesis of α-trifluoromethyl-dihydropyrans **121** [58].



Scheme 39: Tyrosine-derived tertiary amino-thiourea **123** catalyzed Michael hemiaketalization reaction [59].

The same year Zhao and co-workers applied the same principles, in order to produce another class of chiral dihydropyrans **122**. They utilized the novel tyrosine-derived tertiary amine-thiourea **123** in quite low catalyst loading to catalyze the reaction between α-cyanoketones **118** and β,γ-unsaturated α-ketoesters **87** (Scheme 39) [59]. Initially a Michael reaction occurs, followed by a hemiacetalization reaction, providing wide range of products in excellent yields (up to 95%) and selectivities (87–96% ee), confirming the generality of the protocol.



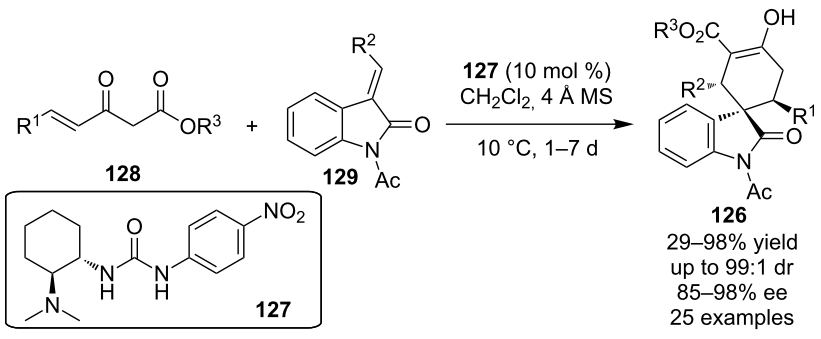
Scheme 40: Enantioselective entry to bicyclo[3.2.1]octane unit [60].

In 2010, Zhong and co-workers demonstated that bifunctional thiourea **56** could catalyze the domino Michael–Henry reaction between nitroalkenes **82** and methyl 2,5-dioxocyclohexanecarboxyalate **124** to produce bicyclo[3.2.1]octane unit (Scheme 40) [60]. The reaction proceeded smoothly to afford a wide variety of products **125** in good to excellent yields and selectivities.

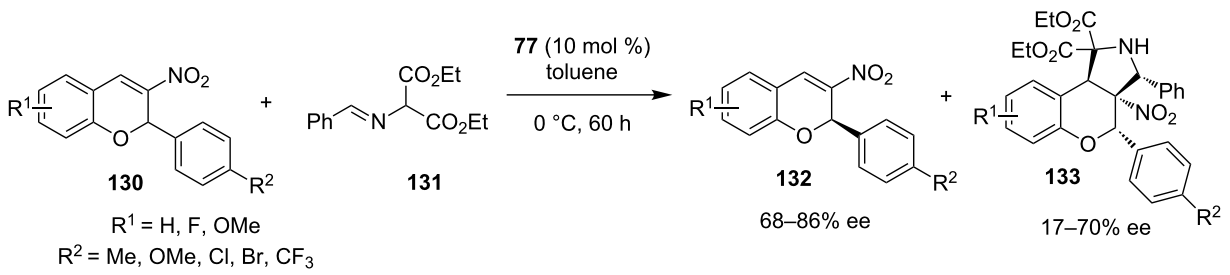
In 2010, Gong and co-workers developed an asymmetric process en route to spiro[4-cyclohexanone-1,3'-oxindoline] **126** catalyzed by the bifunctional urea **127** (Scheme 41) [61]. The transformation follows a Michael–Michael mechanism and is considered a formal [4 + 2] cycloaddition of **128** (bearing a nucleophilic carbon as well as an electrophilic carbon) and protected methylene-indolinones **129**. A wide range of substrates were tested and the desired products were isolated in good to excellent yields (up to 98%), diastereoselectivities (up to 99:1) and enantioselectivities (up to 98%).

In 2010, Xie and co-workers reported the kinetic resolution of racemic 3-nitro-2*H*-chromenes **130** catalyzed by Takemoto's organocatalyst **77** (Scheme 42) [62]. The resulting (*R*)-3-nitro-2*H*-chromene was isolated in rather moderate optical purity.

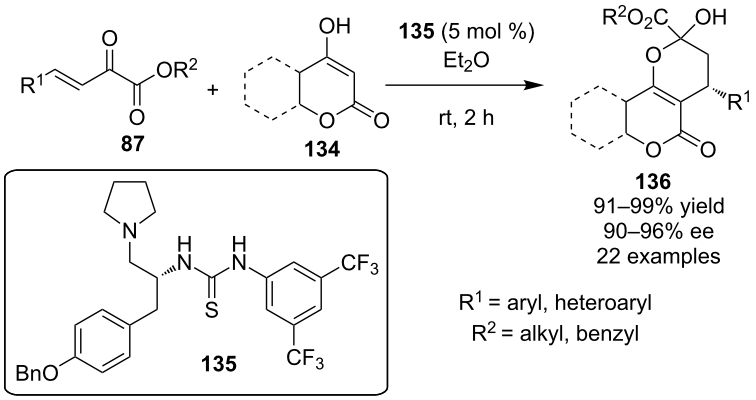
In 2010, a domino Michael hemiacetalization reaction was reported between cyclic 1,3-dicarbonyl compounds **134** and β-unsaturated α-ketoesters **87** utilizing a novel tyrosine-derived thiourea **135** (Scheme 43) [63].



Scheme 41: Asymmetric synthesis of spiro[4-cyclohexanone-1,3'-oxindoline] **126** [61].



Scheme 42: Kinetic resolution of 3-nitro-2*H*-chromene **130** [62].



Scheme 43: Asymmetric synthesis of chromanes **136** [63].

In 2010 and 2011, Wang demonstrated that the versatile β-unsaturated α-ketoesters **87** are capable of participating in multiple cascades, initiated by Michael addition of preformed stable enols **137** and **138**. As a result, this methodology provided a highly efficient route to coumarins **139** and napthoquinone derivatives **140** in excellent yields and selectivities (Scheme 44) [64,65]. In both cases, a bifunctional activation of substrates was proposed by the authors.

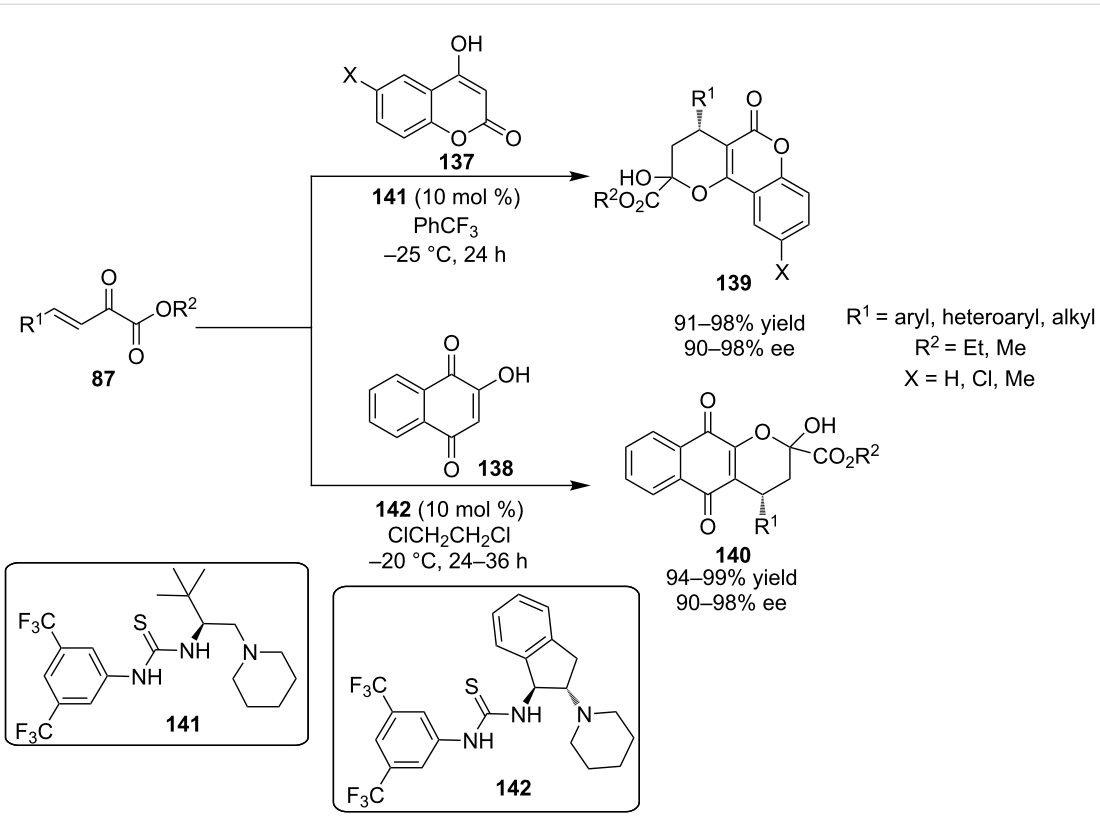
In 2011, Yan and co-workers reported the organocatalytic cascade Michael hemiketalization, using the same versatile reagent, β-unsaturated α-ketoester **87**, and 4,4,4-trifluoroacetoacetate **143** to produce trifluoromethyl-substituted dihydropyrans **144** (Scheme 45) [66]. The process is catalyzed by the bifunctional cinchonine-derived thiourea **57**. A number of substrates were presented and the methodology is tolerant to many functional groups.

The same year Zhao, Zhu and co-workers developed a new class of thiourea organocatalyst **145** bearing a trifluoromethyl group. The combination of this group and phenylalanine provided an efficient catalyst for the domino reaction between ethyl 4,4,4-trifluoro-3-oxobutanoate **146** and β-unsaturated α-ketoesters **87** (Scheme 46) [67]. A wide range of products were obtained in moderate to good yields and excellent selectivities following this methodology.

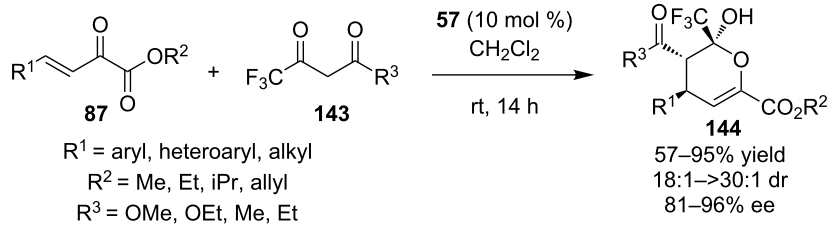
The same year Zhao and co-workers reported a similar type reaction (organocatalytic cascade Michael hemiketalization) between 3-oxo-phenylpropanenitrile **118** and (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** catalyzed by bifunctional thiourea (*R*)-**120** producing α-trichloromethyldihydropyrans **149** (Scheme 47) [68]. Utilizing a quite low catalyst loading (2 mol %), good yields and selectivities were achieved.

In 2011, Lee and co-workers disclosed the enantioselective synthesis of 3,4-dihydrocoumarins **150** bearing an all-carbon spiro-quaternary stereocenter utilizing Takemoto's organocatalyst **77** (Scheme 48) [69]. The domino process is initiated by a Michael addition followed by acetalization, and subsequent PCC oxidation in an one-pot transformation.

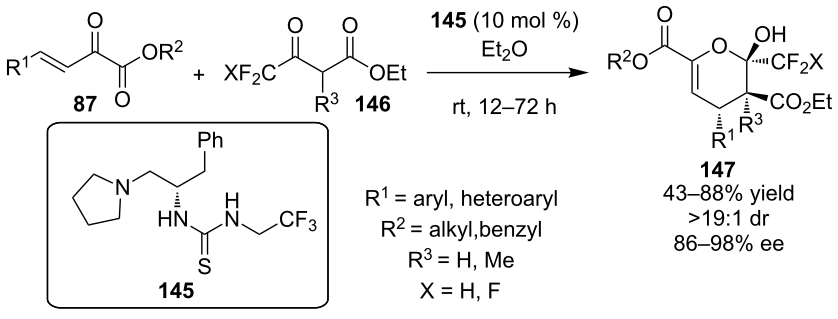
In 2012, Enders and co-workers described the three-component domino Michael–Michael aldol reaction between β-ketoesters **153**, nitroalkenes **77** and α,β-unsaturated aldehydes **154**, producing heavily substituted cyclohexanes **155** containing



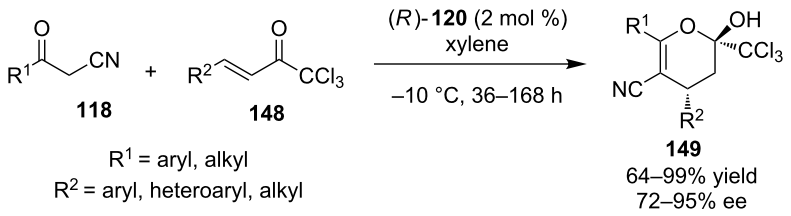
Scheme 44: Wang's utilization of β-unsaturated α-ketoesters **87** [64,65].



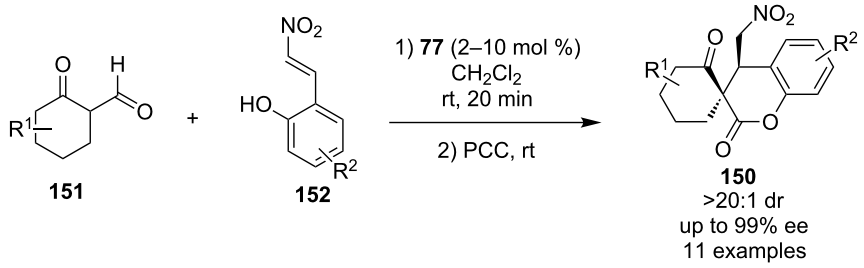
Scheme 45: Asymmetric entry to trifluoromethyl-substituted dihydropyrans **144** [66].



Scheme 46: Phenylalanine-derived thiourea-catalyzed domino Michael hemiaketalization reaction [67].



Scheme 47: Asymmetric synthesis of α-trichloromethyldihydropyrans **149** [68].



Scheme 48: Takemoto's thiourea-catalyzed domino Michael hemiaketalization reaction [69].

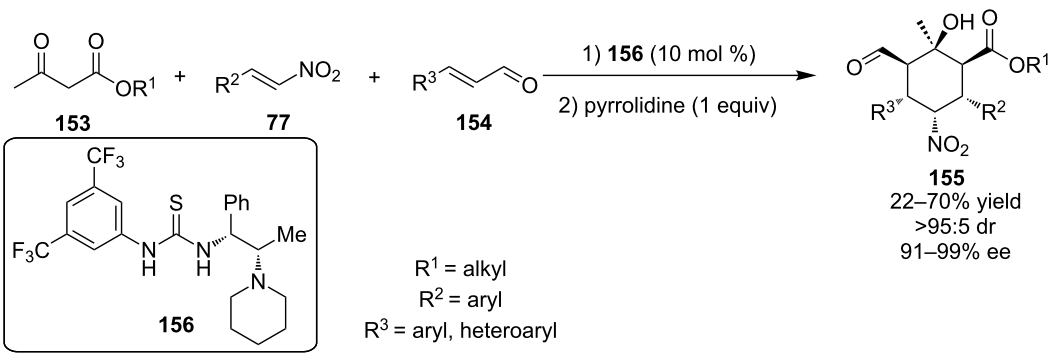
six contiguous stereocenters with excellent stereocontrol (Scheme 49) [70]. In order to complete the cascade, the authors employed a bifunctional thiourea **156** and pyrrolidine in an one-pot protocol. Overall, the reaction proceeded smoothly and the products were obtained in moderate to good yields (up to 70%), but in excellent selectivities (>95:5 dr and up to 99% ee).

Recently, Liang, Xu and co-workers developed a domino process in order to construct polysubstituted chromeno[4,3-*b*]pyrrolidine derivatives **157**, utilizing a bifunctional organocatalyst **57** (Scheme 50) [71]. The transformation is quite powerful, utilizing under mild conditions and a very low catalyst loading. The transformation is initiated by a Michael addition of **158** to alkylidene azlactone **159**, followed by a Mannich reaction and finally transesterification.

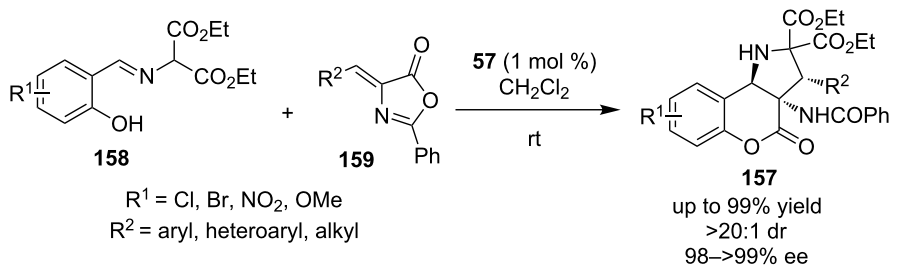
The same year, Yuan and co-workers reported the double Michael reaction between **160** and alkylidene azlactone **161** to produce the spiro-fused cyclohexanone/5-oxazolone scaffolds **162** (Scheme 51) [72]. A broad range of both reagents were well tolerated, producing the desired product in moderate to high yields (up to 93%) and diastereoselectivities (up to 99:1 dr) and moderate to good enantioselectivities.

Cascade/domino/tandem reactions producing six-membered rings initiated by oxy/aza/sulfa-Michael addition

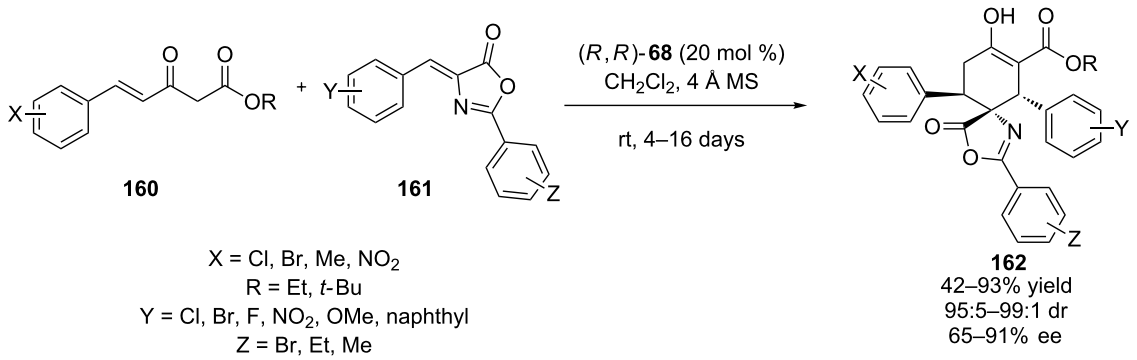
In 2007, Wang and co-workers utilized 2-mercaptobenzaldehydes **163** and α,β-unsaturated systems as Michael acceptors, such as α,β-unsaturated oxazolidinones **164** and maleimides **52**, in order to catalyze Michael aldol cascades to construct versa-



Scheme 49: Asymmetric synthesis of densely substituted cyclohexanes [70].



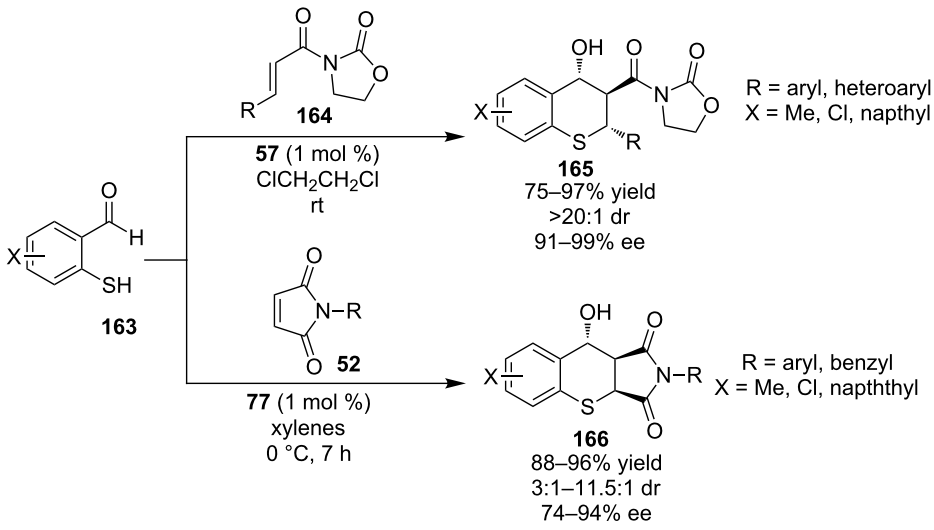
Scheme 50: Enantioselective synthesis of polysubstituted chromeno [4,3-*b*]pyrrolidine derivatines **157** [71].



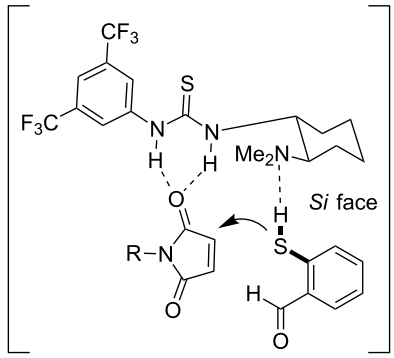
Scheme 51: Enantioselective synthesis of spiro-fused cyclohexanone/5-oxazolone scaffolds **162** [72].

tile benzothiopyrans derivatives **165** and **166** (Scheme 52) [73,74]. The reactions operate through a sulfa-Michael aldol mechanism. Those transformations are useful because they produce products containing three contiguous stereocenters in high yields and excellent stereoselectivities utilizing only 1 mol % catalyst loading.

The authors proposed a bifunctional mode of activation. More specifically, the thiourea moiety activates the maleimide through hydrogen-bonding and the tertiary amine recognizes the thiol group, again through hydrogen-bonding, and orients the thiol attacking from the *Si*-face of the maleimides **52** (Scheme 53).



Scheme 52: Utilizing 2-mercaptobenzaldehydes **163** in cascade processes [73,74].

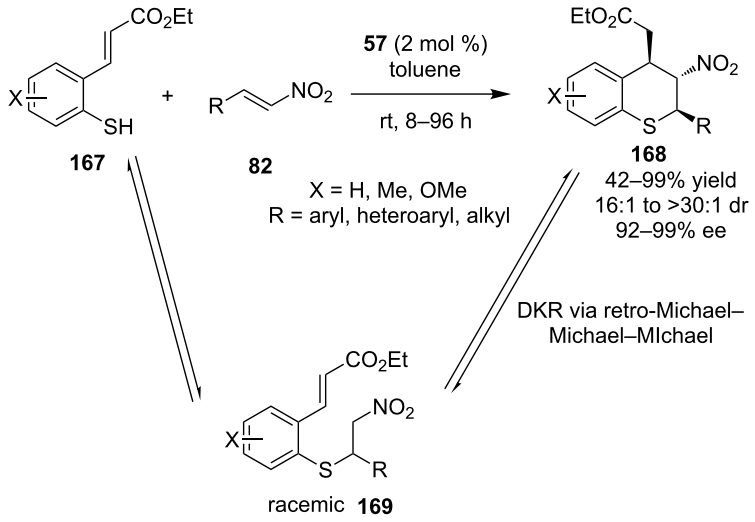


Scheme 53: Proposed transition state of the initial sulfa-Michael step [74].

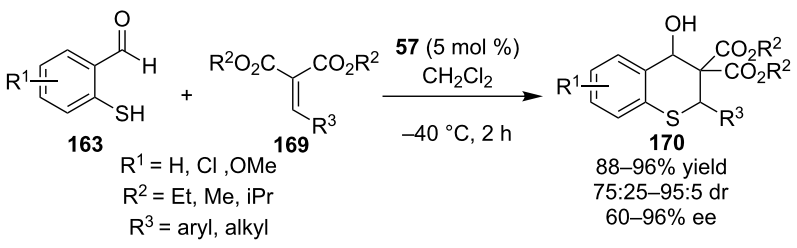
In 2008, Wang and co-workers described a very interesting Michael–Michael cascade of *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl esters **167** and nitroalkenes **82** to produce thiochromane derivatives **168** catalyzed by the bifunctional thiourea **57** (Scheme 54) [75]. The reaction proceeded smoothly for a wide range of substrates with high stereoselectivity, that fact is inconsistent with the current literature as the sulfa-Michael reaction is not catalyzed efficiently by this catalyst. In order to explain the high selectivity of the reaction, they proposed a dynamic kinetic resolution (DKR) pathway of a Michael–*retro*-Michael–Michael–Michael reaction.

The same year Zhao and co-workers reported a novel domino Michael–Knoevenagel reaction between 2-mercaptobenzaldehydes **163** and easily accessible Michael acceptors **169** catalyzed by 9-*epi*-aminoquinine thiourea **57** (Scheme 55) [76]. Various adducts were obtained in good to excellent yields (up to 96%) and moderate to excellent selectivities.

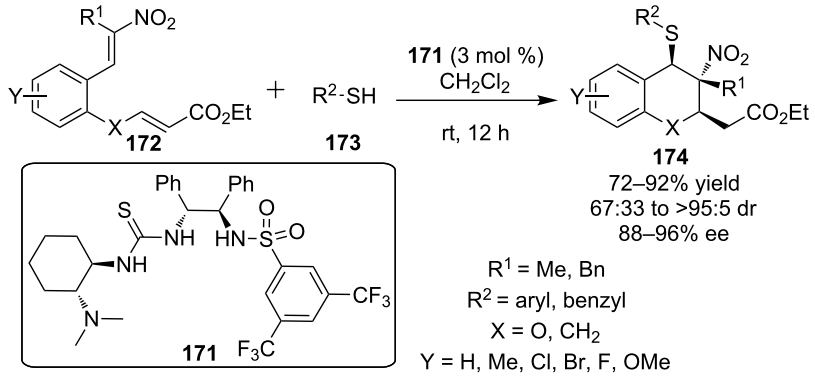
In 2010, Chen, Xiao and co-workers described a domino sulfa-Michael–Michael reaction catalyzed by the novel multifunctional thiourea **171** (Scheme 56) [77]. The cascade is initiated by the addition of thiol **173** to the more electrophilic double bond of **172**, those in conjugation with the nitro group, and subsequent addition of the nitronate to the remaining double bond.



Scheme 54: Asymmetric thiochroman synthesis via dynamic kinetic resolution [75].



Scheme 55: Enantioselective synthesis of thiochromans [76].



Scheme 56: Enantioselective synthesis of chromans and thiochromans synthesis [77].

A wide range of substrates were tested and the desired products **174** were obtained in good to excellent yields (up to 92 %) and selectivities (>95:5 dr and up to 96% ee), employing only 3 mol % catalyst loading. The synthetic utility of the process was further expanded by the multigram version of the reaction utilizing only 0.5 mol % catalyst loading and by the transformations of the adducts into other synthetic intermediates by oxidation either of the nitro group or the thioether group.

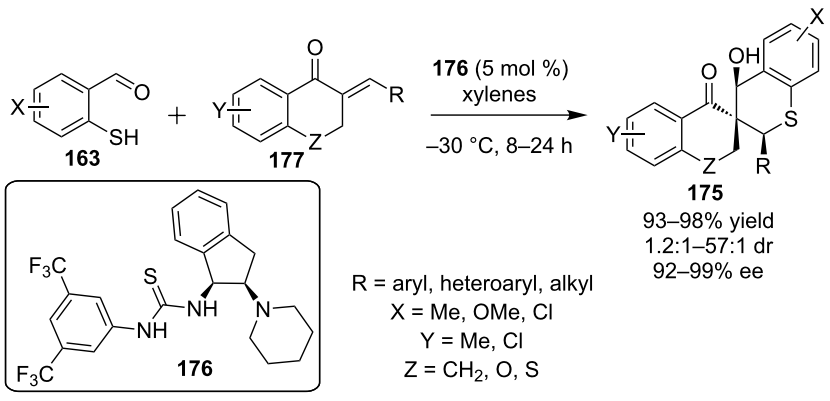
The same year Wang and co-workers reported the enantioselective synthesis of spiro-chromanone-thiochroman compounds **175** catalyzed by a bifunctional indane-based thiourea **176** (Scheme 57) [78]. The cascade is initiated by the sulfa-Michael addition of 2-mercaptobenzaldehyde **163** to the *exo*-α,β-unsaturated ketone **177** and subsequent aldol reaction between the newly-formed enolate and the aldehyde moiety. The desired products were obtained utilizing low catalytic loading (5 mol %) in excellent yields (up to 98%) and enantioselectivities (up to 99% ee), but low to excellent diastereoselectivities (1.2:1–57:1 dr).

In 2011, Chen, Xiao and co-workers, based on their previous work [77], described the aza-Michael–Michael cascade between substituted anilines **178** and nitroolefin enoates **172**, utilizing a bifunctional cinchonine-derived thiourea **57** (Scheme 58) [79]. The reaction proceeds very smoothly for a variety of substrates affording the desired products in excellent yields and selectivities.

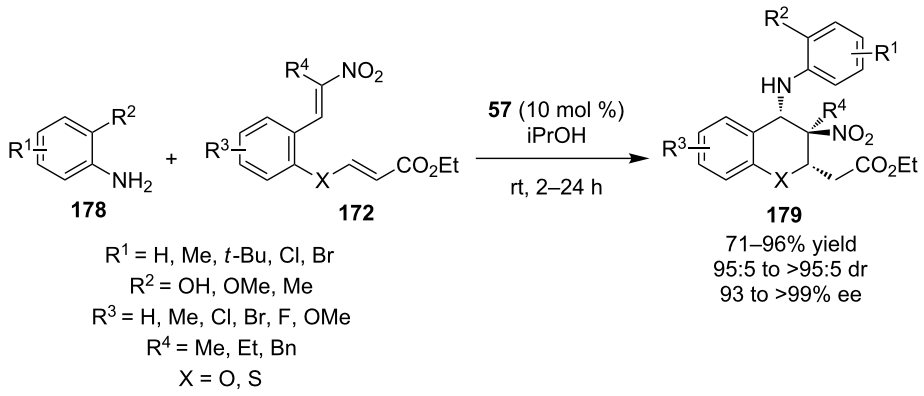
In 2012, Xu and co-workers described an alternative route to highly-functionalized tetrahydroquinolines employing a domino aza-Michael–Michael reaction of substituted anilines **180** and nitroolefin **77** catalyzed by a bifunctional thiourea **181** (Scheme 59) [80]. The combined yields of the products **182** and **183** was good (up to 96%) but the selectivity was moderate.

Miscellaneous cascade/domino/tandem reactions

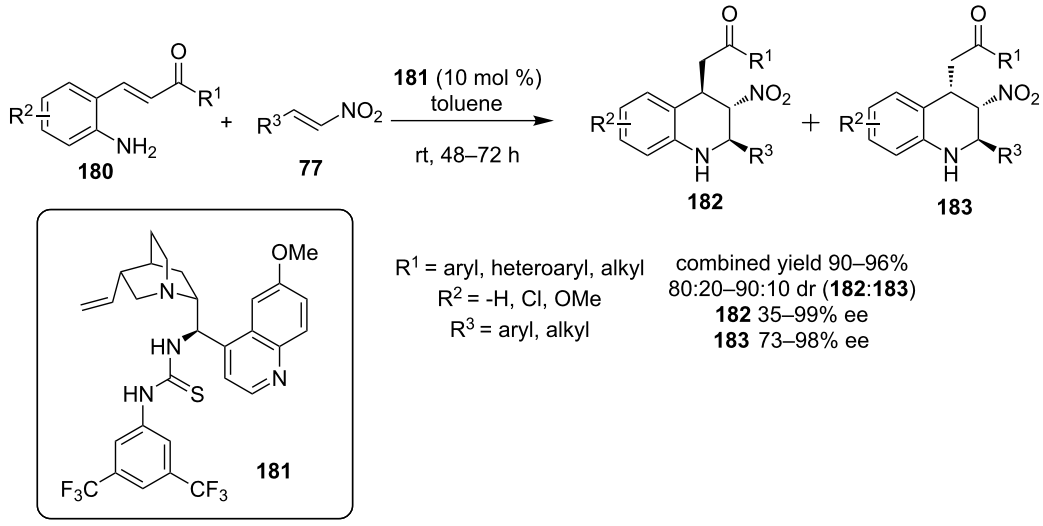
In 2012, Wang and co-workers disclosed a novel domino Mannich–Michael reaction between malonitirile **184** and substituted aromatic imine **185** catalyzed by bifunctional thiourea **88** (Scheme 60) [81]. Many functional groups were tolerated, ob-



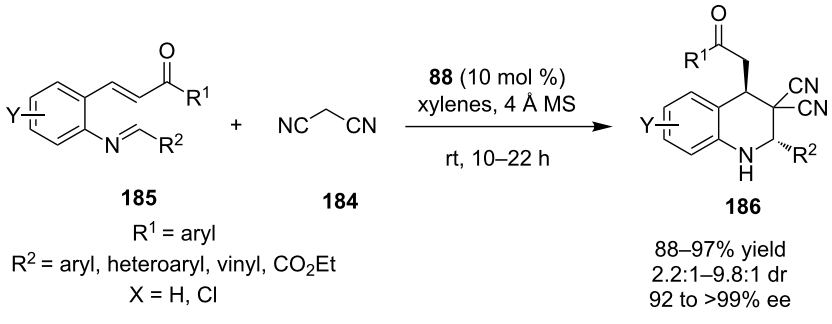
Scheme 57: Enantioselective sulfa-Michael aldol reaction en route to spiro compounds [78].



Scheme 58: Enantioselective synthesis of 4-aminobenzo(thio)pyrans **179** [79].



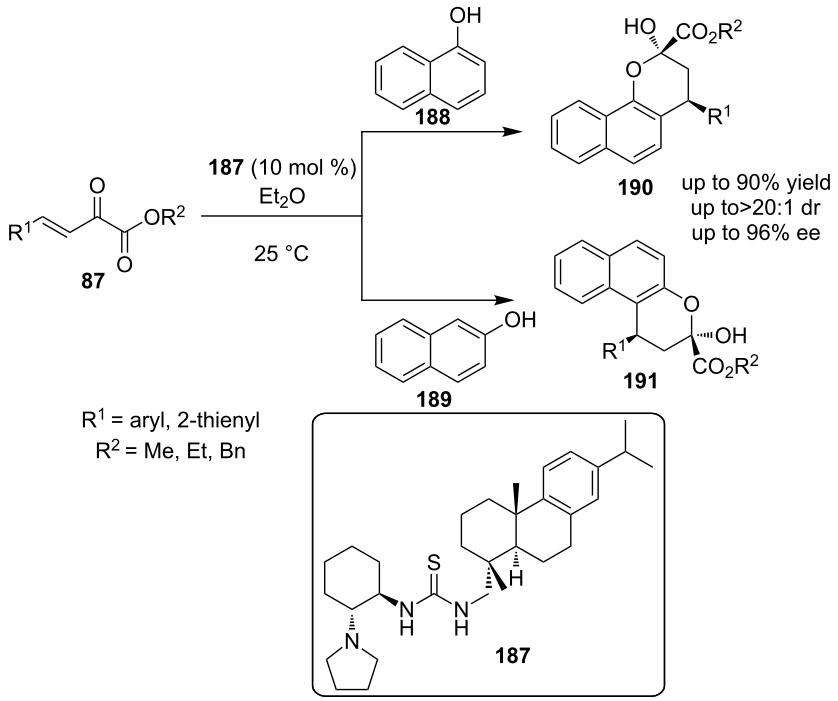
Scheme 59: Asymmetric synthesis of tetrahydroquinolines [80].



Scheme 60: Novel asymmetric Mannich–Michael sequence producing tetrahydroquinolines **186** [81].

taining the desired densely functionalized tetrahydroquinolines **186**. Additional mechanistic studies by the authors strongly suggest the Mannich–Michael pathway instead of the more "reasonable" Michael–Mannich pathway.

In 2012, Wang and co-workers reported a novel domino Friedel–Crafts alkylation (via conjugate addition)-hemiacetalization catalyzed by rosin-derived tertiary amine-thiourea **187** (Scheme 61) [82]. Reagent **87** was successfully combined with

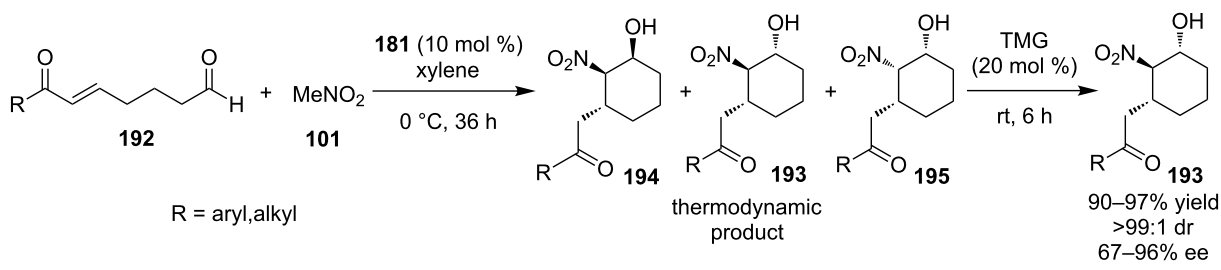


Scheme 61: Enantioselective synthesis of biologically interesting chromanes **190** and **191** [82].

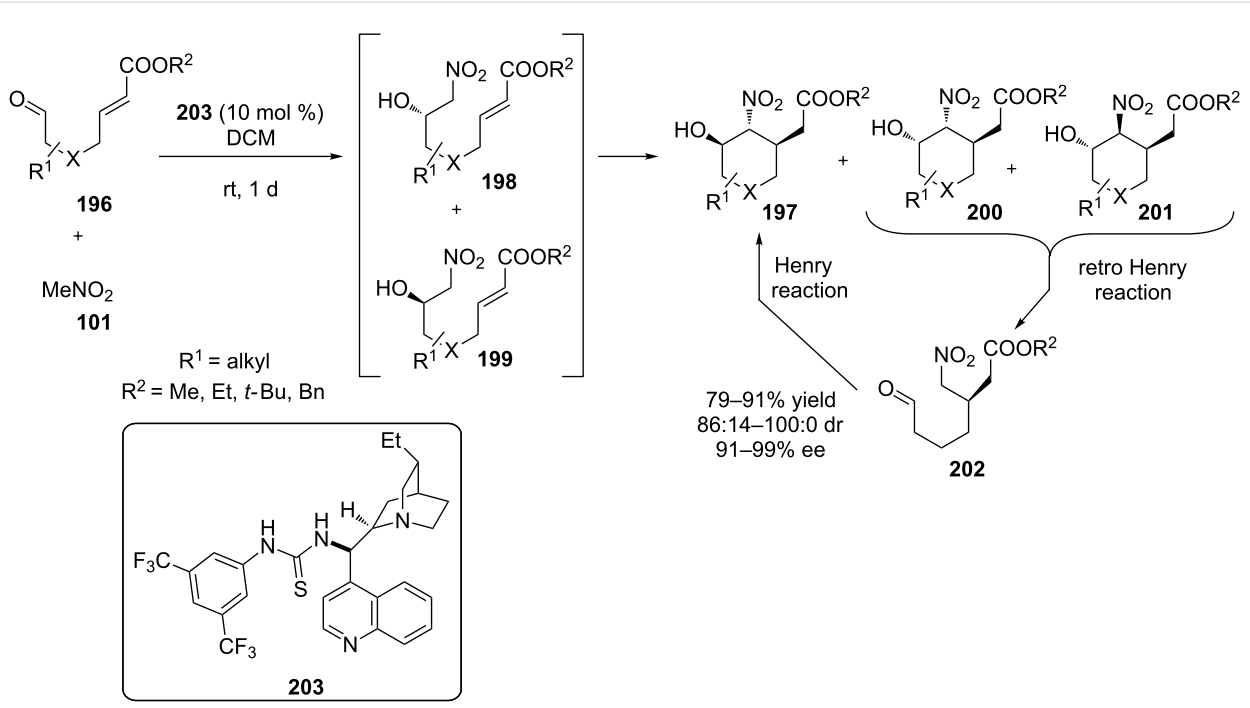
nucleophilic naphthols **188** and **189** to produce medicinally interesting chromane derivates **190** and **191** respectively.

Zhao and co-workers employed the bifunctional cinchona-derived thiourea **181** to catalyze the tandem Henry–Michael reaction of nitromethane (**101**) to the enal **192**, but the reaction resulted in three diastereoisomers (Scheme 62) [83]. With this in hand, they envisioned the interconversion of the kinetic products to the most stable product. In order to achieve that, they designed an one-pot two-step process, where upon completion of the tandem Henry–Michael reaction, TMG catalyzed the epimerization to the sole product **193**. Their postulation is based on the fact that Henry reactions are typically reversible, so **194** and **195** could be involved in a retro-Henry and subsequent diastereoselective Henry reaction, where the stereochemical outcome is inducted by the C_2 stereochemistry. This is further supported by some additional mechanistic experiments they conducted. The substrate scope was also examined and the nature of the R group does not affect the outcome of the reaction, as the reaction proceeds smoothly with excellent selectivity.

In 2013, Quintavalla and co-workers disclosed an interesting Henry–Michael–retro-Henry–Henry domino cascade to furnish substituted cyclohexanes with three adjacent stereocenters [84]. A wide range of aldehydes **196** were tested, obtaining the desired products **197** in good yields and good stereoselectivities (Scheme 63). The process follows an interesting mechanism, proposed by the authors, supported by experimental data. The initial Henry reaction provides the two nitro alcohols **198**, **199** as a mixture of low optical purity. Subsequent Michael addition provides **197**, **200** and **201**. Compounds **200** and **201**



Scheme 62: Asymmetric tandem Henry–Michael reaction [83].



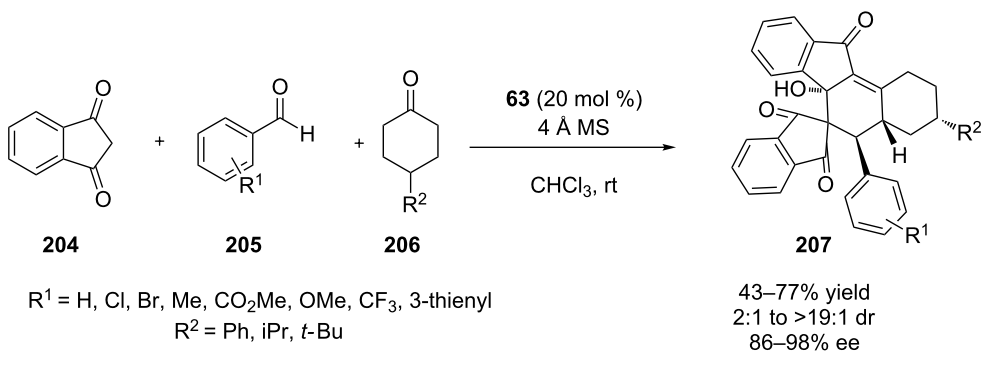
Scheme 63: An asymmetric synthesis of substituted cyclohexanes via a dynamic kinetic resolution [84].

equilibrate to **197** via a retro-Henry reaction to **202**, followed by a Henry ring closure.

In 2015, Chen and co-workers envisaged a three-component organo-cascade quadruple reaction, that yielded highly functionalized polycarbocycles [85]. The authors utilized multiple aromatic aldehydes **205** and some 4-substituted cyclohexanones **206**, affording the desired products **207** in good yield and stereoselectivity, given the high molecular complexity that is being achieved in one step (Scheme 64). The researchers suggested that diketone **204** and benzaldehyde **205** reacts through Knoevenagel condensation, to produce 2-arylidene-1,3-indanediones, which is subsequently attacked by the enolate of cyclohexanone. Two subsequent aldol reactions furnished the desired product.

Miscellaneous thiourea-catalysts and catalytic systems promoting asymmetric transformations that lead to a six-membered ring

The discovery of L-proline as an organocatalyst for the aldol reaction was of major importance and therefore many asymmetric reactions that could not be achieved, are now possible. There are many reactions catalyzed by L-proline, affording stereoselective products in high yields and enantiomeric excess, nevertheless there are many limitations. For that reason, it has emerged the need for the synthesis of new molecules that would

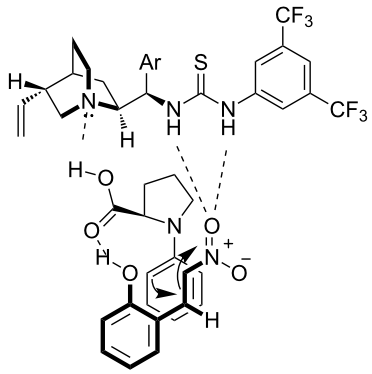


Scheme 64: Three component-organocascade initiated by Knoevenagel reaction [85].

have the same reactivity with L-proline in catalyzed asymmetric reactions and better properties.

The combination of proline with other molecules to provide a catalytic system was exploited by Ramachary and co-workers in an enamine-based Michael reaction between 2-(2-nitrovinyl)phenol (**208**) and cyclohexanone (**209**, Scheme 65) [86]. When that reaction has been performed under the "regular" conditions for a Michael reaction, product **210** has been obtained in low yields. To overcome this problem, catalysts **57** and **211** were combined and the reaction goes through a more rigid pre-TS assembly. Reduction of the hemiacetal **210**, afforded product **212** in 90% yield and >99% ee.

A mechanism for the above reaction, where the *s-cis* enamine attacks the electrophilic double bond of 2-hydroxynitrostyrene, was proposed (Scheme 66).

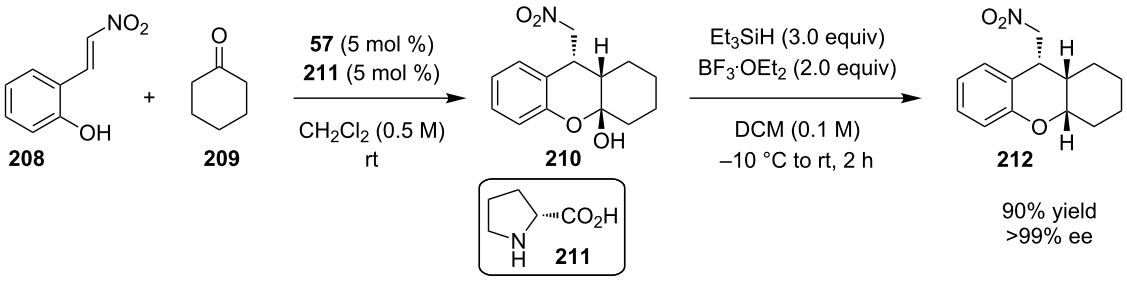


Scheme 66: Proposed mechanism for the asymmetric Michael reaction catalyzed by catalysts **57** and **211** [86].

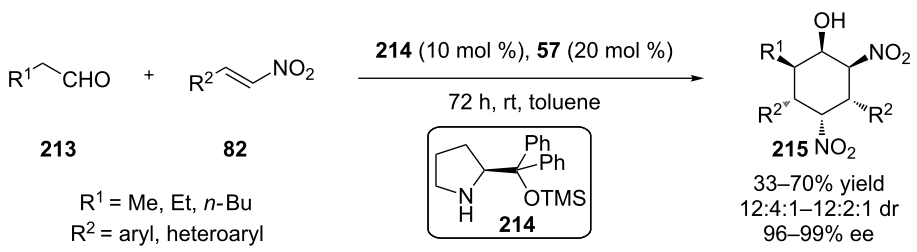
In 2012, Wang and co-workers developed a dual organocatalyst catalytic system, en route to hexasubstituted hexanes, utilizing some aldehydes **213** and a wide range of nitroolefins **82** [87]. The products were obtained in good yields and good to excellent stereoselectivities (Scheme 67).

The researchers proposed that the diaryl silyl prolinol **214** condenses with the aldehyde to form the corresponding enamine, that in turn reacts with the nitroolefin to produce the Michael adduct **216**. **216** is being deprotonated by the chiral thiourea to afford a nucleophilic nitronate, which attacks the nitroolefin. Subsequent Henry reaction afforded the desired product (Scheme 68).

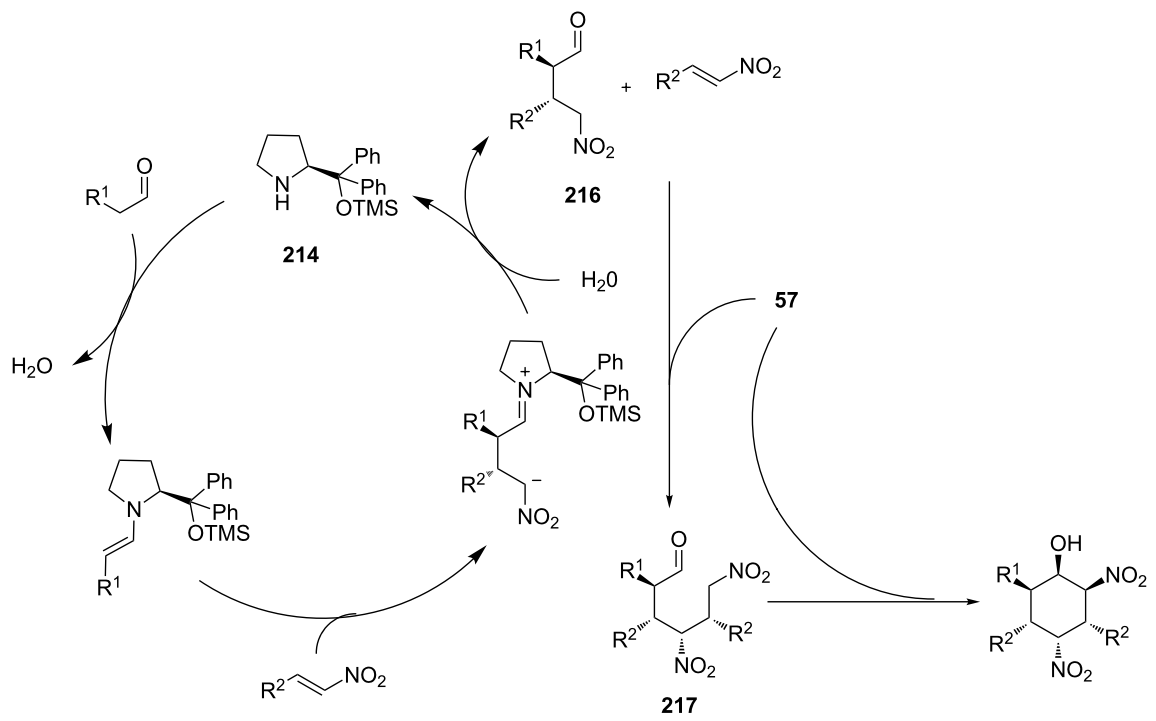
Among the same lines, Zhou, Li and co-workers reported a cascade process affording six-membered spiro-cyclic oxindoles with five adjacent stereocenters. The authors proposed that the reaction proceeds via an asymmetric Michael–Michael aldol sequence (Scheme 69) [88]. In this protocol, when a different derivative of L-diphenylprolinol is used, a different diastereomer of the product is obtained. When along with *N*-Boc-substituted oxindole **18**, substituted derived nitro-alkene **82** and substi-



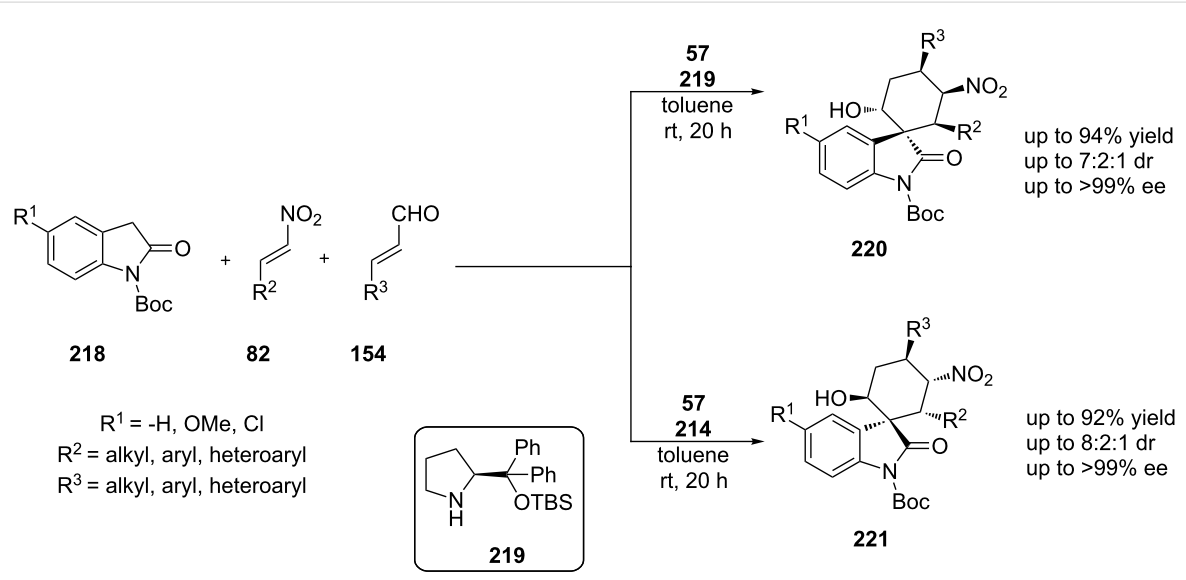
Scheme 65: Asymmetric Michael reaction catalyzed by catalysts **57** and **211** [86].



Scheme 67: Asymmetric facile synthesis of hexasubstituted cyclohexanes [87].



Scheme 68: Dual activation catalytic mechanism [87].



Scheme 69: Asymmetric Michael–Michael/aldol reaction catalyzed by catalysts **57**, **219** and **214** [88].

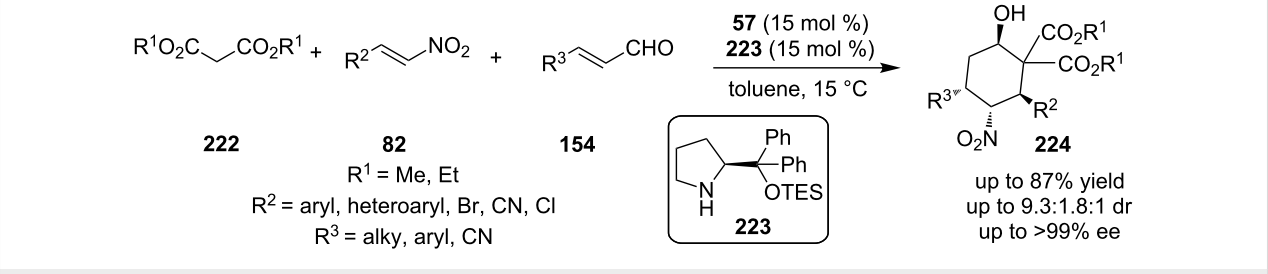
tuted unsaturated aldehyde **154**, a bifunctional quinine-derived thiourea **57** and L-diphenylprolinol-*tert*-butylsilyl ether **219** were used, the substituted *N*-Boc-substituted spiro-oxindoles **220** were obtained. This domino Michael–Michael aldol reaction provides the product in an excellent 94% yield, excellent enantiomeric excess (>99%) and good diastereoselectivity (7:2:1). Utilizing organocatalyst **57** with another derivative of **220**, organocatalyst **214**, another diastereomer was obtained of the desired product **221** (Scheme 69). This domino Michael–Michael aldol reaction provides the product in an excellent 92% yield, excellent enantiomeric excess (>99%) and good diastereoselectivity (9:2.5:1).

Dixon, Xu and co-workers described a three-compound reaction between dialkyl malonate **222**, nitro-alkene **82** and substituted enal **154**, catalyzed by the chiral quinine-derived thiourea **57** and organocatalyst **223**, affording product **224** with a substituted cyclohexane-ring core (Scheme 70) [89]. The experimental results of this reaction were excellent with a 54% yield, 3.1:1:1 dr and >99% ee. The proposed mechanism, begins with an activation of the malonate **222** and the nitro-alkene **82**, so a stereoselective Michael addition occurs. Thus, the formed adduct, through an iminium catalysis pathway caused by catalyst **223**, reacts with the unsaturated aldehyde and affords a pre-aldol substrate. Finally, under basic conditions, an aldol reaction is taking place and gives the final desired substituted cyclohexane.

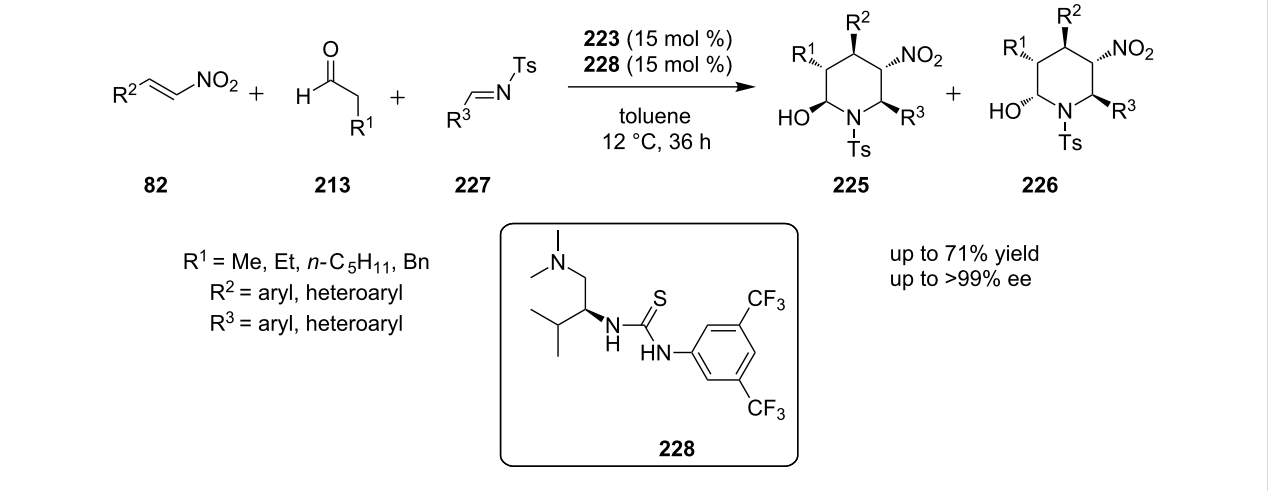
In a similar manner, the same group reported the synthesis of substituted piperidines **225** and **226** through a multiple organocatalytic activation of the substrates which are nitro-alkene **82**, aldehyde **213** and a substituted *(E)*-tosylimine **227** (Scheme 71) [90]. This catalytic reaction gives the product in a good yield and an excellent enantiomeric excess. The proposed mechanism of this reaction starts when catalyst **223** activates aldehyde **213**, through the formation of the corresponding enamine. Then, the enamine reacts with nitro-alkene **82**, which is activated by hydrogen bonding due to catalyst **228**. Thus, the formed intermediate can now participate to a nitro-Mannich reaction, affording a *N*-protected aminoaldehyde product. Finally, the *N*-protected aminoaldehyde product can now be cyclized under the reactions' conditions.

Another stereoselective reaction was attempted by Kotsuki's group presenting an organocatalytic hetero-Diels–Alder reaction between isatin **229** with substituted diene **230**. High pressure had to be employed in order to obtain spiro-dihydropyranoxindole derivatives **231** in good to excellent yields, using catalyst **232** (Scheme 72) [91]. The mechanistic studies showed that the 3,5-bis(trifluoromethyl)phenyl group was an essential component of the thiourea catalyst. After the optimization of the reaction conditions the yields of products **231** were 71–91%.

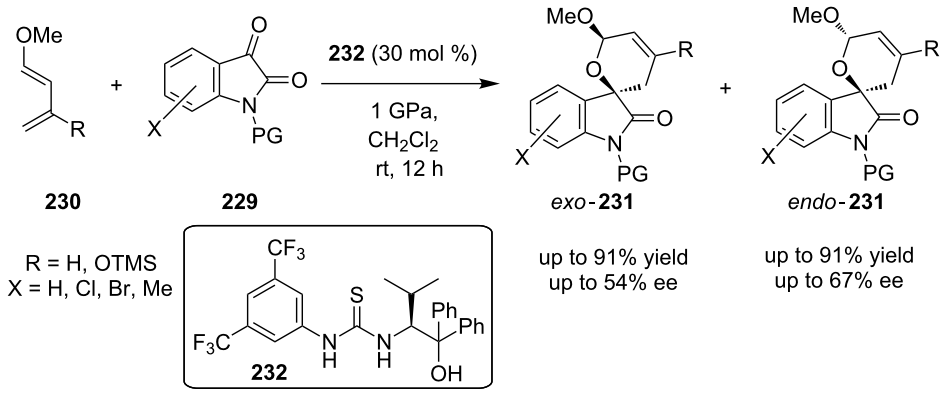
Barbas and co-workers reported the synthesis of carbazole spiro-oxindole derivatives, in a Diels–Alder reaction in very short reaction time (10 min). The reagents were the substituted indoles **233,** benzylidene oxindolinones **234** and the organocata-



Scheme 70: Asymmetric synthesis of substituted cyclohexane derivatives, using catalysts **57** and **223** [89].



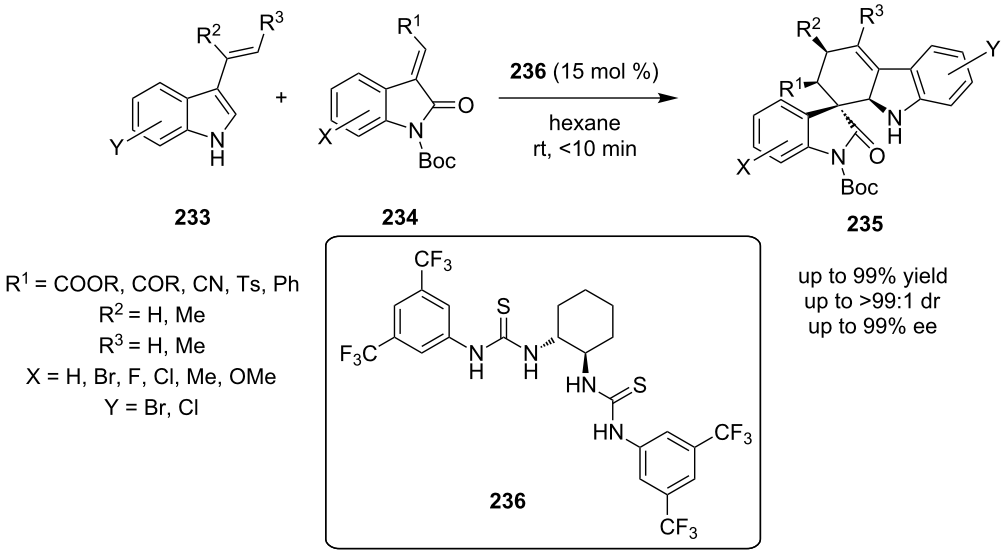
Scheme 71: Asymmetric synthesis of substituted piperidine derivatives, using catalysts **223** and **228** [90].



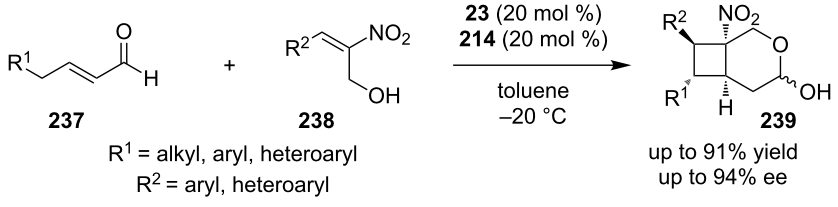
Scheme 72: Asymmetric synthesis of *endo-exo* spiro-dihydropyran-oxindole derivatives catalyzed by catalyst **232** [91].

lyst, a C_2-symmetric bis-thiourea **235** was employed to yield product **236** (Scheme 73) [92]. Suprisingly, a single diastereoisomer was isolated, despite the fact that four new chiral centers were produced. The products were obtained in high yields (75–99%) and ee values 88–99%. The biggest advantage of this reaction is that it can be transferred to large-scale chemical production, due to the difference in the solubilities of the reactants and the products, which means the product and the catalyst can be isolated separately.

In 2012, Carrillo and co-workers reported an enantioselective formal [2 + 2] cycloaddition of enals **237** with nitroalkenes **238** to obtain the oxabicyclo product **239** (Scheme 74) [93]. A combination of catalysts was used, with catalysts **23** and **214**. This



Scheme 73: Asymmetric synthesis of carbazole spiroxindole derivatives, using catalyst **236** [92].



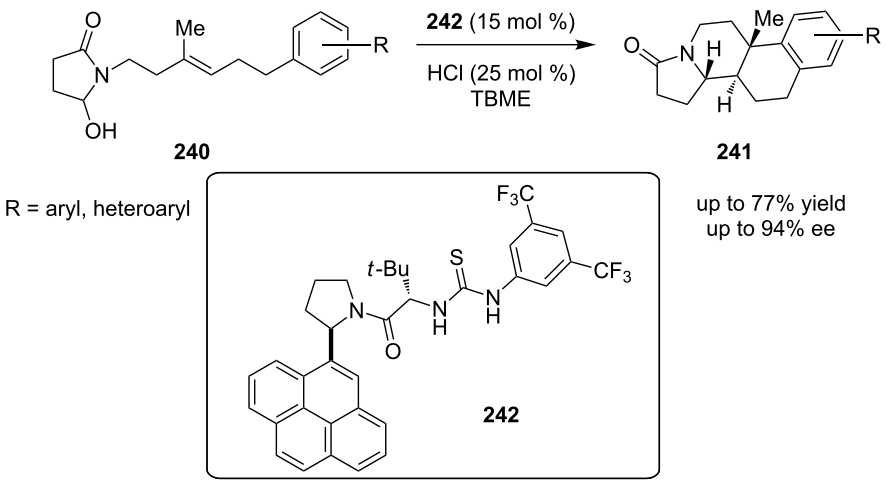
Scheme 74: Enantioselective formal [2 + 2] cycloaddition of enal **209** with nitroalkene **210**, using catalysts **23** and **214** [93].

reaction affords the desired product in 38–91% yield and 85–95% ee.

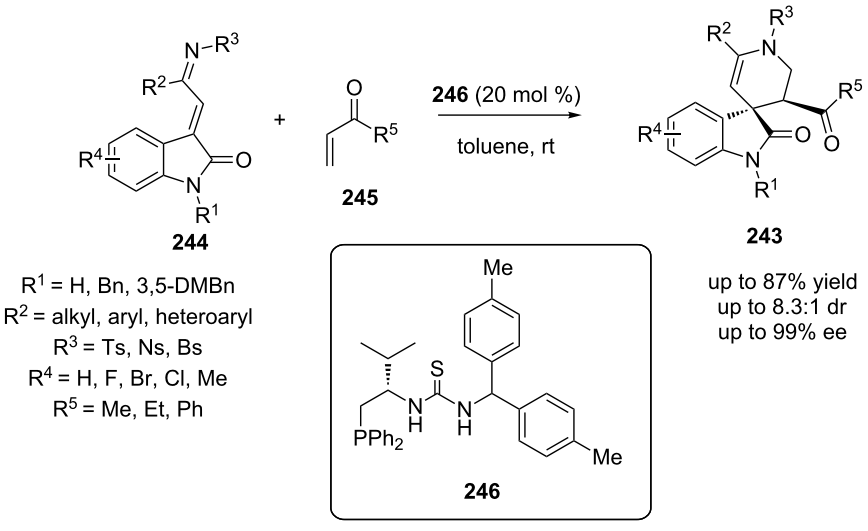
Furthermore, a thiourea catalyzed reaction via a cationic polycyclization of hydroxylactams **240** leads to the corresponding polycyclized products **241**, using organocatalyst **242** (Scheme 75) [94]. The authors postulated that the existence of an extended aromatic framework on the catalyst is very crucial, as the delocalized π-electron system interacts with the *N*-acyliminium ion intermediate through a stabilizing cation–π-interaction. They came to this conclusion, after an extensive catalyst screening.

In 2014, Shi and co-workers presented the synthesis of products **243**, utilizing substrates **244** and α,β-unsaturated aldehyde **245**. Chiral phosphine organocatalyst **246** was employed as the catalyst (Scheme 76) [95]. Product **243** was obtained in high yield (85%), high ee values (up to 99%) and high diastereoselectivity (8.1:1).

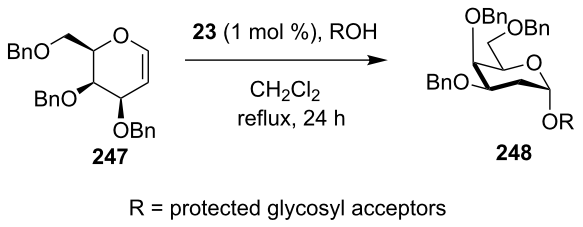
In 2012, an interesting α-selective approach for the synthesis of galactopyranoses using achiral thiourea organocatalyst **20**, was reported from McGarrigle, Galan and co-workers (Scheme 77) [96]. In this reaction the reagent is 2,3,4-trisubstituted dihydropyran **247** and the product is the corresponding α-galactopyra-



Scheme 75: Asymmetric synthesis of polycyclized hydroxylactams derivatives, using catalyst **242** [94].



Scheme 76: Asymmetric synthesis of product **243**, using catalyst **246** [95].



Scheme 77: Formation of the α-stereoselective acetals **248** from the corresponding enol ether **247**, using catalyst **23** [96].

nose **248**. This reaction provides exclusively the α-diastereomer in a yield up to 98%.

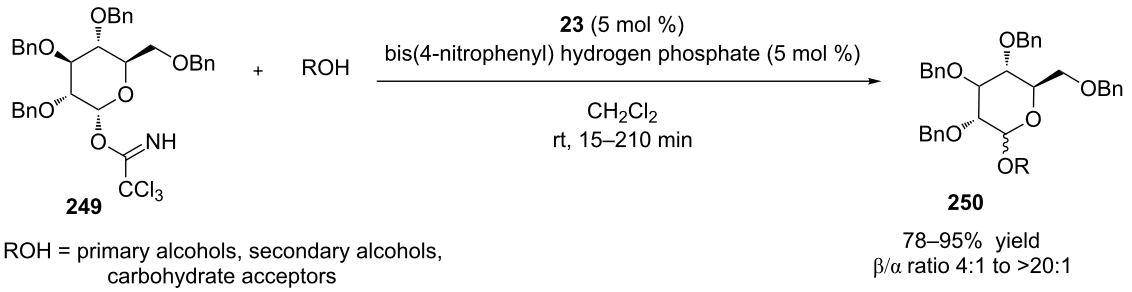
In 2013, Schmidt and co-workers described the use of Shreiner's thiourea as a catalyst in glycosidation with *O*-glycosyl trichloroacetamides as glycosyl donors [97]. α-D-glucopyranosyl trichloroacetimidate **249** was employed as a donor, several alcohols were utilized, achieving moderate to excellent anomeric selectivity (Scheme 78). Other *O*-glycosyl donors were tested, giving similar results.

Conclusion

Throughout this review, efficient ways of activating both substrates by interactions via hydrogen bonds, derived from thiourea moieties, were presented. Reactions providing enantiopure products were shown to be catalyzed by primary, secondary and tertiary chiral amine-thioureas, or a combination of catalysts. Products were obtained in one-pot or step-economic domino processes, achieving high increase of molecular complexity in step-economy transformations. There is no doubt that this scientific field will grow in the near future, providing more efficient ways of constructing six-membered rings.

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Scheme 78: Selective glycosidation, catalyzed by Shreiner's catalyst **23** [97].

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The aminoindanol core as a key scaffold in bifunctional organocatalysts

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Review

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Abstract

The 1,2-aminoindanol scaffold has been found to be very efficient, enhancing the enantioselectivity when present in organocatalysts. This may be explained by its ability to induce a bifunctional activation of the substrates involved in the reaction. Thus, it is easy to find hydrogen-bonding organocatalysts ((thio)ureas, squaramides, quinolinium thioamide, etc.) in the literature containing this favored structural core. They have been successfully employed in reactions such as Friedel–Crafts alkylation, Michael addition, Diels–Alder and aza-Henry reactions. However, the 1,2-aminoindanol core incorporated into proline derivatives has been scarcely explored. Herein, the most representative and illustrative examples are compiled and this review will be mainly focused on the cases where the aminoindanol moiety confers bifunctionality to the organocatalysts.

Introduction

The structural and chemical properties of the 1,2-aminoindanol scaffold **1** have transformed aminoindanol derivatives into versatile building blocks for the construction of catalysts and the efficient induction of chirality in asymmetric processes (Figure 1). Some examples of these properties are rigidity, disposition of the two stereogenic centers, ability of the hydroxy and amino groups to coordinate to some metals or to act as hydrogen-bond donors/acceptors, the different catalytic activity of these chemical groups and their possible derivatization. Thus, in the last decade, it has been widely employed in the field of asymmetric catalysis. Regarding the use of aminoindanol derivatives as ligands in organometallic catalytic complexes, the results have been outstanding. Examples are found in (a) the vanadium-catalyzed asymmetric oxidation of disulfides and sulfides, which are involved in the synthesis of ligands and pharmaceutical chiral synthetic precursors [1,2] and in (b) the transfer-hydrogenation reaction catalyzed by bifunctional chiral ruthenium complexes, employed in the synthesis of peptide

mimics with an interesting trifluoroethylamine moiety [3-5]. However, it is in the field of asymmetric organocatalysis [6-8] where the aminoindanol core has gained more importance, being a recurrent structural motif in several organocatalytic species. Some examples are (a) the enantioselective reduction of ketones through the in situ formation of catalytically active oxazaborolidines using *cis*-1,2-aminoindanol derivatives [9,10] and (b) the synthesis of more active cooperative thiourea-urea-based organocatalysts, which employ the aminoindanol framework as structural linker between two hydrogen-bond-donor moieties [11]. The latter ones have exhibited efficient catalytic activity in the asymmetric Mannich reaction. In fact, the use of simple *trans*-(1*R*,2*R*)-aminoindanol (**1c**) as an efficient organocatalyst in the enantioselective synthesis of natural products as the TMC-954 core [12,13], has been recently reported. These examples show the high catalytic potential that this versatile motif exhibits [14].

The concept of bifunctionality has been extensively explored in organocatalysis in the last decade [15,16]. The bifunctional organocatalyst contains two chemical groups that interact simultaneously with the substrates. This mode of activation increases the efficiency of the process, since the interactions favor a selective approach of the reactants. In the transition state, the chiral and rigid aminoindanol scaffold can be involved in different interactions with the substrates due to its capacity to interact through the hydroxy and amino groups. Although the aminoindanol scaffold appears in the structure of different catalysts (providing a suitable way to induce chirality), it is not always directly involved in the bifunctional activation of the substrates [17]. Herein, we show only those cases where the aminoindanol moiety confers bifunctionality to the organocatalysts, interacting with the reactants through both the hydroxy and amino groups.

Review

Bifunctional hydrogen-bonding-based organocatalysts

Most of the examples of bifunctional aminoindanol-containing organocatalysts present in literature correspond to catalysts acting through hydrogen bonding, such as thiourea, urea, squaramide, and thioamide frameworks. These have been efficiently employed in a few organocatalytic processes such as Friedel–Crafts alkylations, Michael additions, Diels–Alder reactions and aza-Henry reactions, as discussed below.

Friedel–Crafts-type alkylation reaction of indoles

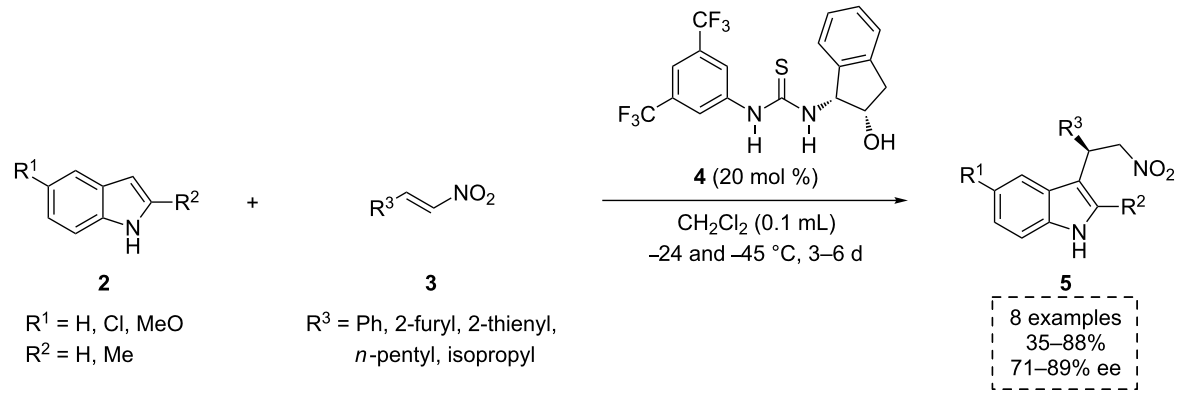
To the best of our knowledge, the first example of an aminoindanol-containing bifunctional organocatalyst was reported by Ricci and co-workers in 2005 [18]. In this pioneering study, the authors used the easily prepared *cis*-(1*R*,2*S*)-aminoindanol-based thiourea derivative **4** to develop the first organocatalytic enantioselective Friedel–Crafts (F–C) alkylation of indoles, employing nitroalkenes as versatile electrophiles. In the presence of catalyst **4**, the differently functionalized indole derivatives **2** reacted with aryl and alkyl nitroalkenes **3** in dichloromethane at low temperature. This afforded the optically active 2-indolyl-1-nitro compounds **5** (up to 88% yield and up to 89% ee, Scheme 1). These products were found to be valuable synthetic precursors of biologically active compounds such as tryptamines [19,20] and 1,2,3,4-tetrahydro-β-carbolines [21].

In order to explain the sense of the asymmetric induction observed in the reaction, some experiments with structurally modified catalysts (**4'** and **4''**) were carried out. The results obtained using indole (**2a**) and β-nitrostyrene (**3a**) supported the importance of the hydroxy group, since low yield and selectivity were observed when this group was trimethylsylilated (**4'**) or was not present (**4''**) in the catalytic structure (Figure 2). Moreover, poor selectivity was also observed using *N*-methylindole, which supported a plausible catalyst–substrate interaction through the indolic proton.

The authors proposed then a dual role of catalyst **4** in the activation of the substrates. Thus, in the transition state **TS1** (Figure 3a), the substrates and catalyst would form a ternary complex where the thiourea moiety would activate the nitro group of the nitroalkene through hydrogen bonds. Simultaneously, the oxygen atom of the hydroxy group would interact with the NH of the indole by a weak hydrogen bond, driving the attack to the *Si* face of the nitroalkene in a stereocontrolled manner.



Figure 1: Different configurations of 1,2-aminoindanol **1a**–**d**.



Scheme 1: Asymmetric F–C alkylation catalyzed by thiourea **4**.

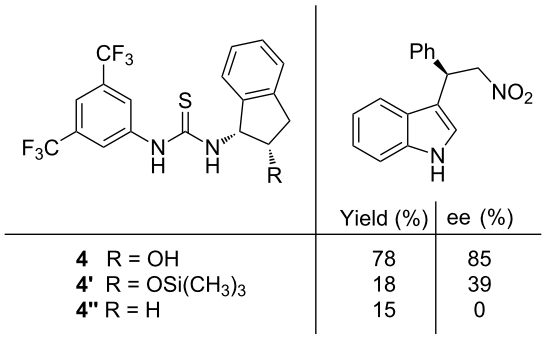


Figure 2: Results for the F–C reaction carried out with catalyst **4** and the structurally modified analogues, **4'** and **4''**.

In a recent study of this F–C alkylation, Herrera's group has provided computational evidence of the reaction pathway, which confirms the proposed bifunctional activation mode played by the thiourea catalyst **4** [22]. Remarkably, an interesting hydrogen-bonding interaction between the hydrogen atom of the hydroxy group and the nitro group was detected in this work (Figure 3b). This could explain the low reactivity (18% yield) and selectivity (39% ee) that the silyl ether-protected catalyst **4''** exhibited (Figure 2).

Encouraged by the development of more efficient organocatalytic systems, the same research group explored the influence of external acidic additives in this reaction. The authors envisioned that a cooperative effect between the chiral thiourea organocatalyst and a Brønsted acid (AH) could provide better results in terms of reactivity and enantioselectivity. Thus, in 2011, they published an article where it was proved that the synergic system between the thiourea *ent*-**4** and mandelic acid led to the final products **5** with a significant increase of conversion and enantiomeric excess (Scheme 2) [23].

Experimental proofs exploring different catalysts and acids suggested that it is the thiourea which provides the sense of the enantioinduction. Therefore, the authors assumed the bifunctional transition state **TS2**, similar to the above mentioned **TS1**, where the external acid (AH) would only coordinate to the thiourea moiety enhancing its acidity and thus forming a more active catalytic species (Figure 4).

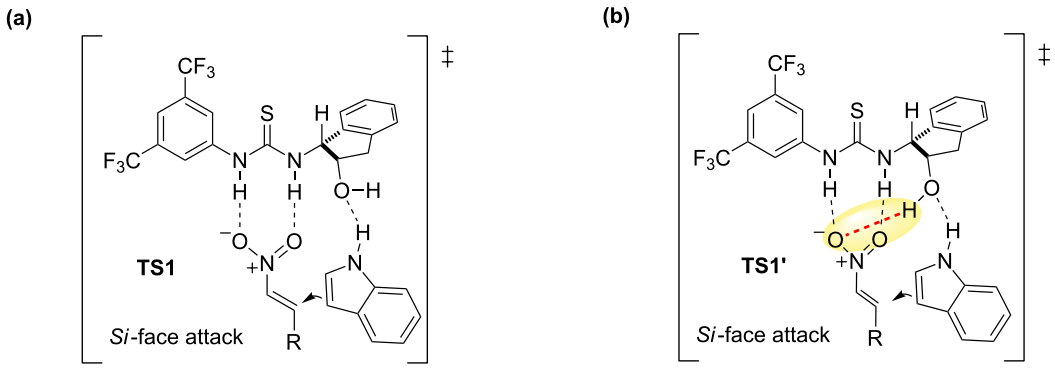
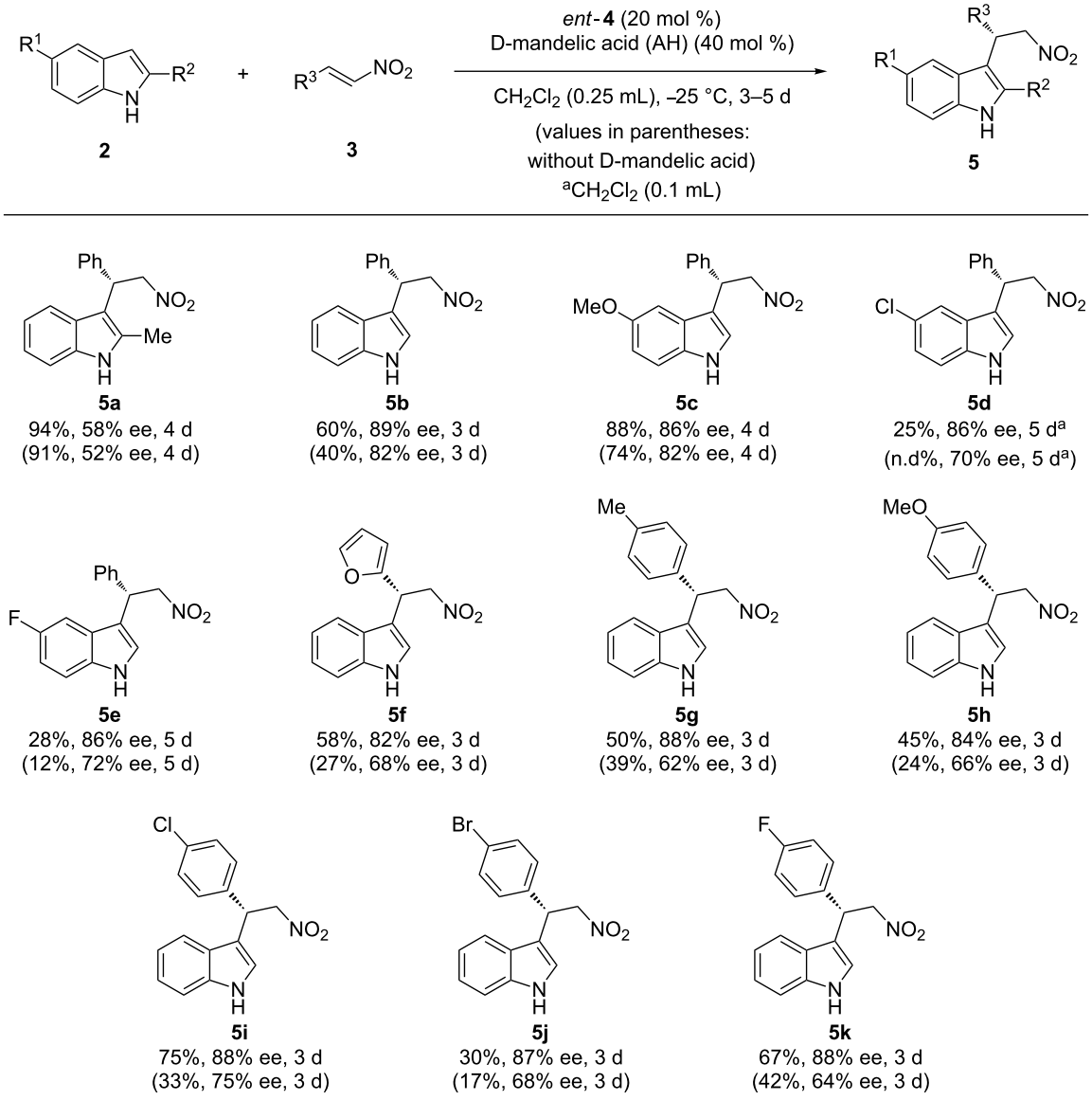


Figure 3: (a) Transition state **TS1** originally proposed for the F–C reaction catalyzed by thiourea **4** [18]. (b) Transition state **TS1'** proposed later, based on computational calculations [22].



Scheme 2: Asymmetric F–C alkylation catalyzed by thiourea *ent*-**4** in the presence of D-mandelic acid as a Brønsted acid additive.

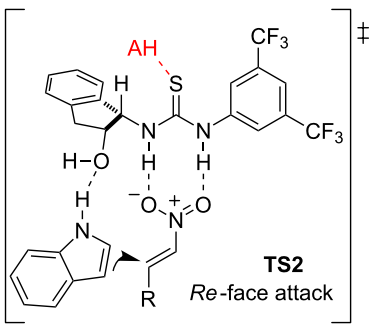


Figure 4: Transition state **TS2** proposed for the activation of the thiourea-based catalyst *ent*-**4** by an external Brønsted acid.

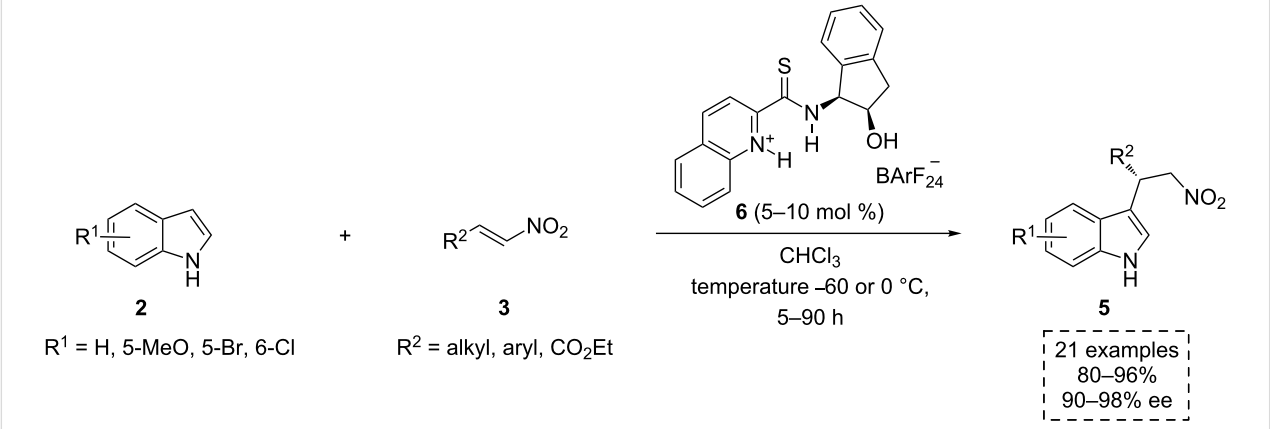
Since the pioneering aminoindanol-containing organocatalyst **4**, reported in 2005 [18], other research groups have studied the possibility of incorporating this scaffold into diverse organocatalysts.

In 2008, Seidel's group published a new example of an asymmetric addition of indoles to nitroalkenes, employing a novel catalyst design [24]. The authors envisioned that a protonated 2-pyridyl substituent could increase the acidity of the thiourea group through an intramolecular N–H···S hydrogen-bonding interaction (analogous to the C–H···S that exists with the 3,5-bis-trifluoromethylphenyl moiety, commonly used in thiourea-based organocatalysts) [25]. Although this first approach did

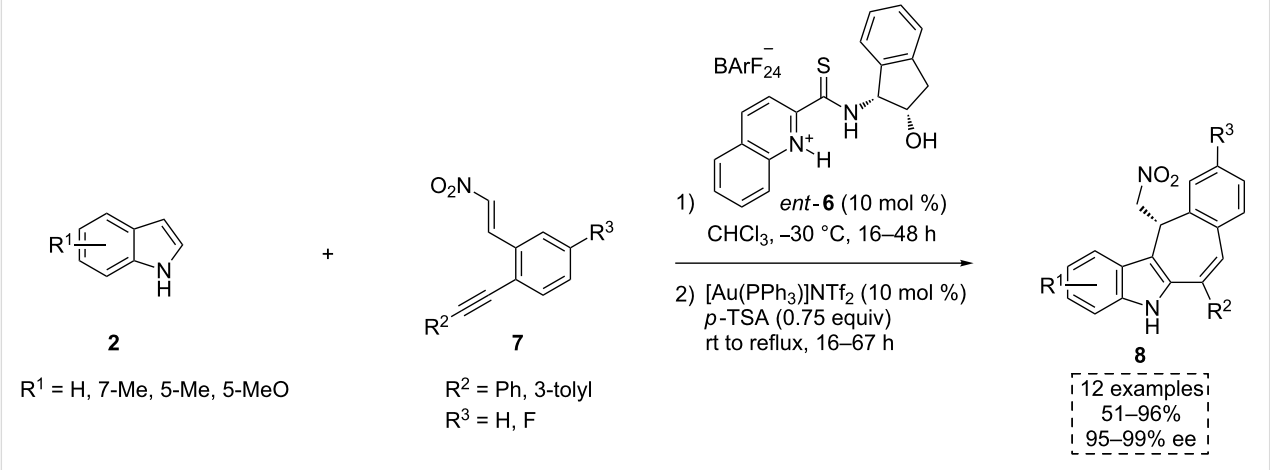
not provide a significant increase of the enantioselectivity, further modifications of the catalytic structure led to highly active catalysts. Indeed, the best results were obtained with the quinolinium thioamide **6**, where the NH moiety adjacent to the pyridine ring of the analogous thiourea was "removed". Likely, in this case, the intramolecular hydrogen-bonding interaction described above would yield a negligible stabilization due to the distance between N–H and S moieties. In contrast, it is suspected that both the thioamide N–H as well as the N–H on the quinolinium moiety are engaged in substrate binding, and thus, provide higher yields and selectivity in comparison with the catalyst **4** (up to 96% yield, up to 98% ee) (Scheme 3).

The authors do not comment on whether the catalyst **6** acts in a bifunctional fashion or not, but it is reasonable to assume that the OH group is again involved in the transition state by a possible interaction with the indole derivatives **2**. Indeed, as discussed below, other authors proposed the compound **6** as a plausible bifunctional catalyst. The Enders' group used its enantiomer (*ent*-**6**) to develop a pioneering scalable one-pot multicatalytic method for the C2/C3-annulation of the indoles **2** (Scheme 4) [26]. In this work, an efficient enantioselective and sequential double Friedel–Crafts alkylation provided direct access to the tetracyclic seven-membered ring containing indoles **8**. These pharmaceutically intriguing compounds exhibit anticancer [27] and antiproliferative activity [28].

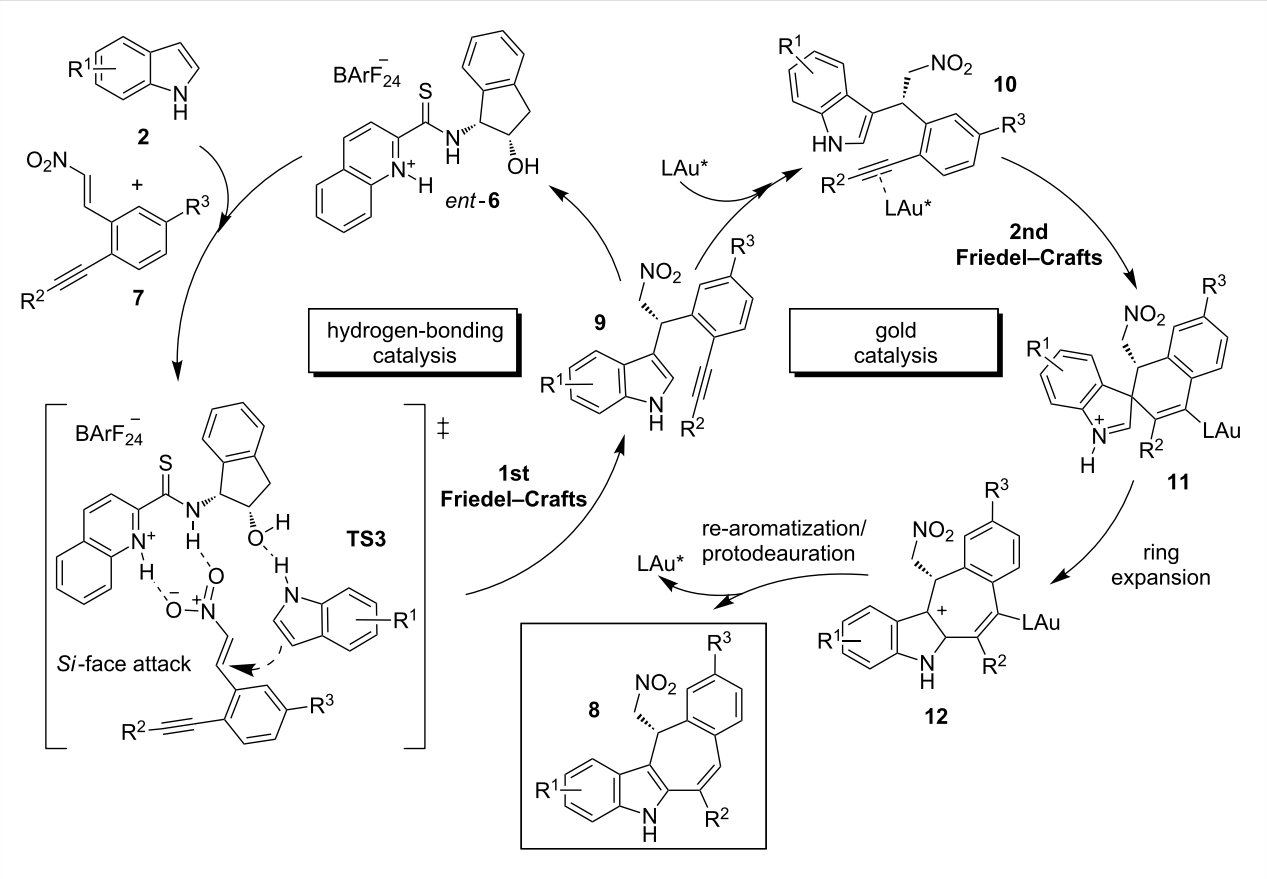
In the first catalytic cycle of the authors' mechanistic hypothesis, the β-nitroalkene derivatives **7** are proposed to react with the indoles **2** in the presence of the organocatalyst *ent*-**6** to afford the intermediates **9** with excellent enantioselectivity (Scheme 5). Furthermore, a bifunctional activation mode through the transition state **TS3** was proposed. Herein, the NH from the thioamide and the protonated quinoline moiety would activate and fix the nitroalkene framework through hydrogen-bonding interactions. Simultaneously, the oxygen atom of the



Scheme 3: Friedel–Crafts alkylation of indoles catalyzed by the chiral thioamide **6**.



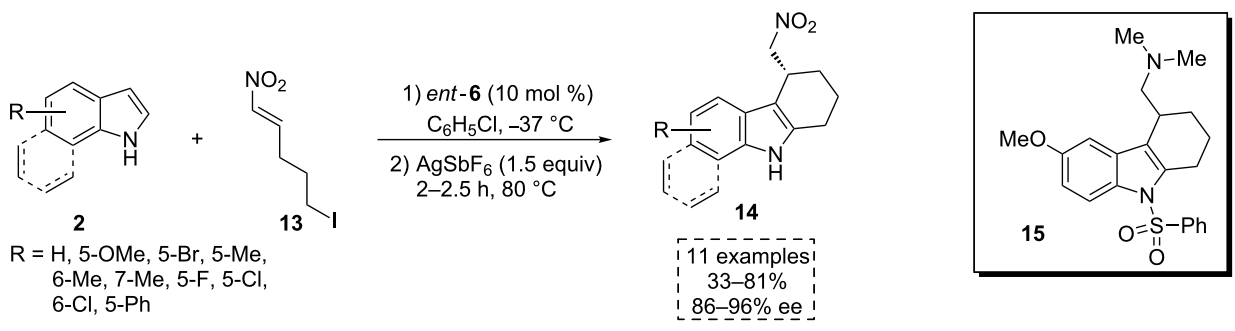
Scheme 4: Scalable tandem C2/C3-annulation of indoles, catalyzed by the thioamide *ent*-**6**.



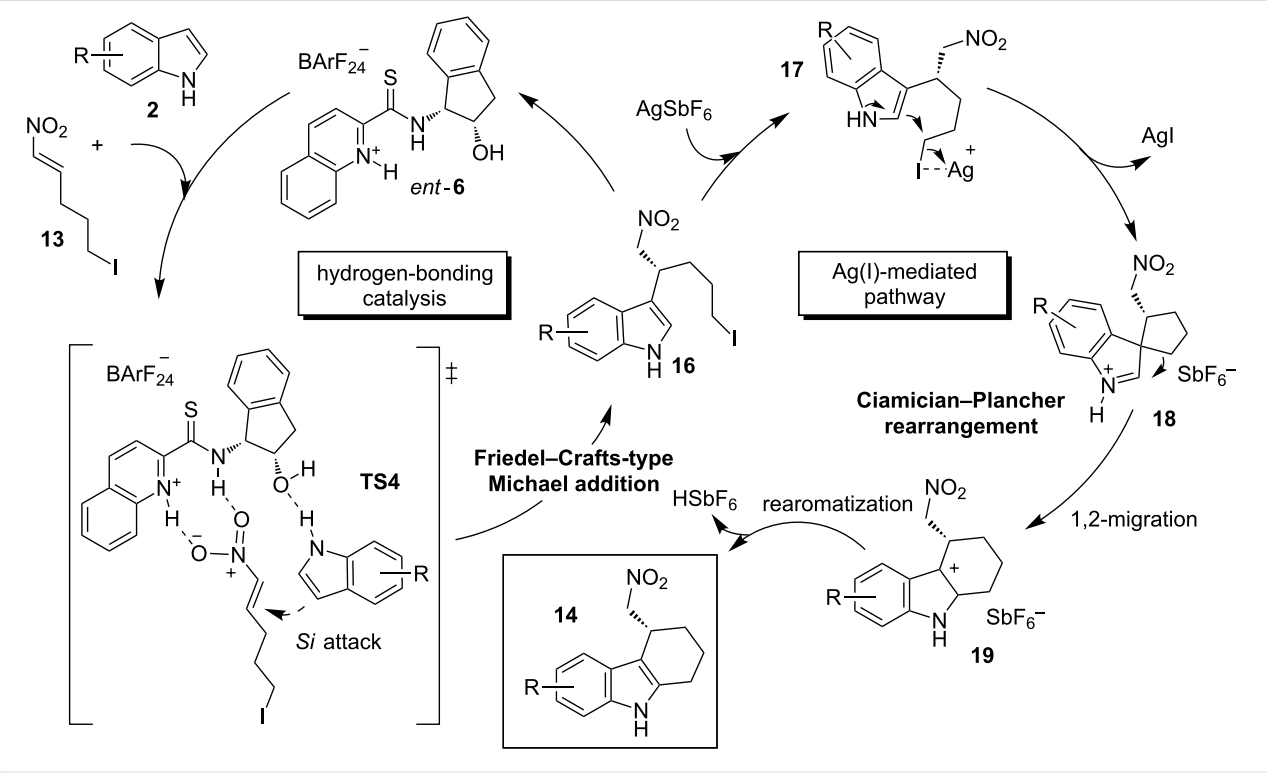
Scheme 5: Plausible tandem process mechanism for the sequential, double Friedel–Crafts alkylation, which involves the hydrogen-bonding catalyst *ent*-**6** and gold catalysis and leads to the tetracyclic indoles **8**.

hydroxy group would orientate the attack of the indole by the *Si* face through the formation of a hydrogen bond with the indolic proton. In the second catalytic cycle, the intermediates **9** would react to give an intramolecular Friedel–Crafts alkylation. The alkyne moiety of **9** would be previously activated by a gold complex in the presence of *p*-toluenesulfonic acid hydrate as the additive. The final tetracyclic indoles **8** are released from the spirocyclic intermediates **11**, following a ring-expansion and rearomatization/final protodeauration cascade process (Scheme 5) [26].

In 2012, the same group reported an additional example of a one-pot multisequence reaction following a similar mode of activation. This method provided a route to access the enantiomerically enriched tetrahydrocarbazole scaffold-containing compounds **14** (Scheme 6 and Scheme 7) [29]. One of these valu-



Scheme 6: One-pot multisequence process that allows the synthesis of interesting compounds **14**. The pharmacologically active compound **15** can be obtained from the properly substituted product **14**.

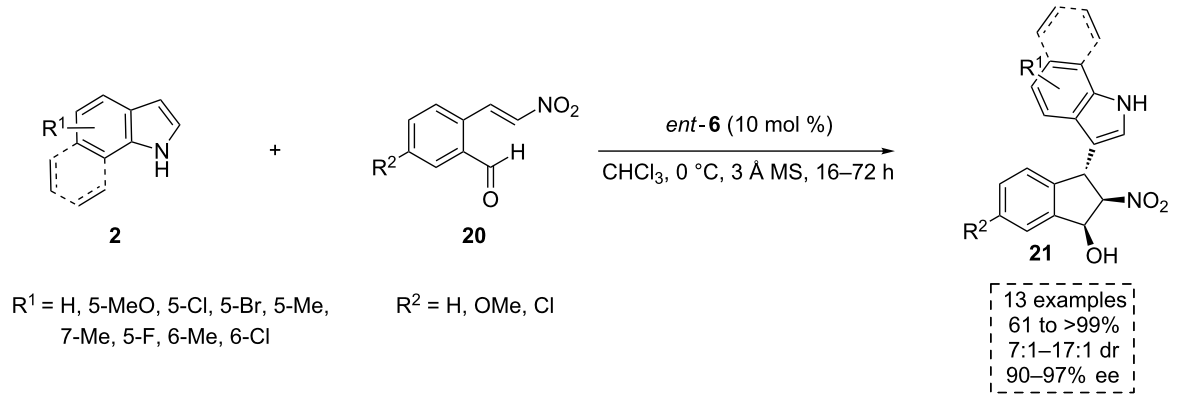


Scheme 7: Reaction pathway proposed for the preparation of the compounds **14**.

able products is a synthetic precursor of the pharmacologically active compound **15**, used to treat Alzheimer and other central nervous system diseases [30-34].

In the proposed reaction pathway, the nucleophilic addition of the indole derivatives **2** to the nitroalkene **13** progresses in a stereocontrolled manner due to the creation of a ternary complex with the chiral bifunctional thioamide *ent*-**6** (**TS4**, Scheme 7). Herein, the catalyst activates both substrates simultaneously through hydrogen-bonding interactions between the thioamidic NH and the nitro group, and between the hydroxy group and the indolic proton. In the presence of $AgSbF_6$, a soft Lewis acid, the stereogenic center-containing intermediates **16** are activated. This triggers an S_N2-type attack/Ciamician–Plancher rearrangement [35]/rearomatization cascade process, affording the final products **14** (Scheme 7).

More recently, the same authors also provided an elegant and efficient solution to give direct access to *cis*-vicinal-substituted indane scaffolds through an organocatalyzed asymmetric domino-Michael addition/Henry reaction (Scheme 8) [36]. These heterocyclic products are important chiral building

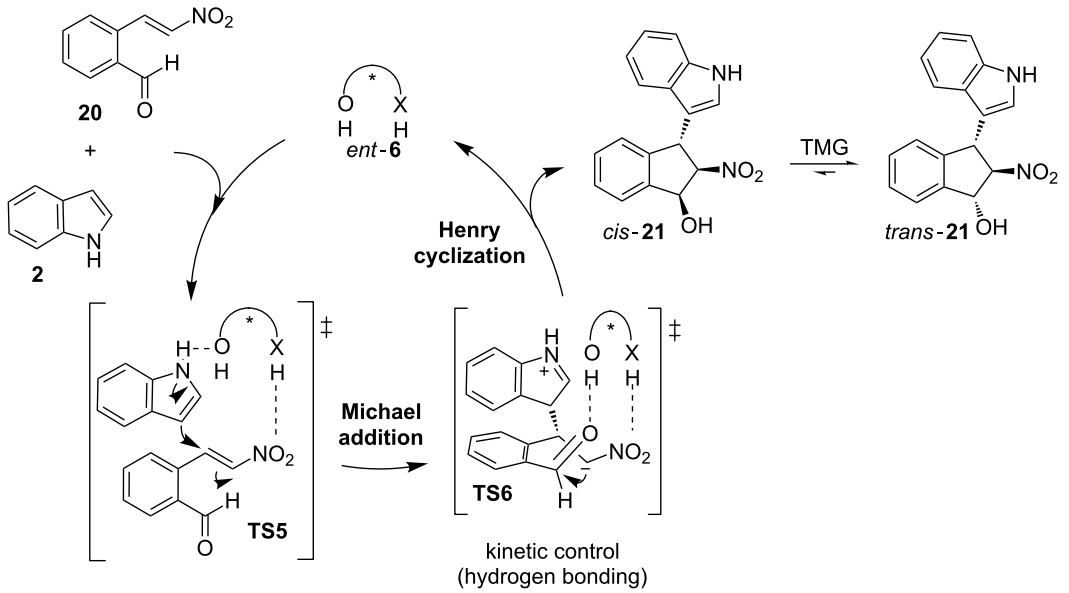


Scheme 8: The enantioselective synthesis of *cis*-vicinal-substituted indane scaffolds **21**, catalyzed by *ent*-**6**.

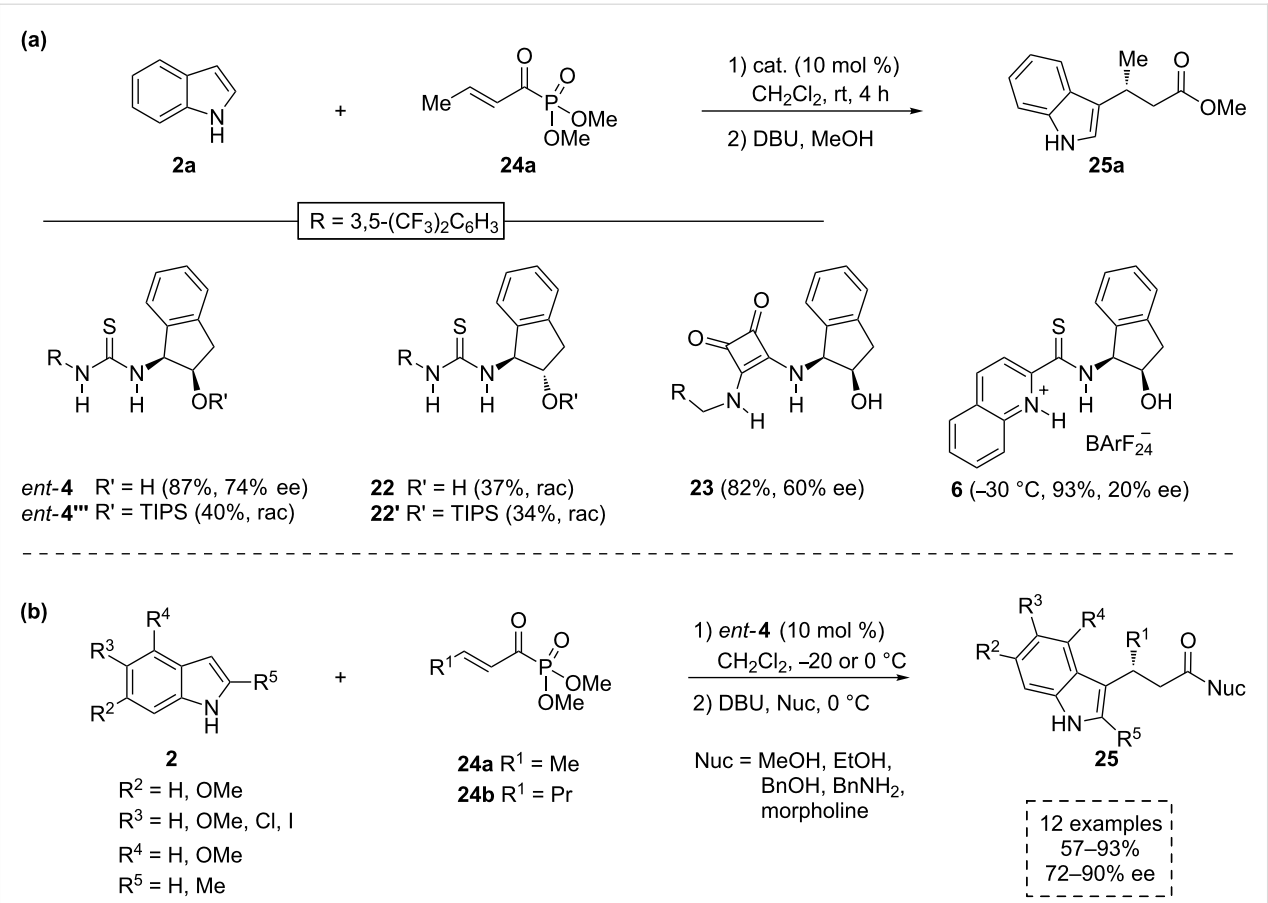
blocks for the synthesis of organocatalytic frameworks and ligands for chiral metal complexes, both with the potential ability to induce chirality. They also belong to a class of privileged pharmaceutical scaffolds and exhibit different biological activities, as it is the case of Crixivan [37,38], an HIV protease inhibitor which has been employed for AIDS treatment. The thermodynamic unfavorable *cis* conformation of these compounds represents a challenge for the development of suitable methods for their synthesis. Interestingly, the chiral thioamide *ent*-**6**, which contains a *cis*-vicinal-substituted indane motif, provided the best choice to this purpose. Therefore, in the presence of such a catalyst, the indole derivatives **2** reacted with 2-(2-nitrovinyl)benzaldehyde derivatives **20** to give the highly functionalized *cis*-1-hydroxy-2-nitroindane-based indole compounds **21** with excellent yield, high selectivity and good diastereomeric ratios (dr) (Scheme 8).

In the reaction pathway proposed to explain this domino reaction, both substrates are activated by the catalyst *ent*-**6** through hydrogen-bonding interactions in a bifunctional manner. Thus, the ternary complex formed in the transition state **TS5** leads to an enantioselective Friedel–Crafts-type Michael addition by the attack of indole **2** to the electrophilic prochiral center on the nitroalkene **20** in a stereocontrolled manner (Scheme 9). Afterwards, the hydrogen-bonding interactions are reorganized inside the complex, producing a bifunctional activation of both the nitro and the aldehyde groups through a *cis*-matched transition state **TS6**. It allows a kinetic controlled, enantioselective Henry reaction that leads to the final *cis*-product **21**. The thermodynamically favorable *trans*-product **21** can be obtained through a tetramethylguanidine (TMG)-catalyzed epimerization process.

Other possible electrophiles have been contemplated in the Friedel–Crafts alkylation of indoles. For instance, Jørgensen's group studied the use of α,β-unsaturated acyl phosphonates as suitable electrophiles for this kind of reaction, using several bifunctional aminoindanol-based organocatalytic scaffolds as catalysts (Scheme 10) [39]. Hence, the authors demonstrated that acyl phosphonates can be used as efficient hydrogen-bonding acceptors in their activation through hydrogen-bonding catalysis. The corresponding final esters or amides are obtained after proper treatment of the reaction mixture. During the screening of catalysts, the best enantioselectivity (74% ee) was obtained using *ent*-**4** in the addition of indole (**2a**) to the acyl phosphonate **24a**, in dichloromethane at room temperature, with subsequent addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and methanol to give the corresponding ester derivative **25a** (Scheme 10a) [39]. The use of the analog squaramide **23** afforded the product with slightly lower selectivity (60% ee) and the Seidel's thioamide **6** provided better activation (93% yield at −30 °C) of substrates but with an important loss of selectivity (20% ee). The removal of a hydrogen atom from the hydroxy group of the aminoindanol structure (such as in TIPS-ether catalysts *ent*-**4'''** and **22'**) and the loss of *cis* relationship between the hydroxy and amino groups (such as in catalyst **22**) led to racemic mixtures (Scheme 10a). Under optimal condi-



Scheme 9: Asymmetric domino procedure (Michael addition/Henry cyclization), catalyzed by the thioamide *ent*-**6** which involves a *cis*-matched transition state (**TS6**) that allows a kinetic control of the second reaction.



Scheme 10: The enantioselective addition of indoles **2** to α,β-unsaturated acyl phosphonates **24**, a) screening of different catalysts and b) optimized conditions using catalyst *ent*-**4**.

tions, the acyl phosphonates **24** reacted with indoles **2** in the presence of catalyst *ent*-**4** providing the corresponding products **25** with high selectivity (up to 90% ee) (Scheme 10b) [39].

Based on the experimental results, the authors proposed a bifunctional mode of activation (**TS7**), where the electrophile is fixed and activated by the thiourea framework through several hydrogen bonds. At the same time, the indole is oriented to attack the *Re* face of the Michael-type acceptor, by weak hydrogen-bonding interaction between the oxygen atom of the hydroxy group and the indolic proton (Figure 5).

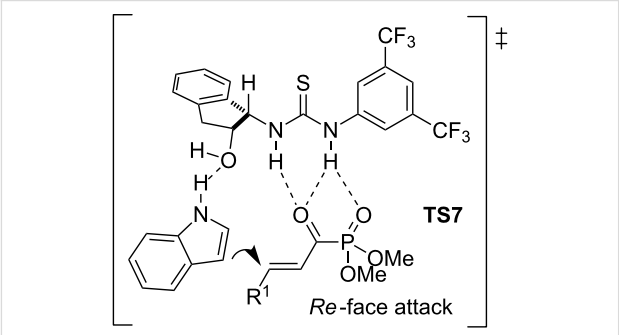
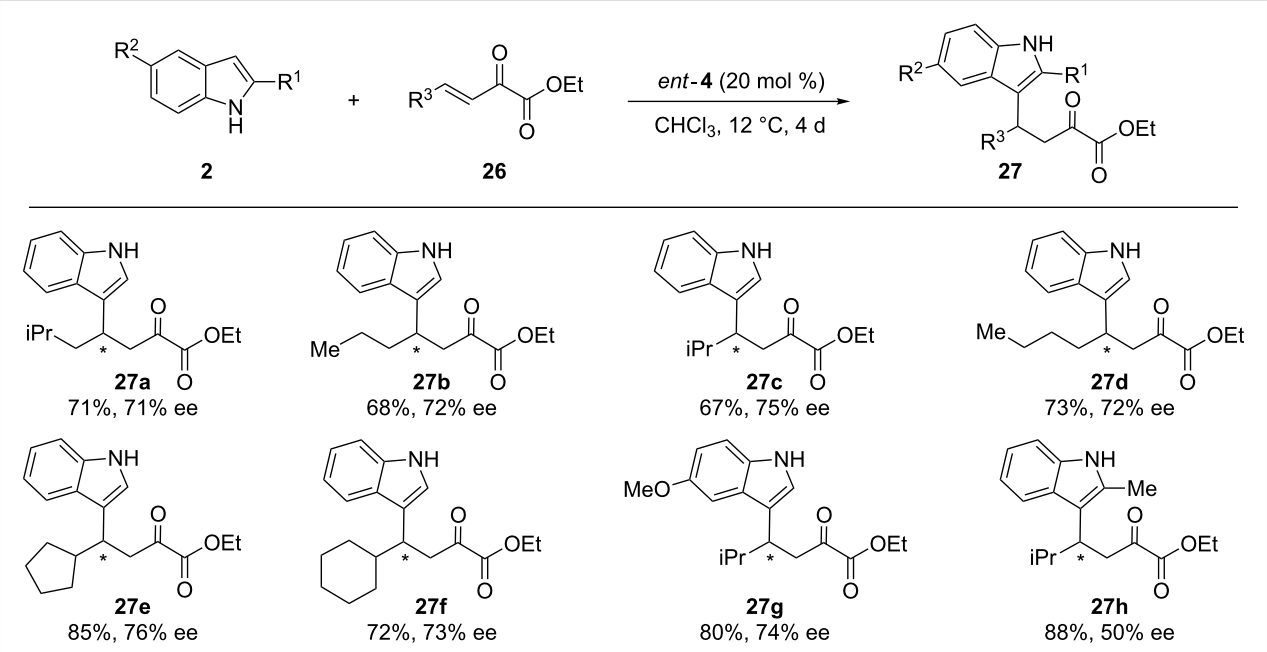


Figure 5: Proposed transition state **TS7** for the Friedel–Crafts reaction of indole and α,β-unsaturated acyl phosphonates catalyzed by *ent*-**4**.

Recently, the conjugated addition of indole derivatives to β,γ-unsaturated α-ketoesters was explored [40]. To this end, the catalytic activity of several chiral thioureas was studied, revealing the aminoindanol-based thiourea *ent*-**4** as the most suitable catalyst for this process. The authors studied aliphatic derivatives because for this reaction these compounds had been much less explored than the aromatic ones. Thus, the different aliphatic β,γ-unsaturated α-ketoesters **26a**–**f** reacted with the substituted indoles **2** in the presence of *ent*-**4** to achieve the corresponding adducts **27** with good yields and enantioselectivities (up to 88% yield, up to 76% ee) (Scheme 11).

Although the absolute configuration was unknown at that point, the authors envisioned a plausible reaction pathway based on previously reported transition states (Figure 6). The catalyst *ent*-**4** would activate and fix the electrophile through several



Scheme 11: Study of aliphatic β,γ-unsaturated α-ketoesters **26** as substrates in the F–C alkylation of indoles catalyzed by *ent*-**4**.

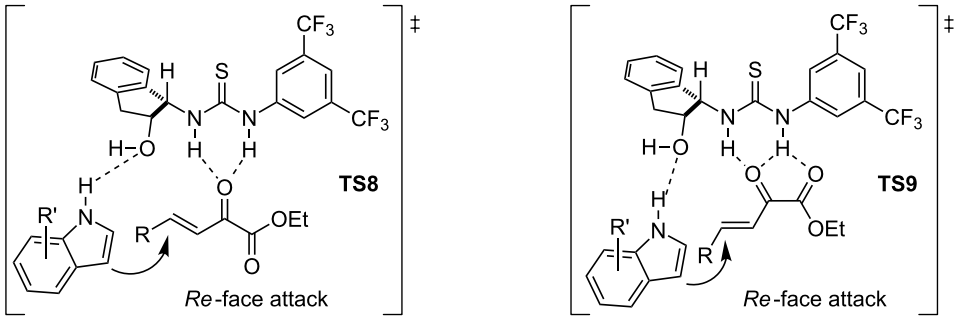


Figure 6: Possible transition states **TS8** and **TS9** in the asymmetric addition of indoles **2** to the β,γ-unsaturated α-ketoesters **26** catalyzed by *ent*-**4**.

hydrogen-bonding interactions with the NH groups of the thiourea. Simultaneously, the hydroxy group would be involved in the activation of the nucleophile, establishing a hydrogen bond with the indolic proton. This would conduct its attack over the *Re* face of the β,γ-unsaturated α-ketoesters, producing the addition in a stereocontrolled fashion. Some additional experimental proofs provided in the article supported this hypothesis [40].

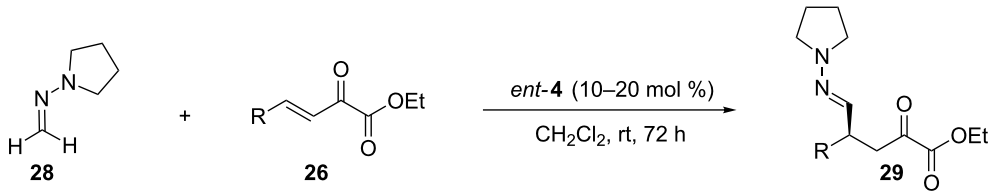
Michael addition to α,β-unsaturated compounds

Fernández, Lassaleta and co-workers provided an elegant, versatile and mild umpolung strategy, which leads to key synthetic precursors using the thiourea *ent*-**4**. In this study, an organocatalytic enantioselective addition of nucleophilic *N*,*N*-dialkylhydrazones to electron-deficient β,γ-unsaturated α-ketoesters was reported (Table 1) [41]. In the presence of catalyst *ent*-**4**, 1-methyleneaminopyrrolidine (**28**) reacted with the different β,γ-unsaturated α-ketoesters **26** in dichloromethane at low temperature to give the corresponding products **29**, which are useful masked 1,4-dicarbonyl compounds with moderate to high yield and high selectivity, after moderate reaction times (Table 1).

The authors proposed the plausible transition state **TS10**, where the acidic hydrogen atoms of the thiourea could activate the β,γ-unsaturated α-ketoesters **26**. Simultaneously, the hydrogen atom of the hydroxy group would coordinate and direct the hydrazone **28** to the *Re* face of the esters **26** in order to afford the absolute configuration found in the final products **29** of this process (Figure 7).

Another example of the bifunctional action of the indanol-based thiourea **4** was reported by Sibi's group. There, 100 mol % of

Table 1: Asymmetric addition of 1-methyleneaminopyrrolidine (**28**) to β,γ-unsaturated α-ketoesters **26**, catalyzed by *ent*-**4**.



Entry	**26** (R)	Temp. (ºC)	Yield **29** (%)	ee **29** (%)
1	Me	−60	60	80
2	iPr	−45	80	78
3	iBu	−45	75	78
4	*n*-C_5H_{11}	−60	61	70
5	$(CH_3)_3CH_2$	−45	64	58
6	Cy	−45	82	72

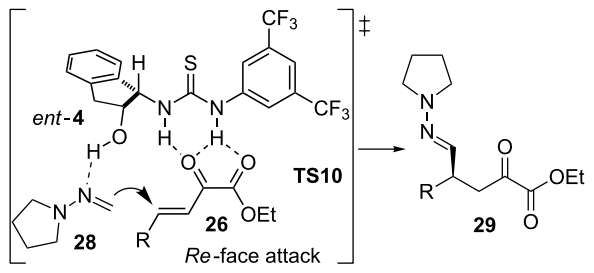
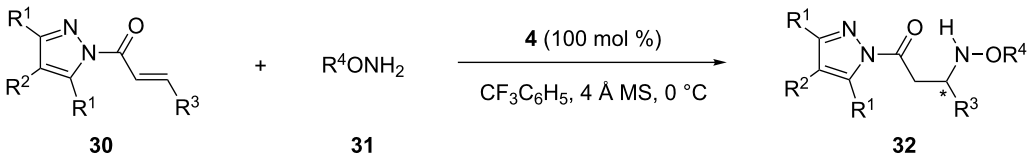


Figure 7: Transition state **TS10** proposed for the asymmetric addition of dialkylhydrazone **28** to the β,γ-unsaturated α-ketoesters **26** catalyzed by *ent*-**4**.

this compound was employed in the enantioselective conjugate addition of the hydroxylamine derivatives **31** to the enoates **30**, affording the final products **32** with good yield (up to 98%) and high enantiomeric excess (up to 98% ee). This provided an efficient method that allows the preparation of biologically interesting β-amino acid derivatives (Table 2) [42].

In this work, the authors compared the results achieved by means of **4** with other urea- and thiourea-based organocatalysts in order to understand the effect of the acidity, the structural rigidity, and the bifunctionality of the promoter. These reactions were performed in trifluorotoluene at room temperature

Table 2: The enantioselective addition of the hydroxylamine derivatives **31** to the enoates **30** promoted by **4**.



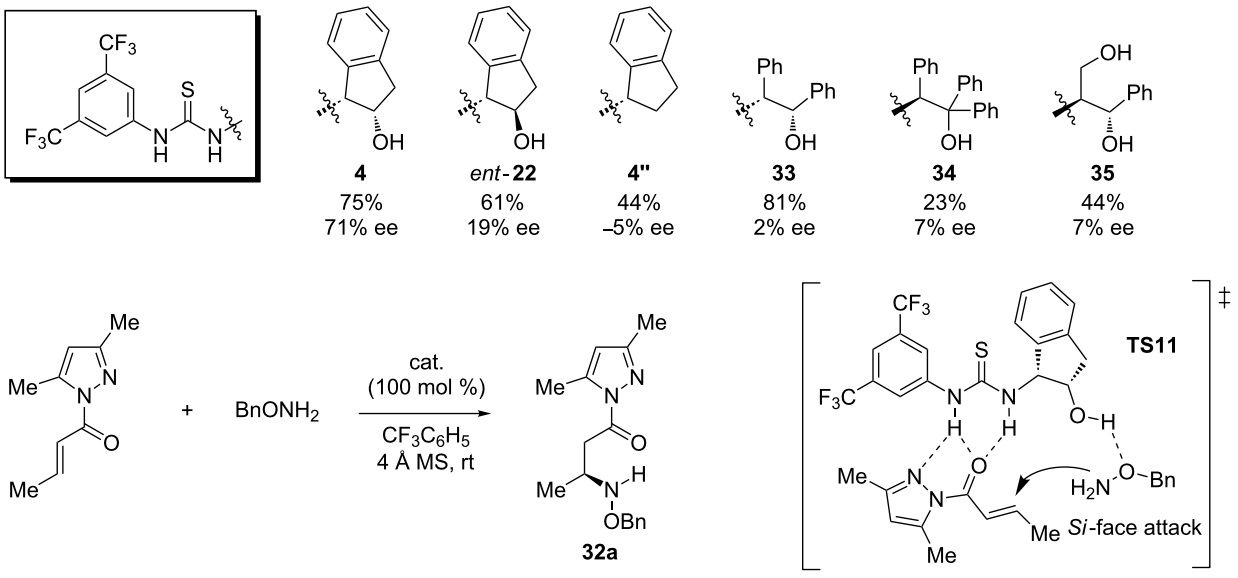
Entry	**30** (R^1, R^2, R^3)	**31** (R^4)	Time (h)	Yield **32** (%)	ee **32** (%)
1[a]	Me, H, Me	$PhCH_2$	24	75 (**32a**)	71
2[a,b]	Me, H, Me	$PhCH_2$	168	63 (**32a**)	71
3	Me, H, Me	$PhCH_2$	72	82 (**32a**)	87
4[a]	Me, Br, Me	$PhCH_2$	24	85 (**32b**)	61
5[a]	Ph, H, Me	$PhCH_2$	14	76 (**32c**)	45

Table 2: The enantioselective addition of the hydroxylamine derivatives **31** to the enoates **30** promoted by **4**. (continued)

6[a]	Ph, Br, Me	$PhCH_2$	12	72 (**32d**)	31
7	Me, H, Me	Ph_2CH	96	86 (**32e**)	89
8	Me, H, CO_2Et	Ph_2CH	96	50 (**32f**)	94
9	Me, H, CO_2Et	TBDMS	96	42 (**32g**)	90
10	Me, H, Et	Ph_2CH	168	92 (**32h**)	91
11	Me, H, *n*-Pr	Ph_2CH	138	84 (**32i**)	88
12	Me, H, iPr	Ph_2CH	216	68 (**32j**)	90
13	Me, H, *c*-C_6H_{11}	Ph_2CH	288	59 (**32k**)	89
14[b]	Me, H, CH_2OPMP	Ph_2CH	24	98 (**32l**)	98
15[a]	Me, H, Ph	$PhCH_2$	72	19 (**32m**)	67
16	Me, H, Me	TBDMS	120	82 (**32n**)	94

[a]Reaction carried out at room temperature. [b]30 mol % of catalyst **4**.

with the Michael acceptor **30** (R^1, R^2, R^3 = Me, H, Me) and *O*-benzylhydroxylamine (**31**, R^4 = $PhCH_2$), using a stoichiometric amount of the chiral activator and MS 4 Å as an additive. Some of the reported experiments supported the ability of the *cis*-2-aminoindanol structure to provide an adequate scaffold to induce chirality. In contrast, the catalysts *ent*-**22** (with the *trans*-2-aminoindanol) or **4''** (with the aminoindane motif) and the flexible analogues **33**–**35**, provided lower enantioselectivities or led to nearly racemic mixtures (Scheme 12). In the proposed transition state **TS11**, the α,β-unsaturated substrate is activated by an acidic thiourea template. Moreover, the hydroxylamine derivative is simultaneously oriented to attack the *Si* face of the Michel acceptor, through its interaction with the hydroxy group of the aminoindanol framework. In this case, a pyrazole moiety presents additional H-bond acceptor sites. These could play an important role in fixing the substrate to the catalyst and favoring



Scheme 12: Different β-hydroxylamino-based catalysts tested in a Michael addition, and the transition state **TS11** proposed for this reaction catalyzed by **4**.

a more rigid transition state (**TS11**) and thus leading to better selectivity (Scheme 12). The absolute configuration is only given for the compounds **32a**–**d**, being *S*.

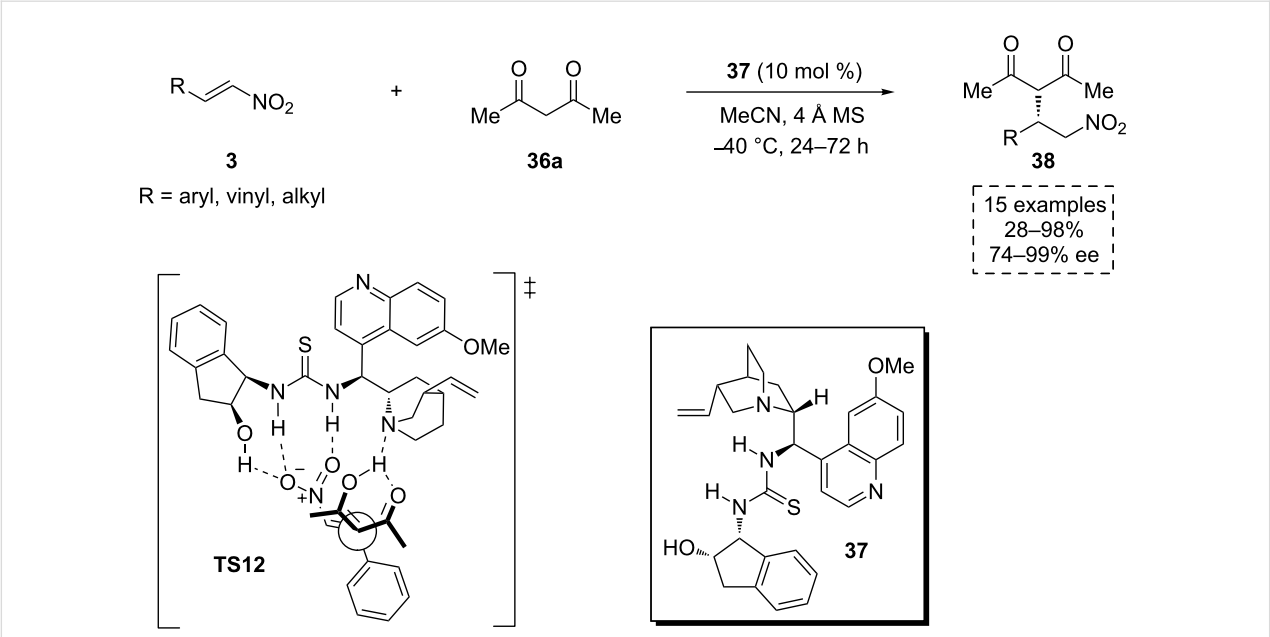
Later, He and co-workers reported the use of several chiral multiple hydrogen-bond donating tertiary amine-based organocatalysts in the asymmetric addition of acetylacetone (**36a**) to the β-nitroalkenes **3**. They found the thiourea **37** as a highly suitable catalytic structure to induce chirality in this process (Scheme 13) [43]. Under optimal conditions, this method provided highly enantioenriched γ-nitrocarbonyl compounds **38**, which are versatile synthetic intermediates for the preparation of diverse chiral scaffolds.

Once again, a bifunctional activation mode as the origin of the asymmetric induction was proposed. In the plausible transition state **TS12**, acidic hydrogen atoms from both hydroxy and thiourea moieties would activate and fix the nitroalkene. Simultaneously, the tertiary amine of the cinchona framework would deprotonate the acidic proton of acetylacetone (**36a**), driving the attack of the nucleophile. The chiral environment present in the resulting ternary complex would confer the proper facial selectivity to afford the observed absolute configuration in the final products **38**.

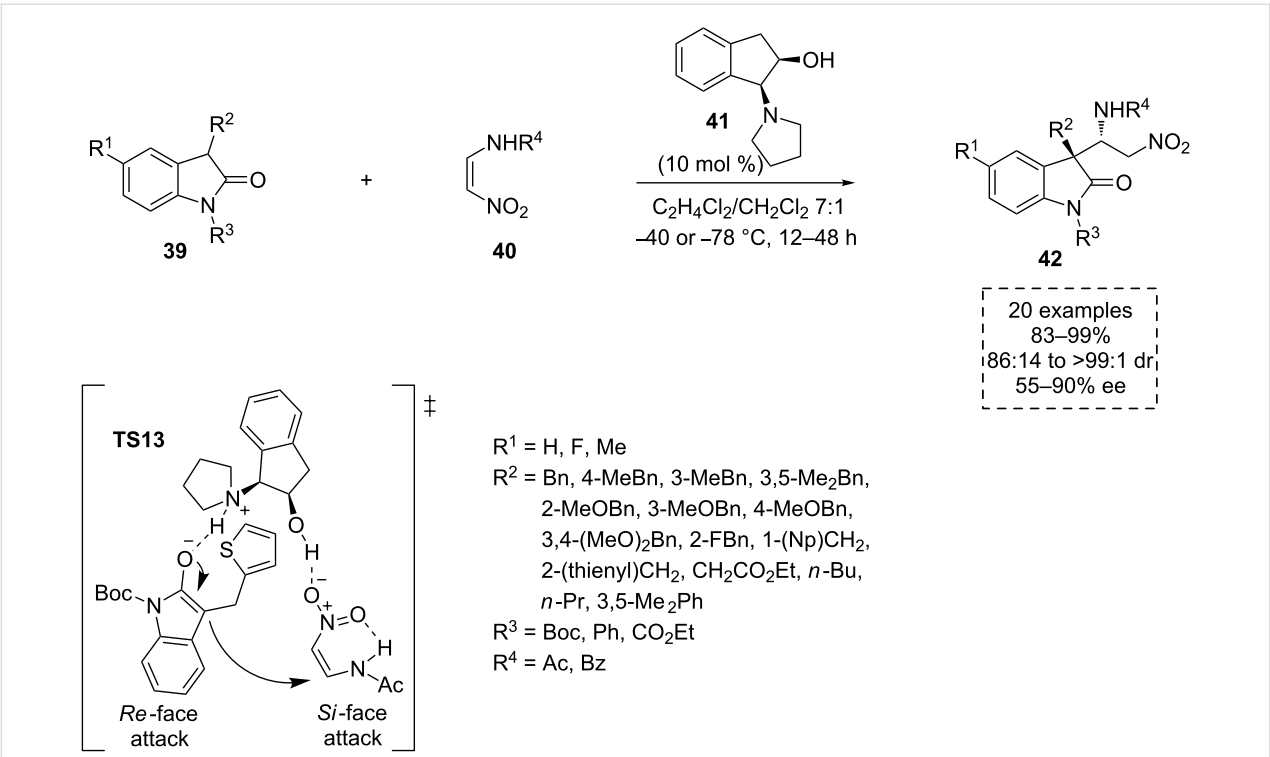
At the same time, Yuan and co-workers developed an interesting example of a scalable asymmetric Michael addition of 3-substituted oxindoles **39** to the protected 2-amino-1-nitroethenes **40**, using the bifunctional tertiary amine aminoindanol-based organocatalyst **41** (Scheme 14) [44]. This catalytic study provides a straightforward synthetic route of the highly functionalized α,β-diamino-3,3'-disubstituted-oxindoles **42**. These are key intermediates for the preparation of biologically and pharmacologically attractive compounds, such as (+)-alantrypinone [45], (−)-serantrypinone [46] and (−)-lapatin [47]. In the presence of the catalyst **41** (10 mol %), a broad scope of the oxindoles **39** reacted to give the quaternary stereocenters-containing products **42** with high diastereoselectivity (up to > 99:1 dr) and enantioselectivity (up to 90% ee).

A bifunctional role played by the catalyst was again envisioned by the authors. In the transition state **TS13** the tertiary amine group of the catalyst would activate the resulting enolized oxindole reagent **39** via deprotonation. Thus, **39** would be disposed to attack by its *Re* face to the *Si* face of the nitroethene derivative **40**. Simultaneously, the latter would be fixed and activated by a hydrogen-bonding interaction with the hydroxy moiety of the catalyst, in its *Z* form, which is stabilized due to an intramolecular hydrogen bond (Scheme 14).

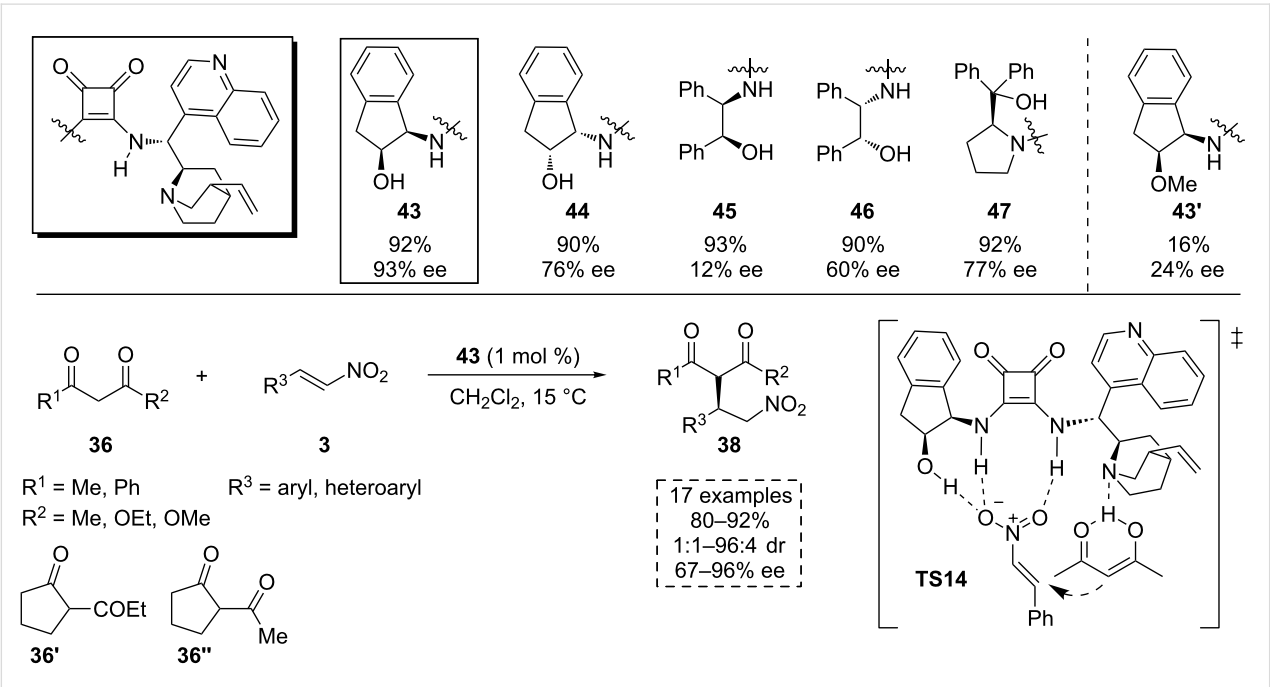
In 2012, Dong and co-workers studied the catalytic activity of several β-amino alcohol-based squaramide organocatalysts involved in the Michael addition of acetylacetone (**36a**) to β-nitrostyrene (**3a**) in dichloromethane at 15 °C (Scheme 15) [48]. Although high yields were obtained in all cases, the best enantioselectivity was provided by the bifunctional *cis*-aminoindanol-based squaramide **43**. Under these conditions, several



Scheme 13: Enantioselective addition of acetylacetone (**36a**) to nitroalkenes **3**, catalyzed by **37** and the proposed transition state **TS12**.



Scheme 14: Addition of 3-oxindoles **39** to 2-amino-1-nitroethenes **40**, catalyzed by **41**.



Scheme 15: Michael addition of 1,3-dicarbonyl compounds **36** to the nitroalkenes **3** catalyzed by the squaramide **43**.

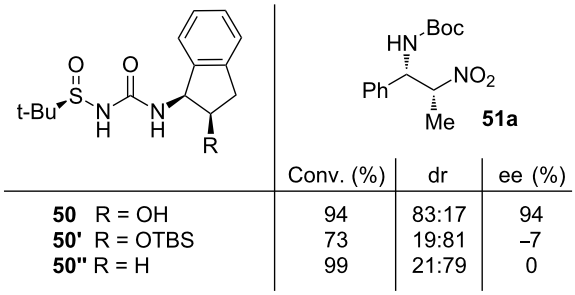
1,3-dicarbonyl compounds **36** reacted with many different nitrostyrene derivatives **3** with very low catalytic charge (1 mol %), affording a broad scope of the enantiomerically enriched β-nitroalkyl products **38**. A possible drawback of the method would be the low diastereoselectivity generally achieved for the nonsymmetrical 1,3-dicarbonyl compounds **36**.

In order to understand the role of the catalyst, the hydroxy group of the squaramide **43** was methylated (**43'**). Its catalytic activity was tested in the reaction of acetylacetone (**36a**) and β-nitrostyrene (**3a**), leading to very low enantiomeric excess (24% ee). This fact suggested the important role played by the hydroxy group in the activation and in the chiral induction of the process. The authors proposed the transition state **TS14**, where the NH groups and the OH group of the squaramide would coordinate to the nitroalkene **3** through hydrogen-bonding interactions with the nitro group. Simultaneously, the amine in the cinchona alkaloid would activate the 1,3-dicarbonyl compound **36** (Scheme 15). We would like to remark that although the authors indicated that the *S* enantiomer is obtained in their final products, they depicted the *R* configuration, as is drawn in the Scheme 15.

Aza-Henry reaction

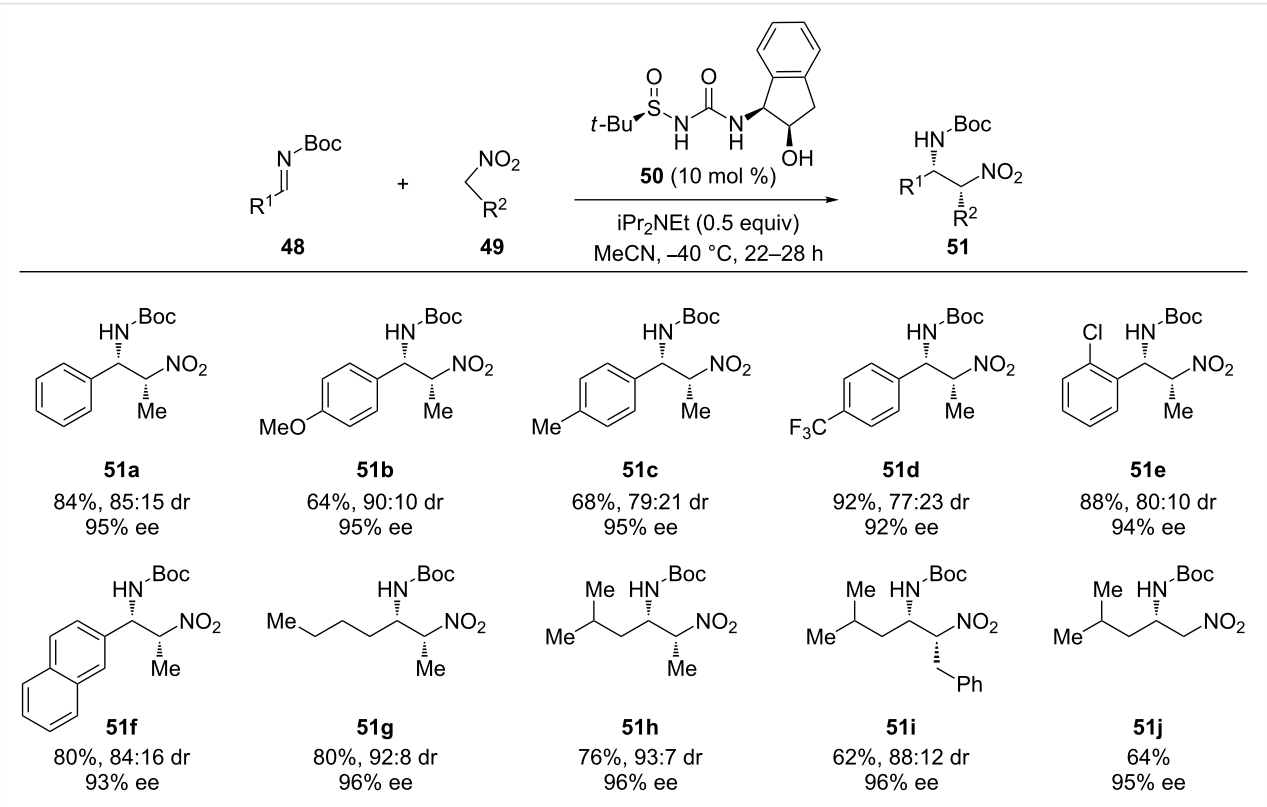
Ellman's group designed a set of pioneering (thio)urea scaffold-containing hydrogen-bonding organocatalysts with an *N*-sulfinyl moiety. As previously demonstrated, this chemical group increased the acidity of the catalyst and also served as a chiral controller [49-54]. Hence, in the presence of the catalyst **50** and diisopropylethylamine, a wide scope of the *N*-Boc-protected imines **48**, including aliphatic ones, reacted with an excess of the nitroalkanes **49** at low temperature. This afforded the corresponding products **51** with high yield, diastereomeric ratio and excellent enantioselectivity (Scheme 16) [55].

Some experimental results using the differently substituted aminoindane-derived sulfinyl ureas **50–50''** showed the important effect of the indanol framework in the diastereo- and enantio-selectivity of the process. The catalysts **50'** (with the TBS-protected hydroxy group (TBS, *tert*-butyldimethylsilyl)) and **50''** (without the hydroxy group) exhibited poor enantioselectivity. These effects may suggest and support the bifunctional role played by the catalyst (Figure 8).



	Conv. (%)	dr	ee (%)
50 R = OH	94	83:17	94
50' R = OTBS	73	19:81	–7
50'' R = H	99	21:79	0

Figure 8: Results for the aza-Henry reaction carried out with the structurally modified catalysts **50–50''**.



Scheme 16: Asymmetric aza-Henry reaction catalyzed by the aminoindanol-derived sulfinyl urea **50**.

Diels–Alder reaction

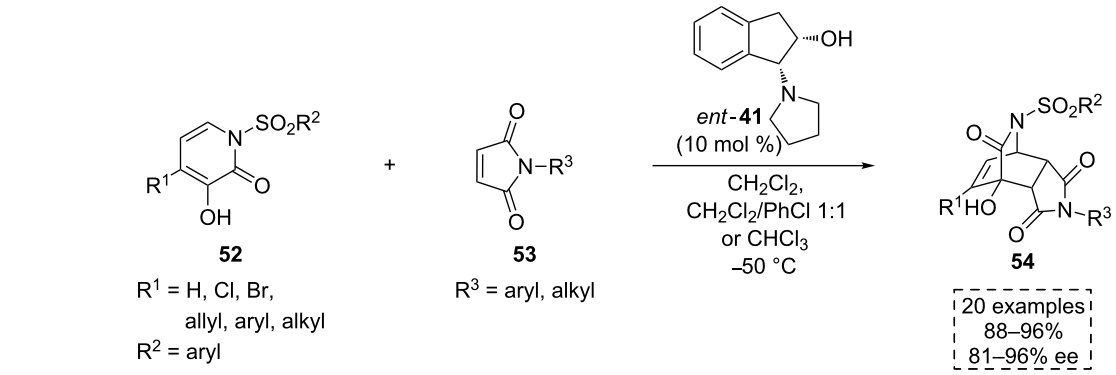
An important contribution in the construction of highly substituted carbocyclic compounds was disclosed by Tan's group in 2009. In this work, the asymmetric Diels–Alder (D–A) reaction between the *N*-sulfonamide-3-hydroxy-2-pyridone-based dienes **52** and different dienophile substrates was developed using the bifunctional *cis*-2-trialkylaminoindanol organocatalyst *ent*-**41** [56]. We show herein the reactivity of this family of dienes with several substituted maleimides **53**, which in the presence of the above mentioned catalyst, afforded the highly substituted *endo*-adducts **54** with high yield and enantiomeric excess (Scheme 17). In this approach, the *cis* orientation of the hydroxy and cyclopentylamine groups of the catalyst was crucial to achieve high enantioselectivity.

Aminocatalysis

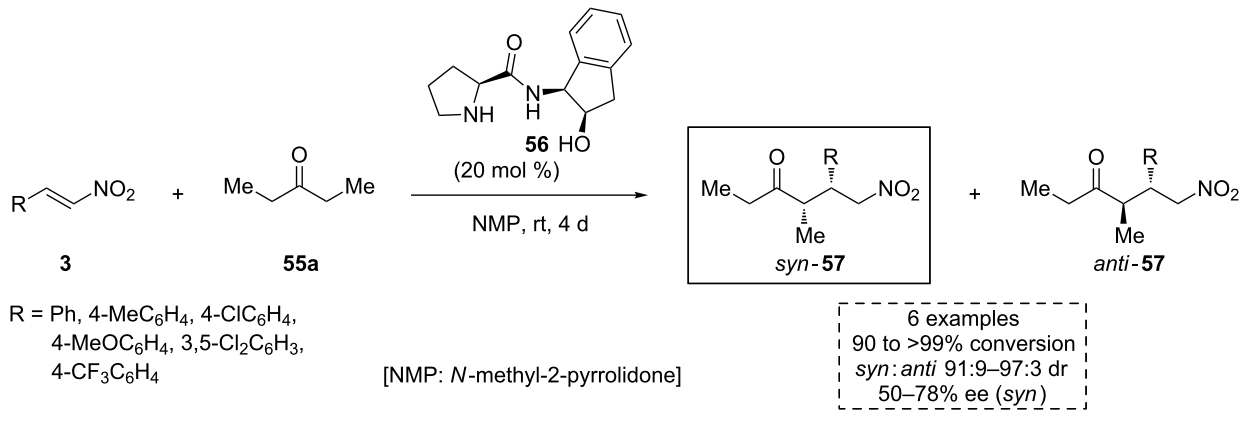
Although aminoindanol-derived catalysts have been scarcely used in aminocatalysis, some relevant examples have been found in the literature, especially in the enantioselective addition of ketones to nitroalkene compounds. In this context, Alonso, Nájera and co-workers designed different alcohol-amino-derived prolinamide organocatalysts and in 2006 published an organocatalyzed direct asymmetric Michael addition of 3-pentanone (**55a**) to the nitrostyrenes **3** [57]. The corresponding *syn*-adducts **57** were obtained with excellent conversion, diastereomeric ratio and high enantiomeric excess when the *cis*-aminoindanol-based prolinamide **56**, acting as bifunctional recyclable catalyst, was used (Scheme 18).

Later, based on this previous work, the same research group extended the methodology to different ketones **55**, rendering the *syn*-products **57** with excellent yield and high selectivity (Scheme 19) [58].

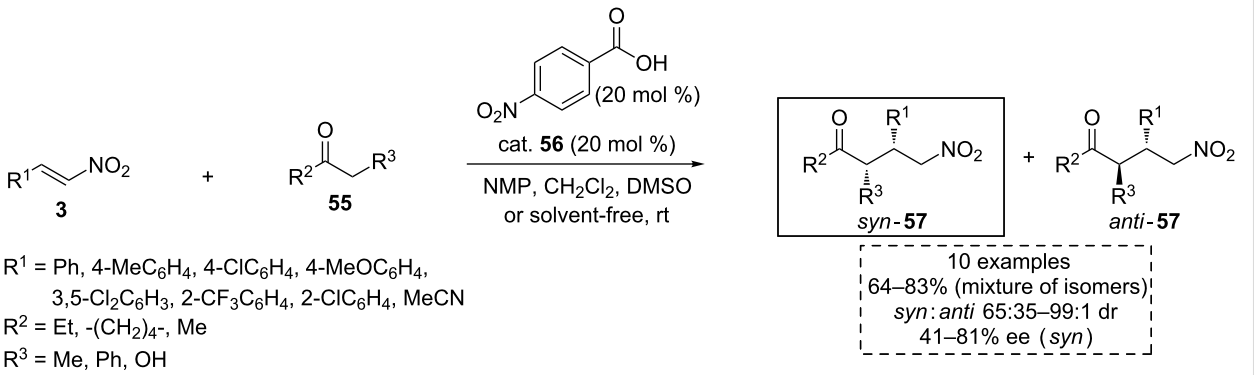
In this case, the hydroxy group seems again to play an important role in the activation of the substrates, as well as in the selectivity of the process. The rigidity of the hydroxylamino moiety represents another important factor, where aminoindanol was the most appropriate scaffold for this asymmetric methodology among the catalysts tested. Based on the experi-



Scheme 17: Diels–Alder reaction catalyzed by the aminoindanol derivative *ent*-**41**.



Scheme 18: Asymmetric Michael addition of 3-pentanone (**55a**) to the nitroalkenes **3** through aminocatalysis.



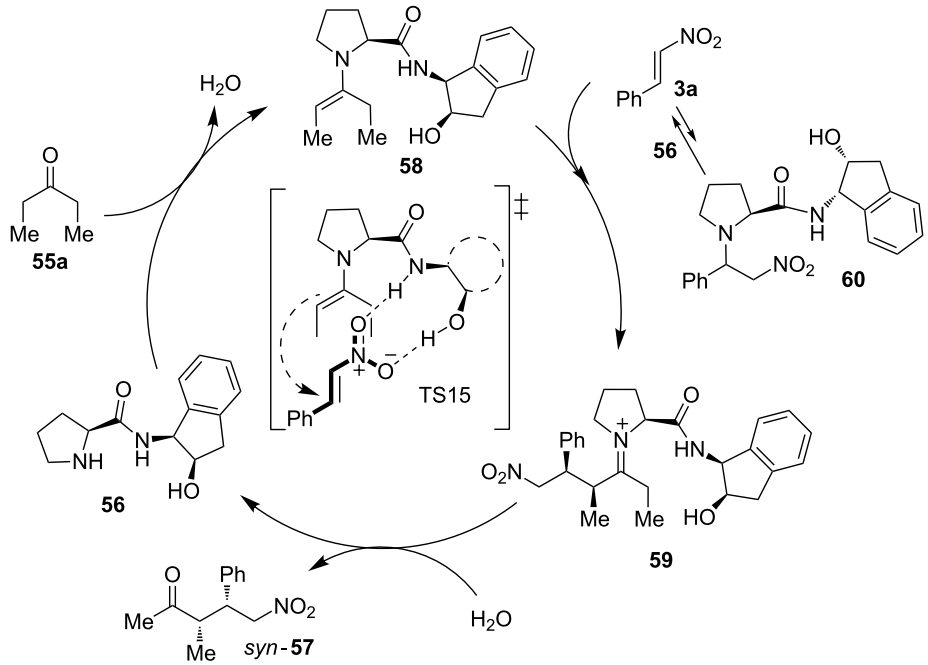
Scheme 19: Substrate scope extension for the asymmetric Michael addition between the ketones **55** and the nitroalkenes **3** through aminocatalysis.

mental results and computational calculations (DFT and B3LYP76-31G*), the authors proposed a reaction mechanism in which the catalyst **56** acts in a bifunctional way following the route depicted in Scheme 20. Thus, Michael addition of the enamine **58**, formed from 3-pentanone (**55a**) and the catalyst **56**, to the nitroalkene **3a** takes place leading to the intermediate **59**. The last step of the catalytic cycle involves the regeneration of the catalyst by hydrolysis, enabled by the small amount of water present in the solvent.

The transition state **TS15** based upon Seebach's model [59] was envisioned as a plausible activation mode to explain the high asymmetric induction observed and the *syn*-diastereoselectivity exhibited by the catalyst **56**. First, the activation of the ketone via enamine formation is produced. Furthermore, the acidic hydrogen atoms of the amide and the hydroxy groups present in the catalyst would activate and orientate the nitroalkene by hydrogen-bond formation. Thus, the attack of the formed enamine to the *Re* face of the nitroalkene is favored (Scheme 20). In this way, this example shows an efficient combination of covalent and non-covalent interactions in an interesting bifunctional activation mode.

Conclusion

The design, synthesis and application of catalysts acting in a bifunctional manner is a hot topic in the field of organocatal-



Scheme 20: A possible reaction pathway in the presence of the catalyst **56** and the plausible transition state **TS15** proposed for this reaction.

ysis and thus widely investigated. Generally, this particular mode of activation allows the enhancement of both the reactivity and the selectivity of the processes, due to the generation of a more rigid transition state. Among the different ways of conferring this bifunctional character to the catalysts, the incorporation of the aminoindanol core into their structure has shown to be a very suitable method. In most of the examples gathered herein, this can be explained due to the presence of a hydroxy group in the catalyst that normally is able to interact with at least one of the substrates of the reaction, hence facilitating the approach of the reactants in a selective fashion. In many cases, this bifuntional role of the catalyst has been supported with experimental results and sometimes with computational calculations. This smart strategy has allowed the preparation of highly efficient organocatalysts, ranging from very simple structures to more complex ones. These are mainly hydrogen-bonding catalysts, but there is also an example of an aminoindanol-containing aminocatalyst. A broad variety of reactivities has been successfully covered, such as Friedel–Crafts alkylation, Michael addition, Diels–Alder and aza-Henry reactions. However, further exploration into the development of new bifunctional organocatalysts using aminoindanol or another appropriate scaffold and their application in different chemical processes still needs to be performed.

Acknowledgements

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Supported bifunctional thioureas as recoverable and reusable catalysts for enantioselective nitro-Michael reactions

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Full Research Paper

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Abstract

The catalytic activity of different supported bifunctional thioureas on sulfonylpolystyrene resins has been studied in the nitro-Michael addition of different nucleophiles to *trans*-β-nitrostyrene derivatives. The activity of the catalysts depends on the length of the tether linking the chiral thiourea to the polymer. The best results were obtained with the thiourea derived from (L)-valine and 1,6-hexanediamine. The catalysts can be used in only 2 mol % loading, and reused for at least four cycles in neat conditions. The ball milling promoted additions also worked very well.

Introduction

The use of chiral bifunctional thioureas that allow the simultaneous activation of a electrophile, by hydrogen bonding, and a nucleophile, by deprotonation, plays a major role in the stereoselective formation of C–C bonds in different transformations [1-5]. In these processes one of the major problems is related to the recovering of the catalysts. The support of the small molecules on different materials has been proposed as a solution, including their use in continuous flow processes [6-9]. The most popular supports include nanoparticles [10-12], inorganic solids [13,14], and different polystyrene derivatives [15-20].

Bifunctional thioureas were first supported on PEG [21], and later on different materials such as poly(methylhydrosiloxane) [16], polystyrene [18-22], and magnetic nanoparticles [12]. Cinchona-derived thioureas have been also prepared by co-polymerization of polyfunctionalized thiols with olefins [23].

Our interest in the search for novel bifunctional thioureas as organocatalysts [24-27] lead us to consider the preparation of different polymeric materials decorated with chiral bifunctional thioureas looking for a greener process [28], easier recovering and recyclability of the catalyst, and solvent-free reaction conditions. Along these lines, we have recently reported the bottom-up synthesis of polymeric thioureas [29], and the anchorage of (L)-valine-derived thiourea **I** [30] onto

sulfonylpolystyrene resin leading to catalysts **II**–**V** (Figure 1), which differ in the length of the diamine linker or in the substitution pattern of the nitrogen in the sulfonamide. These materials, and the related unsupported thiourea **VI**, have been previously tested as excellent organocatalysts in the stereoselective aza-Henry reaction [31]. Now we describe the results obtained in different stereoselective nitro-Michael additions promoted by these materials.

Results and Discussion

The ability of the supported catalysts (**II**–**V**) to promote the stereoselective nitro-Michael reaction was first tested in the reaction of *trans*-nitrostyrene (**1a**) with diethyl malonate (**2a**), leading to the enantioenriched addition product **4aa** with a single stereocenter. In order to the creation of two tertiary-quaternary contiguous stereocenters (**5aa**) we also used ethyl 2-oxocyclopentanecarboxylate (**3a**) as nucleophile in neat conditions and in different solvents. For comparative purposes, the same reactions were studied in the presence of unsupported catalysts **I** and **VI**, and the results are summarized in Scheme 1 and Table 1.

Initially, the reactions were carried out in neat conditions at rt with twofold excess of nucleophile and 10 mol % of catalysts (entries 1–4 and 9–11 in Table 1). As a general trend, the reactions were faster, and much more stereoselective for ketoester **3a** than for diethyl malonate **2a**, and that the difference was specially remarkable when supported ethylenediamine-derived thioureas **II** and **III** were used as catalysts (compare entries 2 and 3 versus 9 and 10 in Table 1). It is noteworthy that the results obtained in the reaction catalyzed by supported thiourea **IV** were better than those observed in the addition catalyzed by the parent thiourea **I** (compare Table 1, entries 1 and 4).

The catalyst loading was decreased to 5 mol % for supported hexanediamine-derived catalyst **IV**, observing that the level of stereoselectivity was maintained for both reactions, although at expenses of slight increasing the reaction time (compare Table 1, entries 4 versus 5, and 11 versus 12). In these conditions, supported catalyst **V**, which differs from **IV** in the substitution pattern of the sulfonamide, was the best catalyst for the addition of both **2a** and **3a** to nitrostyrene, yielding products **4aa** and **5aa**, respectively, in much better yield maintaining the stereoselectivity in shorter reaction time (compare entries 5 versus 6 and 12 versus 13 in Table 1). An increase in both the yield and the enantioselectivity for the reaction of **1a** with **2a** (Table 1, entries 6 and 7), but no differences in the reaction of **1a** with **3a** (Table 1, entries 13 and 14) were observed when the unsupported thiourea **VI**, homologous to **V**, was used as organocatalyst.

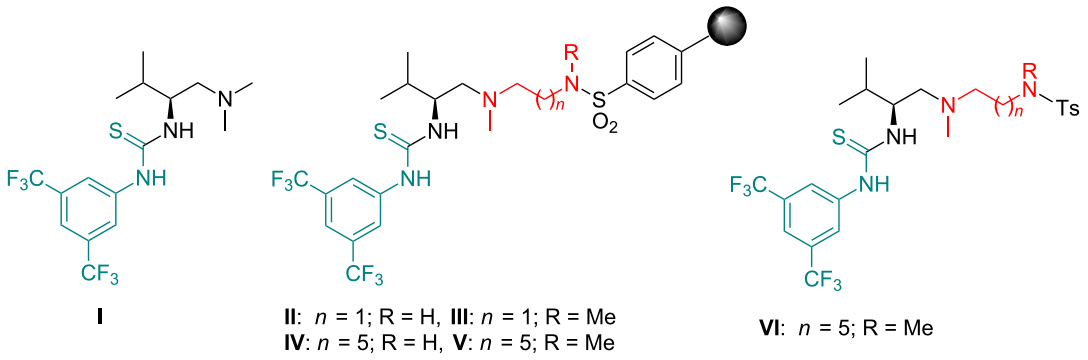
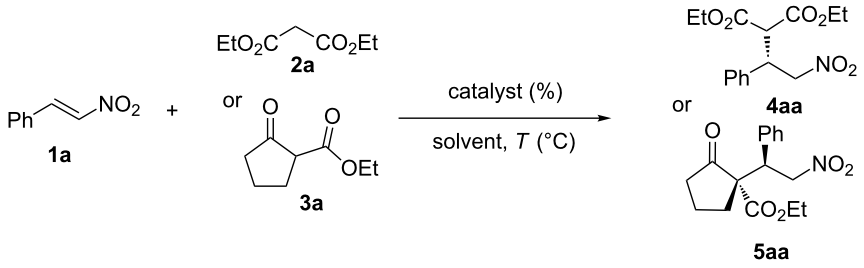


Figure 1: Parent and supported bifunctional thioureas used in this work.



Scheme 1: Reaction of nitrostyrene with diethyl malonate and 2-ethoxycarbonyl cyclopentanone.

Table 1: Screening of catalysts and optimization of the reaction conditions for the additions of diethyl malonate and ethyl 2-oxocyclopentanecarboxylate to β-nitrostyrene.

Entry[a]	Catal. (mol %)	Solvent	*T* (°C)	*t* (h)	Product yield[b] (%)	dr[c]	er[d]
1	**I** (10)	neat	rt	24	**4aa** (80)	–	92:8
2	**II** (10)	neat	rt	120	**4aa** (77)[e]	–	78:22
3	**III** (10)	neat	rt	120	**4aa** (63)[f]	–	85:15
4	**IV** (10)	neat	rt	16	**4aa** (92)	–	91:9
5	**IV** (5)	neat	rt	24	**4aa** (80)	–	90:10
6	**V** (5)	neat	rt	16	**4aa** (92)	–	89:11
7	**VI** (5)	neat	rt	16	**4aa** (100)	–	94:6
8	**I** (5)	neat	rt	1	**5aa** (95)	95:5	95:5
9	**II** (10)	neat	rt	4	**5aa** (100)	89:11	90:10
10	**III** /10)	neat	rt	8	**5aa** (90)	87:13	92:8
11	**IV** (10)	neat	rt	4	**5aa** (100)	88:12	95:5
12	**IV** (5)	neat	rt	7	**5aa** (100)	88:12	95:5
13	**V** (5)	neat	rt	0.5	**5aa** (98)	89:11	95:5
14	**VI** (5)	neat	rt	2	**5aa** (100)	89:11	95:5
15	**V** (2)	neat	rt	1	**5aa** (93)	89:11	95:5
16	**V** (2)	neat	0	24	**5aa** (97)	90:10	94:6
17[g]	**V** (2)	neat	rt	8	**5aa** (86)	88:12	94:6
18[h]	**V** (2)	neat	rt	2.5	**5aa** (83)	88:12	94:6
19	**V** (2)	CH_2Cl_2	rt	1	**5aa** (74)	90:10	93:7
20	**V** (2)	PhMe	rt	5	**5aa** (66)	89:11	94:6
21	**V** (2)	THF	rt	1.5	**5aa** (55)	89:11	94:6
22	**V** (2)	MeCN	rt	1.5	**5aa** (79)	89:11	95:5
23	**V** (2)	MeCN	0	8	**5aa** (82)	88:12	95:5
24[g]	**V** (2)	MeCN	rt	8	**5aa** (86)	89:11	92:8

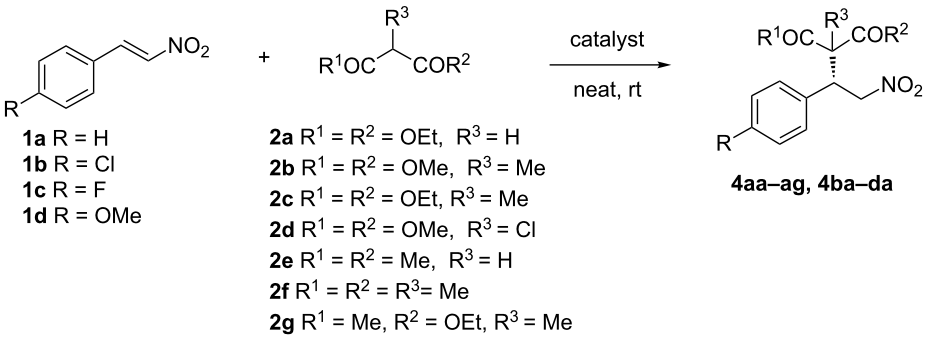
[a]Reaction performed with 2 equiv of nucleophile at room temperature. [b]Yields refer to isolated compounds. [c]Determined by ^{1}H NMR in the reaction mixture. [d]Determined by chiral HPLC. [e]13% of unreacted nitrostyrene was recovered. [f]15% of unreacted nitrostyrene was recovered. [g]Reaction performed with 1.1 equiv of ketoester. [h]Reaction performed with 1.5 equiv of ketoester.

Taking the supported thiourea **V** as the catalyst of choice, the effects of the catalyst loading, the temperature, the ratio of nucleophile, and the use of different solvents were studied for the reaction of **1a** and **3a**. Fortunately, the reduction of the amount of catalyst to 2 mol % did not influence the stereoselectivity, and only slightly decreased the yield to 93% (compare Table 1, entries 13 and 15). The reaction also proceeded at 0 °C, leading to the addition product **5aa** in 97% and very good stereoselectivity, but in those conditions the reaction time increased to 24 h (Table 1, entry 16).

The reduction of the amount of the nucleophile to 1.1 equivalents (Table 1, entry 17) or 1.5 equivalents (Table 1, entry 18) had only a moderate effect on the yield of the reaction time, increasing it to 8 h and 2,5 h, respectively. The yield dropped to 55–74%, without change in the stereoselectivity, when the reaction was carried out in less polar solvents such as DCM, toluene, or THF (Table 1, entries 19–21), although both the yield and diastereo- and enantioselectivity were maintained when acetonitrile, a more polar solvent, was used (Table 1, entries 22–24).

We next consider the reaction of some 4-substituted nitrostyrenes (**1b–d**) with diethyl malonate (**2a**), and the addition of a range of β-functionalized nucleophiles **2b–g** to **1a** promoted by supported catalysts **IV** (5 mol %) and **V** (2 mol %), respectively (Scheme 2 and Table 2). The results obtained in the reactions of 4-chloro- (**1b**) and 4-fluoronitrostyrene (**1c**) were very similar than those obtained in the reaction with β-nitrostyrene (**1a**), maintaining the yield and the enantioselectivity, although **1c** reacted slowly within 48 h (compare entries 1 and 2 in Table 2 versus entry 5 in Table 1), but the less reactive 4-methoxy derivative **1d** only yielded the addition product in moderate 52% yield after 72 h of reaction (entry 3 in Table 2).

The reaction of different nucleophiles (**2a–g**) with **1a** catalyzed by **IV** (5 mol %) also worked well in terms of enantioselectivity, maintaining the er near constant around or higher than 90:10,



Scheme 2: Reaction of nitrostyrenes with malonates and β-diketones.

Table 2: Addition of malonates and β-diketones to nitrostyrenes catalyzed by **IV** and **V**.

Entry[a]	Reagents	Catal. (mol %)	*t* (h)	Product yield[b] (%)	dr[c]	er[d]	Config.
1	**1b/2a**	**IV** (5)	6	**4ba** (76)	–	83:17	(*S*)
2	**1c/2a**	**IV** (5)	48	**4ca** (72)	–	86:14	(*S*)
3	**1d/2a**	**IV** (5)	72	**4da** (52)	–	89:11	(*S*)
4	**1a/2b**	**IV** (5)	36	**4ab** (64)	–	92:8	(*R*)
5	**1a/2d**	**IV** (5)	48	**4ad** (74)	–	92:8	(*S*)
6	**1a/2e**	**IV** (5)	5	**4ae** (88)	–	89:11	(*S*)
7	**1a/2f**	**IV** (5)	6	**4af** (70)	–	93:7	(*R*)
8	**1a/2g**	**IV** (5)	7	**4ag** (99)	75:25	92:8	(2*R*,3*R*)
9	**1a/2b**	**V** (2)	2	**4ab** (46)	–	91:9	(*R*)
10	**1a/2c**	**V** (2)	8	**4ac** (47)	–	91:9	(*R*)
11	**1a/2d**	**V** (2)	2	**4ad** (43)	–	91:9	(*S*)
12	**1a/2e**	**V** (5)	2	**4ae** (87)	–	92:8	(*S*)
13	**1a/2f**	**V** (2)	3	**4af** (65)	–	93:7	(*R*)
14	**1a/2g**	**V** (2)	6	**4ag** (81)	74:26	94:6	(2*R*,3*R*)

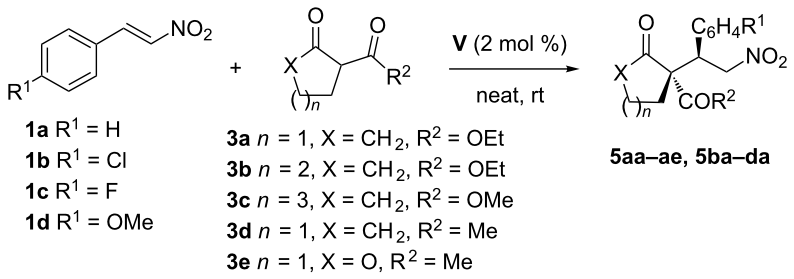
[a]Reaction performed with 2 equiv of nucleophile. [b]Yields determined after chromatographic purifications. [c]Diastereomeric excess determined by ^{1}H NMR of the crude reaction mixture. [d]Enantiomeric ratio determined by chiral HPLC analysis.

although the stereoselectivity for the reaction leading to **4ag**, with two contiguous tertiary–quaternary stereocenters was only moderate (dr 75:25, entry 8 in Table 2). The main difference in those additions was related with the reaction time, because the less reactive malonates (**2b** and **2d**) reacted slower than the acetylacetone (**2e** and **2f**) or ethyl acetoacetate (**2g**) derivatives.

Similar results were obtained when the reaction was run in the presence of only 2 mol % of catalyst **V** (entries 9–14 in Table 2). The level of stereoselectivity was maintained, including the diastereoselectivity for the reaction of **1a** with **2g** (dr 74:26), but the yields for the reactions with 2-substituted malonates (**2b–d**) were only moderate (entries 9–11 in Table 2).

Next, we extend the study to the reaction of different β-functionalized cycloalkanones (**3a–c**), 2-acetylcyclopentanone (**3d**), and 2-acetyl-γ-lactone (**3e**) with nitrostyrene derivatives **1a–d** (Scheme 3 and Table 3). The electronic nature of the nitroolefins only affects the yield and the reaction time, being longer as the donating effect of the substituent increases, but maintaining good diastereoselectivity and excellent enantioselectivity for all reactions (entries 2–4, Table 3).

With respect to the nucleophile, it is noteworthy that there seems to be a correlation: With growing size of the cycloalkanone an increase of the reaction time and a decrease of the yield can be observed. Cycloheptanone **3c**, and specially cyclohexanone **3b** reacted much more slowly than cyclopentanone derivative **3a** (Table 3, entries 5, 6, and 8), although the reaction time could be reduced from 96 h to 10 h in the reaction of **1a** with **3b** by increasing the catalyst loading from 2 mol % to 5 mol % (Table 3, entry 7). It is also noteworthy that 2-acetyl-γ-lactone (**3e)** reacted very well with **1a**, leading to **5ae** in excellent yield and enantioselectivity, but only moderate diastereoselectivity (dr 70:30, Table 3, entry 10).



Scheme 3: Reaction of nitrostyrenes with β-keto esters and β-dicarbonyl compounds.

Table 3: Reaction of nitrostyrenes with β-substituted cycloalkanones catalyzed by **V**.

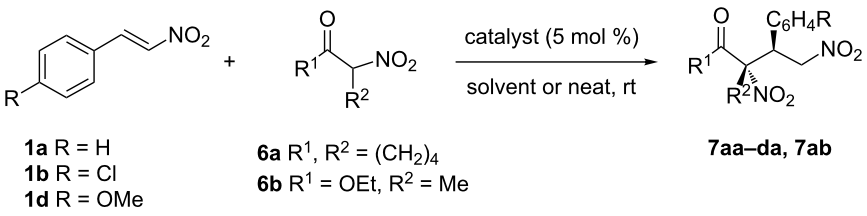
Entry[a]	Reagents	Catal. (mol %)	*t* (h)	Product Yield[b] (%)	dr[c]	er[d]	Config.
1	**1a/3a**	**V** (5)	0.5	**5aa** (98)	89:11	95:5	(*S,R*)
2	**1b/3a**	**V** (2)	1	**5ba** (84)	90:10	94:6	(*S,R*)
3	**1c/3a**	**V** (2)	5	**5ca** (76)	89:11	93:7	(*S,R*)
4	**1d/3a**	**V** (2)	9	**5da** (74)	89:11	95:5	(*S,R*)
5	**1a/3a**	**V** (2)	1	**5aa** (93)	89:11	95:5	(*S,R*)
6	**1a/3b**	**V** (2)	96	**5ab** (63)	88:12	96:4	(*S,R*)
7	**1a/3b**	**V** (5)	10	**5ab** (62)	88:12	96:4	(*S,R*)
8	**1a/3c**	**V** (2)	24	**5ac** (73)	82:18	96:4	(*S,R*)
9	**1a/3d**	**V** (2)	2	**5ad** (92)	83:17	93:7	(*R,R*)
10	**1a/3e**	**V** (2)	1	**5ae** (89)	70:30	92:8	(*R,R*)
11[e]	**1a/3a**	**V** (5)	1	**5aa** (81)	88:12	94:6	(*S,R*)
12[f]	**1a/3a**	**V** (5)	1	**5aa** (76)	88:12	95:5	(*S,R*)
13[g]	**1a/3a**	**V** (5)	2	**5aa** (82)	88:12	94:6	(*S,R*)

[a]Reaction performed with 2 equiv of nucleophile. [b]Yields determined after chromatographic purifications. [c]Diastereomeric excess determined by ^{1}H NMR of the crude reaction mixture. [d]Enantiomeric ratio determined by chiral HPLC analysis. [e]Second cycle for entry 1 by using only 1.5 equivalents of nucleophile. [f]Third cycle for entry 1 by using only 1.5 equivalents of nucleophile. [g]Fourth cycle for entry 1 by using only 1.5 equivalents of nucleophile.

To test the recyclability of catalyst **V** we choose the reaction of **1a** with **3a** in neat conditions and 5 mol % of catalyst as model. Once the reaction had finished (TLC), the catalyst was recovered by filtration, and after washing with methanol and drying to constant weight, the catalyst was used in the next cycle (entries 1 and 11–13 in Table 3). Fortunately, catalyst **V** can be reused for at least four cycles yielding **5aa** in high yields (76–82%), and maintaining both the diastereo- and enantioselectivity.

Finally, α-nitrocyclohexanone (**6a**) and ethyl α-nitropropionate (**6b**) were included in the screening process in order to compare the results obtained with more acidic nucleophiles with those obtained with β-dicarbonyl derivatives. The reactions were carried out under different conditions by varying the solvent, the temperature and using unsupported thioureas **I** and **VI**, and **V** as an example of a supported one (Scheme 4). The most significant difference between the reactions of nitroketone and nitroester refers to the stereoselectivity in both processes. The addition of nitroketone was totally diastereoselective and highly enantioselective (entries 1–12 in Table 4), whereas both the diastero- and enantioselectivities were moderate for the addition of nitroester (Table 4, entries 13–15). Additionally, supported catalyst **V** was able to promote more enantioselective transformations than unsupported catalyst **I** (compare Table 4, entry 13 versus 15). The decrease of the temperature slows down the reaction, increasing the reaction time from 1 h to 6 h for the reaction of **1a** with **6b**, catalyzed by **I** (Table 4, entries 13 and 14), and from 24 h to 48 h for the addition of **6a** to **1a** catalyzed for **VI** (Table 4, entries 7 and 8), but maintaining the diastereoselectivity and slightly increasing the enantioselectivity. The donor character of the substituent in the nitrostyrene derivative plays an important role in the process, increasing the reaction time, and decreasing the yield (compare Table 4, entries 5, 9, and 11).

The recent interest in alternative activation modes [32] for promoting C–C bond formations, led us to consider the catalyt-



Scheme 4: Reaction of nitrostyrenes with α-nitrocyclohexanone and ethyl α-nitropropionate.

Table 4: Reactions of nitrostyrenes with α-nitrocyclohexanone and ethyl α-nitropropionate.

Entry[a]	Reagents	Catal. (mol %)	*t* (h)	Solvent	Product yield[b] (%)	dr[c]	er[d]
1	**1a/6a**	**I** (5)	3	DCM	**7aa** (62)	>98:<2	84:16
2	**1a/6a**	**I** (5)	1.5	neat	**7aa** (65)	>98:<2	90/10
3[e]	**1a/6a**	**I** (5)	1	neat	**7aa** (70)	>98:<2	90:10
4	**1a/6a**	**V** (5)	48	DCM	**7aa** (60)	>98:<2	90:10
5	**1a/6a**	**V** (5)	12	MeCN	**7aa** (77)	>98:<2	91:9
6[e]	**1a/6a**	**V** (5)	12	neat	**7aa** (85)	>98:<2	94:6
7	**1a/6a**	**VI** (5)	24	DCM	**7aa** (64)	>98:<2	85:15
8[f]	**1a/6a**	**VI** (5)	48	DCM	**7aa** (52)	>98:<2	92:8
9	**1b/6a**	**V** (5)	8	MeCN	**7ba** (91)	>98:<2	91:9
10[e]	**1b/6a**	**V** (5)	48	neat	**7ba** (48)[g]	>98:<2	90:10
11	**1d/6a**	**V** (5)	24	MeCN	**7da**(73)	>98:<2	89:11
12[e]	**1d/6a**	**V** (5)	360	neat	**7da**(50)[h]	>98:<2	87:13
13	**1a/6b**	**I** (5)	1	neat	**7ab** (75)	74:26	69:31
14[f]	**1a/6b**	**I** (5)	6	neat	**7ab** (77)	75:25	72:28
15	**1a/6b**	**V** (5)	5	neat	**7ab** (90)	76:24	74:26

[a]Reaction performed with 1.5 equiv of nucleophile. [b]Yields determined after chromatographic purifications. [c]Diastereomeric excess determined by ^{1}H NMR of the crude reaction mixture (>98:<2 means that a single diastereomer was detected). [d]Enantiomeric ratio determined by chiral HPLC analysis. [e]Ball mill conditions. [f]The reaction was carried out at −20 °C. [g]37% of 2-nitrocyclohexanone was recovered unreacted. [h]30% of 2-nitrocyclohexanone was recovered unreacted.

ic addition of α-nitrocyclohexanone (**6a**) to nitrostyrene derivatives **1a**, **1b**, and **1d** under ball milling conditions [33]. We chose these reactions for comparative purposes because they have been previously reported [34]. Although the experimental conditions have not been optimized, we observed that both the unsupported (**I**) and supported (**V**) catalysts worked very well in the reaction of **1a** with **6a** yielding the addition product **7aa** in excellent yields and stereoselectivity (entries 3 and 6 in Table 4). On the contrary, the reactions of **6a** with **1b** and **1d** are very slow and 37% and 30% of the nucleophile were recovered unchanged after 48 h and 360 h of reaction, respectively, although maintaining the stereoselectivity (Table 4, entries 10 and 12). The improvement of that process is under study.

Conclusion

In summary, supported bifunctional thioureas on sulfonylpolystyrene are able to promote highly stereoselective nitro-Michael reactions with different nucleophiles. The activity of the catalysts varies with the length of the tether between the polymer and the thiourea framework, and the best results were obtained by using catalysts **IV** and **V**, derived from 1,6-hexanediamine. The reactions work well by using only 2 mol % of catalyst loading in neat conditions, and the catalysts can easily be recovered and reused for four cycles. The results obtained with the described catalysts are similar to those previously reported by using bottom-up synthesized materials prepared by co-polymerization of monomeric thioureas as organocatalysts [29]. Catalyst **V** has been also used in the addition of α-nitrocyclohexanone (**6a**) to β-nitrostyrene (**1a**) under solvent-free conditions in a ball mill providing the addition product **7aa** in excellent yield, total diastereoselectivity, and very good enantioselectivity.

Experimental

General remarks

^{13}C NMR (126 MHz) and ^{1}H NMR (500 MHz) spectra were recorded in $CDCl_3$ as the solvent. Chemical shifts for carbons are

reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration.

Flash chromatography was carried out using silica gel (230–240 mesh). TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Specific rotations were measured on a digital polarimeter using a 5 mL cell with a 1 dm path length, and a sodium lamp, and the concentration is given in g per 100 mL. Chiral HPLC analysis was performed by using Daicel Chiralcel OD or Chiralpak AD-H, analytical columns (250 × 4.6 mm) by using mixture of *n*-hexane/isopropanol as eluent. UV detection was monitored at 220 or at 254 nm. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system. Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave–activated 4 Å molecular sieves. Supported thioureas **II**–**V** and unsupported thioureas **I** and **VI** were prepared according to reported procedures [30,31]. Racemic reference samples were prepared by using DABCO (5 mol %) following the same procedure as described below.

General procedure for the nitro-Michael reaction using homogeneous catalysts (I and VI). The reactions were carried out as previously described [29]. To a mixture of nitrostyrene (0.3 mmol) and catalyst (0.015 mmol, 0.05 equiv), the 1,3-dicarbonyl compound (0.6 mmol, 2 equiv) was added and the reaction mixture was stirred at rt in a Wheaton vial until consumption of the starting material (monitoring by TLC). The reaction mixture was purified by column chromatography to afford the Michael product. The *anti*- and *syn*-isomers of the Michael products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the purified product.

General procedure for the nitro-Michael reaction using inmobilized catalysts (II, III, IV and V) [29]. To a mixture of β-nitrostyrene (0.3 mmol) and catalyst (0.015 mmol, 0.05 equiv), 1,3-dicarbonyl compound (0.6 mmol, 2 equiv) was added and the reaction mixture was stirred at rt in a Wheaton vial until consumption of the starting material (monitored by TLC). The catalyst was filtered off and washed with MeOH (3 × 1 mL). The solvent was removed under reduced pressure, and the residue was purified by column chromatography. The *anti*- and *syn*-isomers of the Michael products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the purified product.

Recyclability of the supported thiourea catalysts in nitro-Michael reaction. The supported catalysts were recovered from the reaction mixtures by filtration, thoroughly washed with methanol, dried and reused in the next cycle.

General procedure for the Michael addition of 2-nitrocyclohexanone to β-nitrostyrene using immobilized catalyst **VI**

Method A, in organic solvent: The reactions were carried out as previously described [29]. To a stirred solution of 2-nitrocyclohexanone (43 mg, 0.3 mmol) and nitroalkene (0.45 mmol, 1.5 equiv) in an adequate solvent (0.4 mL), catalyst **VI** (15 mg, 0.015 mmol, 0.05 equiv) was added and the reaction mixture was stirred at room temperature in a Wheaton vial until the reaction was finished (TLC). The catalyst was filtered off and washed with DCM (3 × 1 mL). The solvent was removed under reduced pressure, the crude mixture subjected to flash chromatography to afford the Michael adduct. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the purified product. The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

Method B, under ball-milling conditions: Catalyst **VI** (15 mg, 0.015 mmol, 0.05 equiv), 2-nitrocyclohexanone (43 mg, 0.3 mmol) and nitroalkene (0.45 mmol, 1.5 equiv) were transferred to a clean, dry ball milling vessel (cylinder of 5 mL) loaded with two grinding balls with a 7 mm diameter. The vessel was placed in a Mixer Mill MM 200 and the mixture was milled at 5 Hz of vibrational frequency at room temperature until consumption of the starting material (monitored by TLC). The vessel and the balls were washed with CH_2Cl_2, the catalyst was filtered off and washed with CH_2Cl_2 and methanol. The resulting solution was concentrated in vacuo, and the product was purified by flash chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the purified product. The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

Supporting Information

Supporting Information File 1

Physical and spectral data for all the compounds. Copies of ^{1}H, ^{13}C NMR spectra, and HPLC traces for all compounds synthesized.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-61-S1.pdf]

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Stereoselective amine-thiourea-catalysed sulfa-Michael/nitroaldol cascade approach to 3,4,5-substituted tetrahydrothiophenes bearing a quaternary stereocenter

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Letter

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Abstract

An investigation on the stereoselective cascade sulfa-Michael/aldol reaction of nitroalkenes and commercially available 1,4-dithiane-2,5-diol to 3,4,5-substituted tetrahydrothiophenes, bearing a quaternary stereocenter, is presented. A secondary amine thiourea derived from (*R*,*R*)-1,2-diphenylethylamine was found to be the most effective catalyst when using *trans*-β-methyl-β-nitrostyrenes affording the heterocyclic products in good yields and moderate stereoselectivities.

Introduction

The interest toward the development of stereoselective methodologies to prepare tetrahydrothiophenes bearing multiple chiral centers increased over the last years [1]. Indeed, chiral non-racemic functionalized tetrahydrothiophenes are endowed with different biological activities [2-5] and they are useful ligands in asymmetric catalysis [6]. However, few asymmetric approaches are available to obtain this class of compounds and only recently organocatalytic stereoselective cascade reactions have emerged as the most successful, and straightforward approach to access them [7,8]. Aminocatalytic [9-12] and non-covalent organocatalytic cascade sulfa-Michael/Michael [13-15] and sulfa-Michael/aldol reactions [16-20] enabled the synthesis of differently functionalized tetrahydrothiophenes bearing up to three contiguous chiral centers, including quaternary ones, with good to high control of the diastereo- and enantioselectivity.

Surprisingly, to date there has been one report on a dynamic system combining a 1,1,3,3-tetramethylguanidine (TMG)/ZnI_2-catalyzed diastereoselective cascade sulfa-Michael/nitroaldol reaction followed by lipases catalyzed kinetic resolution using

two representative *trans*-β-methyl-β-nitrostyrenes and 1,4-dithiane-2,5-diol as reagents [21]. One diastereoisomer of the racemic tetrahydrothiophenes, present at the equilibrium, was preferentially acylated by the enzyme to give the product in high ee.

Different amines such as Et_3N, DBU, TMG catalyze the sulfa-Michael/nitroaldol process of either *trans*-β-methyl-β-nitrostyrenes [21] and *trans*-β-nitrostyrenes [22] with 1,4-dithiane-2,5-diol. Based on all above considerations and prompted by our interest in asymmetric synthesis of functionalized tetrahydrothiophenes [14], we wondered whether we could use bifunctional organocatalysts to develop a diastereo- and enantioselective cascade sulfa-Michael/nitroaldol reaction and herein we report our preliminary results.

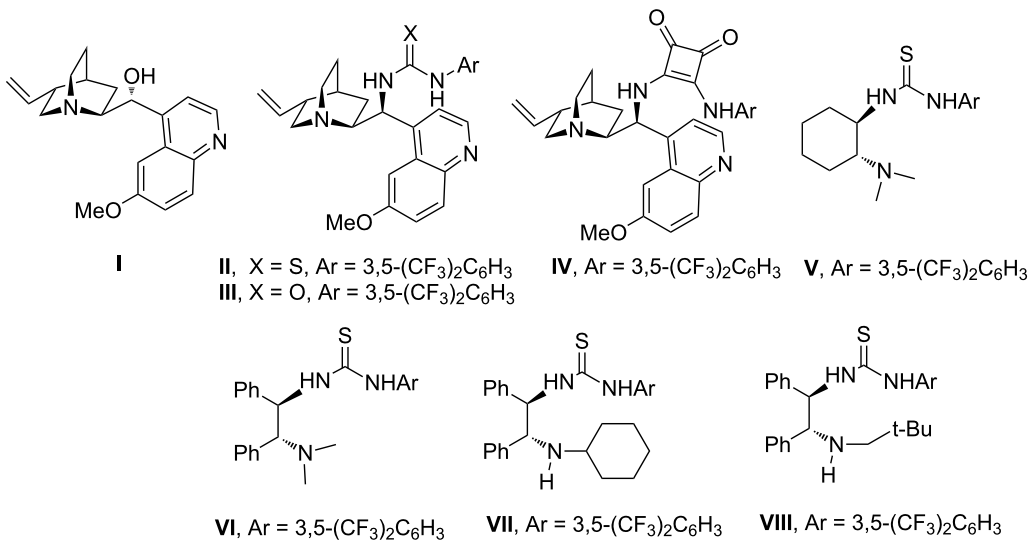
Results and Discussion

According to the literature data, low control of the diastereoselectivity was observed in the cascade reaction of 1,4-dithiane-2,5-diol with *trans*-β-nitrostyrenes, and in the case of (*E*)-1-aryl-2-nitropropene all four diastereoisomeric tetrahydrothiophenes were observed when using tertiary amines such Et_3N, DBU or TMG [21,22].

At the outset, the sulfa-Michael/nitroaldol reaction was studied by reacting *trans*-β-nitrostyrene, (*E*)-1-phenyl-2-nitropropene and (*E*)-1-phenyl-2-nitrobutene in toluene at room temperature with 1,4-dithiane-2,5-diol as precursor of mercaptoacetaldehyde, using 10 mol % loading of different bifunctional organocatalysts (Scheme 1, Table 1).

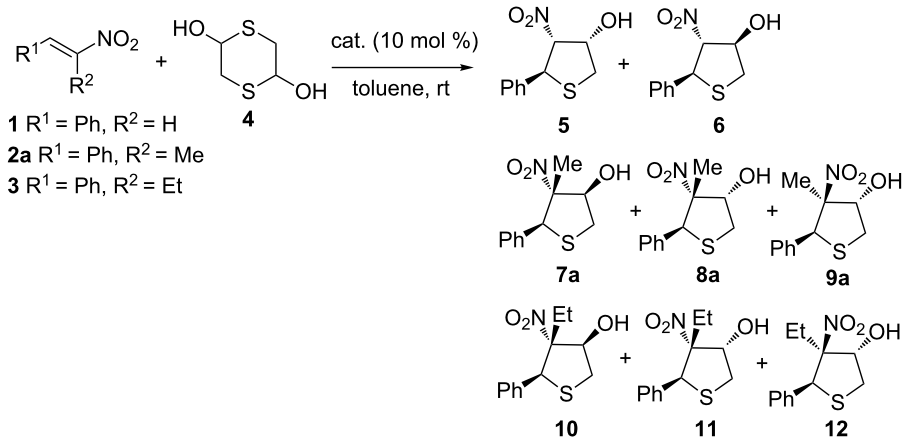
In the case of *trans*-β-nitrostyrene (**1**), a mixture of diastereoisomers **5** and **6** were rapidly formed, irrespective of the catalyst used, with a poor level of diastereo- and enantioselectivity (Table 1, entries 1–5). Thiourea catalyst **VII** afforded the best result, leading to products **5**/**6** in a ratio of 72/28 although with low ee values (Table 1, entry 6). Reacting trisubstituted olefin **2a** with compound **4**, led to three isomers with modest diastereocontrol when using catalysts (**I–VII**). Among the catalysts tested, compound **VII** proved to be the most active and enantioselective, giving the major diastereoisomer **7a** with 44% ee (Table 1, entry 13). Taking into account that amine thiourea **VII**, bearing a sterically hindered secondary amine moiety, was significantly more effective than tertiary amine-based thioureas [14,23], catalyst **VIII**, bearing a sterically demanding neopentyl group, was synthesized in order to check its impact on the stereoselectivity (Scheme 2).

Catalyst **VIII** was easily obtained in a two-step procedure in fair overall yield. Compound **VIII** proved to be less active, affording a comparable level of diastereoselectivity than compound **VII**, but a lower ee value for major diastereoisomer **7a** was measured (Table 1, entry 14). Moreover, the opposite enantiomer of product **7a** was preferentially obtained, thus suggesting that the nature of the alkyl group on the secondary amine moiety greatly affects the stereochemical outcome of the process. The relative configuration of diastereoisomers **7a**/**8a**/**9a** was established by NOESY and NOE analysis on diastereoisomerically pure **7a** and on a diastereoisomeric mixture of compounds **8a** and **9a** (see the Supporting Information File 1) [24].



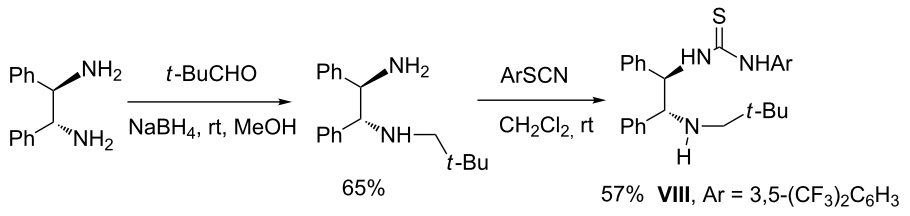
Scheme 1: Organocatalysts screened in the cascade reaction.

Table 1: Asymmetric sulfa-Michael/nitroaldol reaction of nitroalkenes **1**–**3** with 1,4-dithiane-2,5-diol (**4**) catalyzed by catalysts **I**–**VIII**.



entry	cat.	1–3	time (h)	yield [%][a]	dr[b]	ee [%][c]
1	**I**	**1**	5.5	75	58/42 (**5**/**6**)	9 (**5**)/15 (**6**)
2	**II**	**1**	2.5	79	60/40 (**5**/**6**)	rac (**5**)/24 (**6**)
3	**III**	**1**	1.5	53	44/56 (**5**/**6**)	rac (**5**)/12 (**6**)
4	**IV**	**1**	25	52	50/50 (**5**/**6**)	−14 (**5**)/20 (**6**)
5	**V**	**1**	2	89	38/62 (**5**/**6**)	−3 (**5**)/−10 (**6**)
6	**VII**	**1**	2	73	72/28 (**5**/**6**)	−12 (**5**)/−24 (**6**)
7	**I**	**2a**	21	77	66/28/6 (**7a**/**8a**/**9a**)	19 (**7a**)
8	**II**	**2a**	17	77	66/27/7 (**7a**/**8a**/**9a**)	13 (**7a**)
9	**III**	**2a**	17	69	68/24/8 (**7a**/**8a**/**9a**)	4 (**7a**)
10	**IV**	**2a**	27	59	70/23/7 (**7a**/**8a**/**9a**)	2 (**7a**)
11	**V**	**2a**	18	72	68/24/8 (**7a**/**8a**/**9a**)	−19 (**7a**)
12	**VI**	**2a**	44	16	69/25/6 (**7a**/**8a**/**9a**)	1 (**7a**)
13	**VII**	**2a**	28	90	58/30/12 (**7a**/**8a**/**9a**)	−44 (**7a**)
14	**VIII**	**2a**	40	70	65/29/6 (**7a**/**8a**/**9a**)	19 (**7a**)
15	**VII**	**3**	52	80	50/27/23 (**11**/**10**/**12**)	42 (**11**)

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis. Negative values indicate the prevalent formation of the opposite enantiomer.



Scheme 2: Synthesis of catalyst **VIII**.

Finally, catalyst **VII** was checked in the reaction of alkene **3** under the same conditions (Table 1, entry 15). After a longer reaction time, diastereoisomers **10**–**12** were isolated with poor diastereomeric ratio and major isomer **11** was recoverd with 42% ee [25].

The diastereoselective ratios, determined for tetrahydrothiophenes deriving from alkenes **2a** and **3**, are in line with their computed thermodynamic stability in toluene (see the Supporting Information File 1). Indeed, products **8a** and **9a** were found to be 0.7 kcal/mol less stable compared to compound **7a**. In the

case of products **10–12**, the predicted relative free energies for **10**, **11** and **12** fall within a range of 0.1 kcal/mol.

Pleasingly, a solvent screening for the cascade reaction carried out on compound **2a** with catalyst **VII** enabled to improve the diastereoselectivity as only **7a**/**8a** were detected in 75:25 ratio and the enantiocontrol increased to 50% ee for diastereoisomer **7a** when using chlorobenzene as the solvent at room temperature (Table 2, entry 5).

It is worth noting that bifunctional organocatalyst **VII** appears to be more effective in terms of diastereocontrol than previously employed Brønsted base/Lewis acid system TMG/ZnI_2 giving four diastereoisomers instead [21].

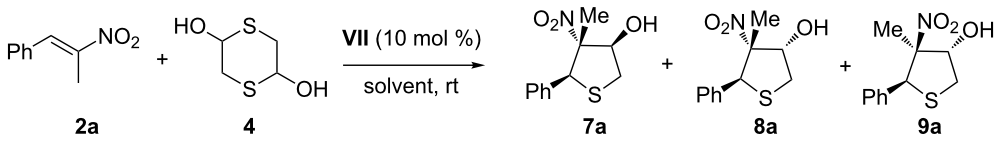
Finally, the sulfa-Michael/nitroaldol cascade reaction was applied to other *trans*-β-methyl-β-nitrostyrenes under the optimized conditions (Table 3).

Tetrahydrothiophenes, bearing three contiguous stereocenters, were isolated in good to high yield, moderate diastereoselectivity and up to 59% ee.

Conclusion

In conclusion, we reported a diastereo- and enantioselective cascade sulfa-Michael/nitroaldol reaction of (*E*)-1-aryl-2-nitropropenes with 1,4-dithiane-2,5-diol. The process was catalyzed by an easily available amine thiourea to give 3,4,5-substituted tetrahydrothiophenes, bearing a quaternary stereocenter, in good yield and moderate enantiocontrol. It has been demonstrated that a simple bifunctional amine thiourea secures a more effective control of the diastereoselectivity than Brønsted base/Lewis acid systems. Data herein illustrated suggest that fine tuning of the bifunctional organocatalyst structure and reaction conditions will be required for further improvements of the challenging cascade process.

Table 2: Solvent screening in the asymmetric Michael/nitroaldol reaction of **2a** with 1,4-dithiane-2,5-diol (**4**) catalysed by amine thiourea **VII**.

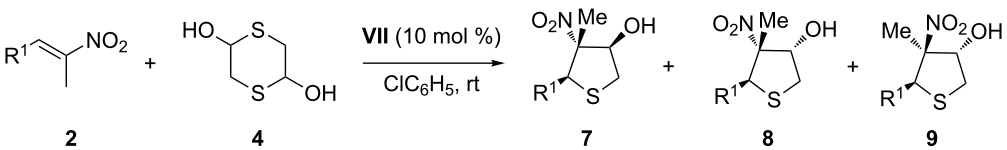


2a **4** **7a** **8a** **9a**

entry	solvent	time (h)	yield [%][a]	dr[b]	ee **7a** [%][c]
1	CH_3CN	21	83	69/31 (**7a**/**8a**)	5
2	CH_3Ot-Bu	47	93	72/24/4 (**7a**/**8a**/**9a**)	30
3	$CHCl_3$	63	56	68/28/4 (**7a**/**8a**/**9a**)	51
4	$ClCH_2CH_2Cl$	63	55	70/30 (**7a**/**8a**)	51
5	C_6H_5Cl	16	69	75/25 (**7a**/**8a**)	50

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Table 3: Asymmetric sulfa-Michael/nitroaldol reaction of nitroalkenes **2** with 1,4-dithiane-2,5-diol (**4**) catalysed by amine thiourea **VII**.



2 **4** **7** **8** **9**

entry	R^1	time (h)	yield [%][a]	dr[b]	ee **7** [%][c]
1	Ph	16	69	75/25 (**7a**/**8a**)	50
2	4-ClC_6H_4	16	66	69/31 (**7b**/**8b**)	51
3	4-MeC_6H_4	40	76	74/26 (**7c**/**8c**)	42
4	2-naphthyl	45	90	66/26/8 (**7d**/**8d**/**9d**)	59

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, NMR spectra of new compounds and HPLC traces of synthesized compounds, computational details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-63-S1.pdf]

Acknowledgements

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24. Diastereoisomers **8a** and **9a** and have the same mobility on TLC.
25. Diastereoisomers **10**, **11** and **12** have very similar mobility on TLC. The relative configurations of diastereoisomers **10**/**11**/**12** were assigned by analogy of chemical shifts observed in the ^{1}H NMR spectra with those of diastereoisomers **7a**/**8a**/**9a**.

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Asymmetric α-amination of 3-substituted oxindoles using chiral bifunctional phosphine catalysts

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Full Research Paper

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Abstract

A highly enantioselective α-amination of 3-substituted oxindoles with azodicarboxylates catalyzed by amino acids-derived chiral phosphine catalysts is reported. The corresponding products containing a tetrasubstituted carbon center attached to a nitrogen atom at the C-3 position of the oxindole were obtained in high yields and with up to 98% ee.

Introduction

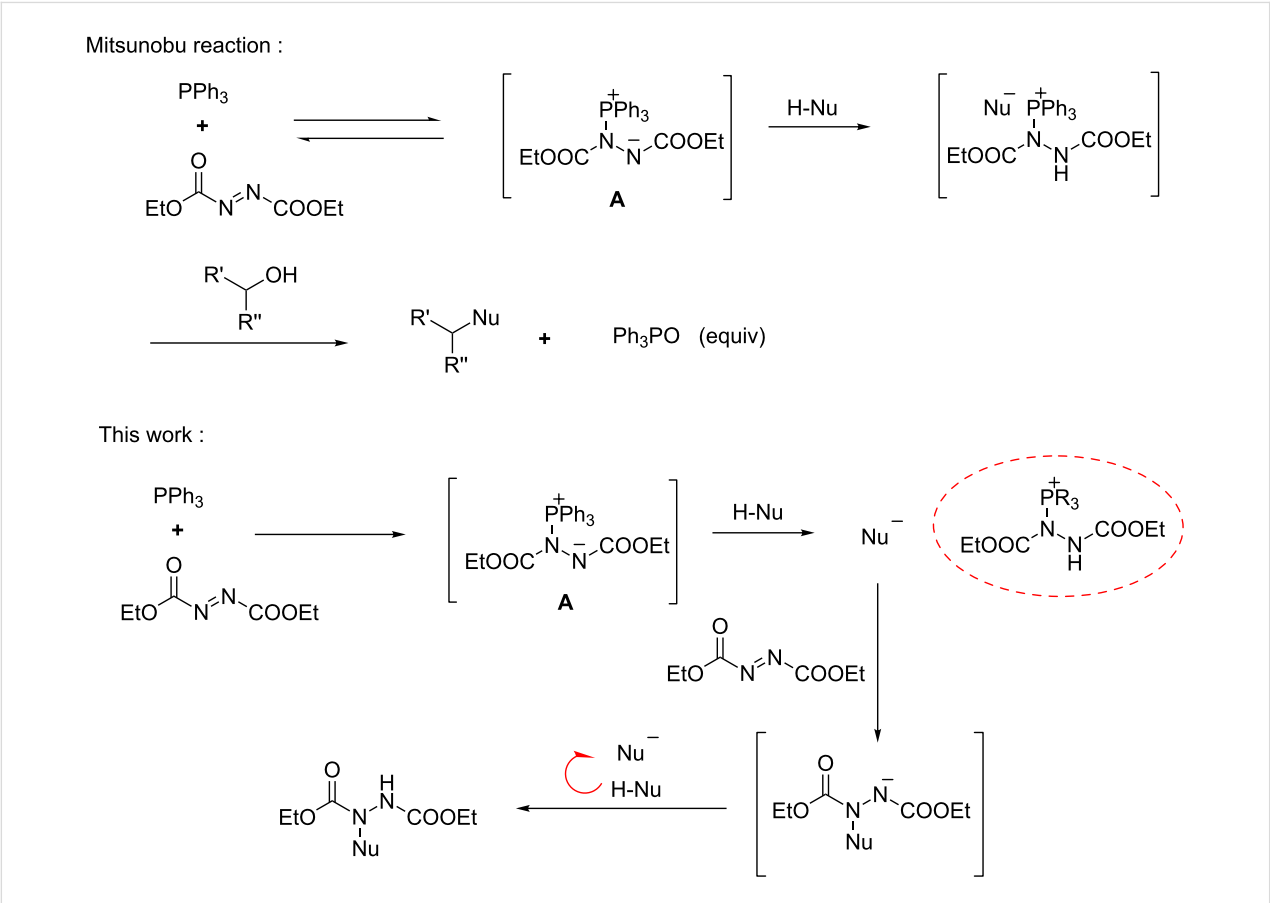
Recently, chiral 3-substituted oxindoles have been attractive targets in asymmetric synthesis due to their abundance in the structures of numerous natural products and pharmaceutically active compounds [1]. In particular, the chiral 3-aminooxindoles containing a tetrasubstituted carbon center have been recognized as core building blocks for the preparation of many biologically active and therapeutic compounds [2-7]. As a type of commercially available electrophilic amination reagents, azodicarboxylates have been extensively used in both asymmetric organocatalysis and metal catalysis for the construction of this type of structures. For example, Chen et al. reported the first organocatalytic enantioselective amination reaction of 2-oxindoles catalyzed by biscinchona alkaloid catalysts [8]. Zhou [9,10] and Barbas [11,12], have independently reported similar organocatalytic processes. In the field of metal catalysis, Shibasaki et al. reported the reaction between C3-substituted oxindole and azodicarboxylates, using homodinuclear or monometallic Ni-Schiff base complexes as catalysts [13]; Feng et al. also developed a similar procedure with chiral *N,N'*-dioxide-Sc(III) complexes as catalysts [14]. Despite these

impressive advances, current catalytic systems still more or less suffer from limitations such as long reaction times, relatively large catalyst loading in most organocatalytic systems and in some cases unsatisfactory yields and/or enantioselectivities. Therefore, the development of more efficient catalytic systems for the asymmetric α-amination of 3-substituted oxindoles with azodicarboxylates is still desirable.

Chiral organophosphine catalysis [15-18] has captured considerable attention over the past decades owing to its high catalytic efficiency in a variety of reactions such as aza-Morita–Baylis–Hillman reactions [19-21], Rauhut–Currier reactions [22-27], Michael addition reactions [28-35], and various cycloadditions [36-39]. In recent years, our group has focused on the development of novel amino acid-derived chiral bifunctional organophosphine catalysts, which have successfully applied to catalyze various asymmetric reactions [40,41]. As a general concept, a tertiary phosphine adds to an electrophilic reactant to form a zwitterion which serves as either a nucleophile or a Bronsted base to participate in the catalytic cycle. In 2015, we reported a novel asymmetric dual-reagent catalysis strategy based on these chiral phosphine catalysts [42], in which the zwitterion in situ generated from the chiral phosphine and methyl acrylate acted as an efficient catalyst for the asymmetric Mannich-type reaction. As an extension of this work, we then wondered if other electrophilic partners instead of methyl acrylate could be used to generate similar catalytically active species in situ. Also inspired by the Mitsunobu reaction [43], we reported herein the reaction of azodicarboxylates with 3-substituted oxindole catalyzed by chiral amino acid-derived organophosphine catalysts, in which the zwitterions in situ generated from the phosphine and azodicarboxylates serve as highly efficient catalysts [44] (Scheme 1).

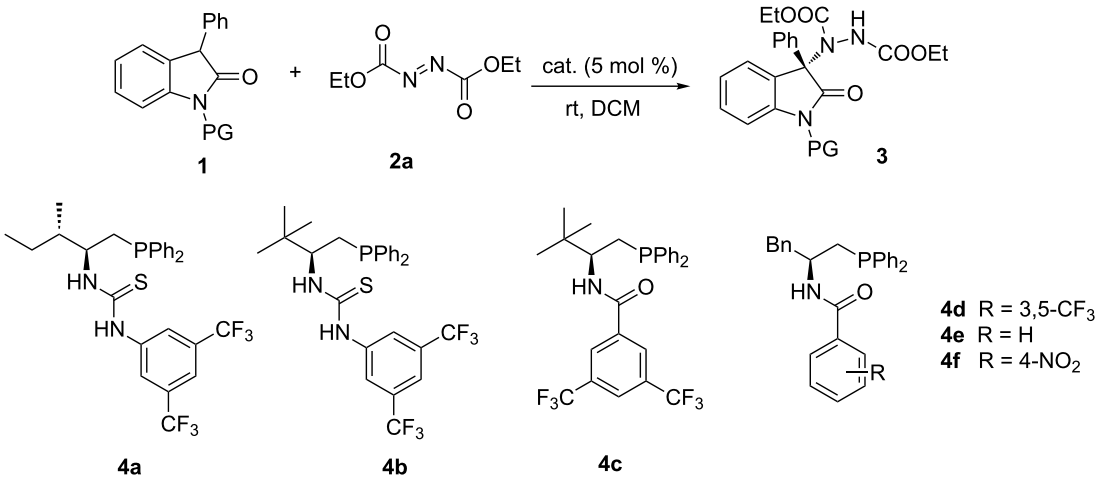
Results and Discussion

Initially, the reaction between 3-phenyloxindole **1a** and DEAD (diethyl azodicarboxylate, **2a**) was selected as the model reaction for the evaluation of chiral phosphine catalysts (Table 1). Using bifunctional thiourea catalysts **4a** and **4b**, the reaction proceeded smoothly at room temperature to afford the product **3a** in good yields, albeit with low enantiomeric excesses (ee) (Table 1, entries 1 and 2). When the thiourea moiety in the catalysts were replaced by amides, the enantioselectivities were greatly improved (Table 1, entries 3–6). The examination of



Scheme 1: The mimetic activation mode of Mitsunobu reaction.

Table 1: Catalyst screening.



Entry[a]	PG	Catalyst	*t* (min)	Yield (%)[b]	ee (%)[c]
1	Boc (**1a**)	**4a**	5	72	17
2	Boc (**1a**)	**4b**	5	79	39
3	Boc (**1a**)	**4c**	5	89	61
4	Boc (**1a**)	**4d**	5	85	83
5	Boc (**1a**)	**4e**	5	88	60
6	Boc (**1a**)	**4f**	5	70	64
7	H (**1b**)	**4d**	40	66	17
8	Bn (**1c**)	**4d**	60	50	0

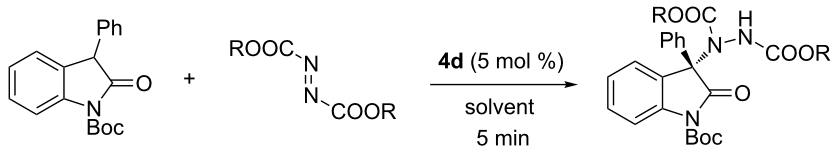
[a]0.1 mmol scale in 1.0 mL of DCM. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

catalysts **4c–f** with further fine-tuning on the acyl group revealed **4d** as the optimal catalyst for this transformation (Table 1, entry 4). Different from *N*-Boc-oxindole, using *N*-unprotected oxindole and *N*-benzyl-substituted oxindole as the substrates, accomplished the reaction with every low enantioselectivity (Table 1, entries 7 and 8), incidated the *N*-Boc protecting group is crucial for this system.

Next, the influence of solvents and reaction temperature on the reaction were investigated with the best catalyst (Table 2). The use of both polar solvents (ethyl ether, tetrahydrofuran, acetone, acetonitrile or ethyl alcohol) including other chlorinated solvents such as chloroform, 1,2-dichloroethane and 1,1,2-trichloroethane or the less polar solvent toluene gave no improvement in enantioselectivity in comparison to the originally used DCM (Table 2, entries 1–9). To our delight, lowering the reaction temperature increased the reaction yield significantly (Table 2, entries 10–16), while the highest ee value (90%) with DEAD was obtained at −30 °C (Table 2, entry 13). Interestingly, the use of other azodicarboxylates with larger R group as amination reagent revealed different optimum reaction temperatures for the best enantioselectivity, and −78 °C was identified as optimal for di-*tert*-butyl azodicarboxylate (**2d**, DBAD, 93% ee, Table 2, entry 20). It's worth mentioning that the reaction could still proceed to completion within 5 minutes under such low reaction temperatures.

With the optimized reaction conditions in hand, a variety of oxindoles **1** and azodicarboxylates **2** were then examined to probe the scope of the reaction (Table 3). In general, the catalytic system showed excellent efficiency for all the substrates examined to provide good to excellent yields and enantioselectivities within a very short reaction time (5 min). The use of the sterically more hindered DBAD is much more favored than DEAD in terms of enantioselectivity. The substitution type including different electronic nature and/or positions of the substituents on the benzene ring of the oxoindole skeleton or 3-aryl group showed no pronounced influence on the reaction in terms of both yield and enantioselectivity. It is noteworthy that products **3i**, **3q**, **3r** and **3s**, which contain a fluorine atom, were obtained in good yield with good to execellent ee (Table 3, entries 6 and 14–16). Enantiomerically enriched fluorine-containing 2-oxoindoles are of great significance in drug discovery and development [45]. Unfortunately, there was no ee observed when

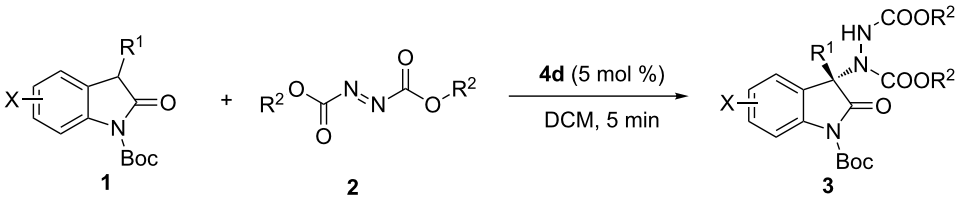
Table 2: Optimization of conditions.



Entry[a]	R	Solvent	*T* (°C)	Yield (%)[b]	ee (%)[c]
1	Et	Et_2O	rt	64 (**3a**)	65
2	Et	THF	rt	62 (**3a**)	39
3	Et	acetone	rt	62 (**3a**)	35
4	Et	acetonitrile	rt	41 (**3a**)	5
5	Et	EtOH	rt	78 (**3a**)	0
6	Et	toluene	rt	70 (**3a**)	79
7	Et	$CHCl_3$	rt	66 (**3a**)	79
8	Et	1,2-dichloroethane	rt	66 (**3a**)	77
9	Et	1,1,2-trichloroethane	rt	74 (**3a**)	53
10	Et	DCM	0	81 (**3a**)	83
11	Et	DCM	−10	93 (**3a**)	84
12	Et	DCM	−20	86 (**3a**)	85
13	Et	DCM	−30	87 (**3a**)	90
14	Et	DCM	−40	87 (**3a**)	84
15	Et	DCM	−50	93 (**3a**)	81
16	Et	DCM	−78	85 (**3a**)	68
17	iPr	DCM	−30	95 (**3b**)	82
18	iPr	DCM	−78	93 (**3b**)	89
19	*t*-Bu	DCM	−30	87 (**3d**)	64
20	*t*-Bu	DCM	−78	80 (**3d**)	93

[a]0.1 mmol scale in 1.0 mL of solvent. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Table 3: Substrate scope.



Entry[a]	X	R^1	R^2	Yield(%)[b]	ee(%)[c]
1	H	Ph	*t*-Bu	87 (**3d**)	93
2	5-Me	Ph	*t*-Bu	85 (**3e**)	96
3	5-OMe	Ph	*t*-Bu	88 (**3f**)	96
4	5-Me	Ph	Et	88 (**3g**)	86
5	5-OMe	Ph	Et	84 (**3h**)	88
6	5-F	Ph	Et	84 (**3i**)	87
7	5-Cl	Ph	Et	85 (**3j**)	90
8	6-Cl	Ph	Et	87 (**3k**)	87
9	H	4-MeC_6H_4	*t*-Bu	89 (**3l**)	81
10	H	4-$OMeC_6H_4$	*t*-Bu	85 (**3m**)	95

Table 3: Substrate scope. (continued)

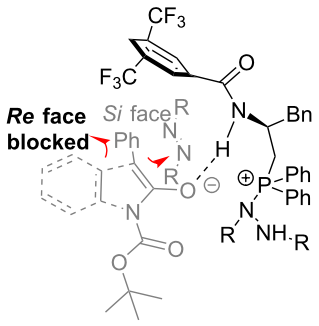
11	H	4-MeC_6H_4	Et	90 (**3n**)	81
12	H	4-*t*-BuC_6H_4	Et	82 (**3o**)	87
13	H	3-OMeC_6H_4	Et	86 (**3p**)	87
14	H	4-FC_6H_4	*t*-Bu	87 (**3q**)	95
15	H	4-FC_6H_4	Et	89 (**3r**)	85
16	5-Me	4-FC_6H_4	*t*-Bu	85 (**3s**)	98
17	5-Me	4-MeC_6H_4	*t*-Bu	86 (**3t**)	96
18	H	Me	Et	72 **(3u)**	0

[a]0.1 mmol scale in 1.0 mL of DCM. At −78 °C when R = *t*-Bu, at −30 °C when R = Et. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

the 3-substituent was changed to an alkyl group (Table 3, entry 18).

Subsequently, a scale-up experiment on 1.0 mmol scale of the reaction was examined, and the corresponding product could be obtained smoothly with a slightly reduced yield (70%) and ee (85%). The ee value of the product could be raised to 96% after a single recrystallization step (Scheme 2). The product could be deprotected to provide the known compound **5** with no deterioration in enantioselectivity. The absolute configuration of **3a** was deduced to be *S* by comparison the specific optical rotation data of **5** with literature data [10,12], and the absolute configurations of other adducts **3b**–**t** were assigned by analogy.

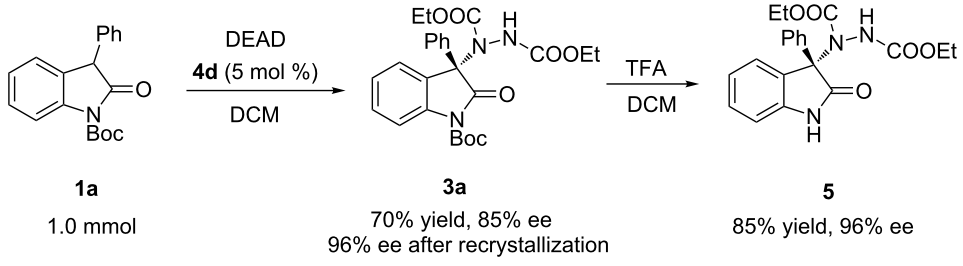
To get some insight into this reaction, ^{31}P NMR of the mixture of **4d** (0.5 mol %) and **2a** (0.12 mmol) in CD_2Cl_2 was monitored, followed by the addition of **1a** (0.1 mmol) in to the mixture (Figure 1). The formation of zwitterion intermediate **A** in Scheme 1, observed as a new ^{31}P NMR chemical shift, was generated at δ = 30 ppm, and did not disappear until the reaction was finished. On the basis of the experimental results and previous related studies, a plausible transition state was proposed to explain the stereochemistry of the product (Scheme 3). We propose that after deprotonation by the basic in situ generated zwitterion, the resultant enolate form of 3-aryloxindoles might interact with the catalyst by both hydrogen bonding as well as static interaction. The presence of the 3,5-CF_3-substituted benzene ring may block the *Re* face of the enolate, driving the electrophile to attack from the *Si* face.



Scheme 3: Proposed transition-state model.

Conclusion

In summary, we have realized enantioselective α-aminations of 3-substitued oxindoles with azodicarboxylates by using amino acid-derived bifunctional phosphine catalysts. These reactions afford a variety of chiral 2-oxindoles with a tetrasubstituted carbon center attached to a nirogen atom at the C-3 position in high yields and excellent enantioselectivities. Further studies regarding the mechanism as well as the development of related reactions using this catalytic mode are currently under investigation.



Scheme 2: Scale-up of the reaction and deprotection of the product.

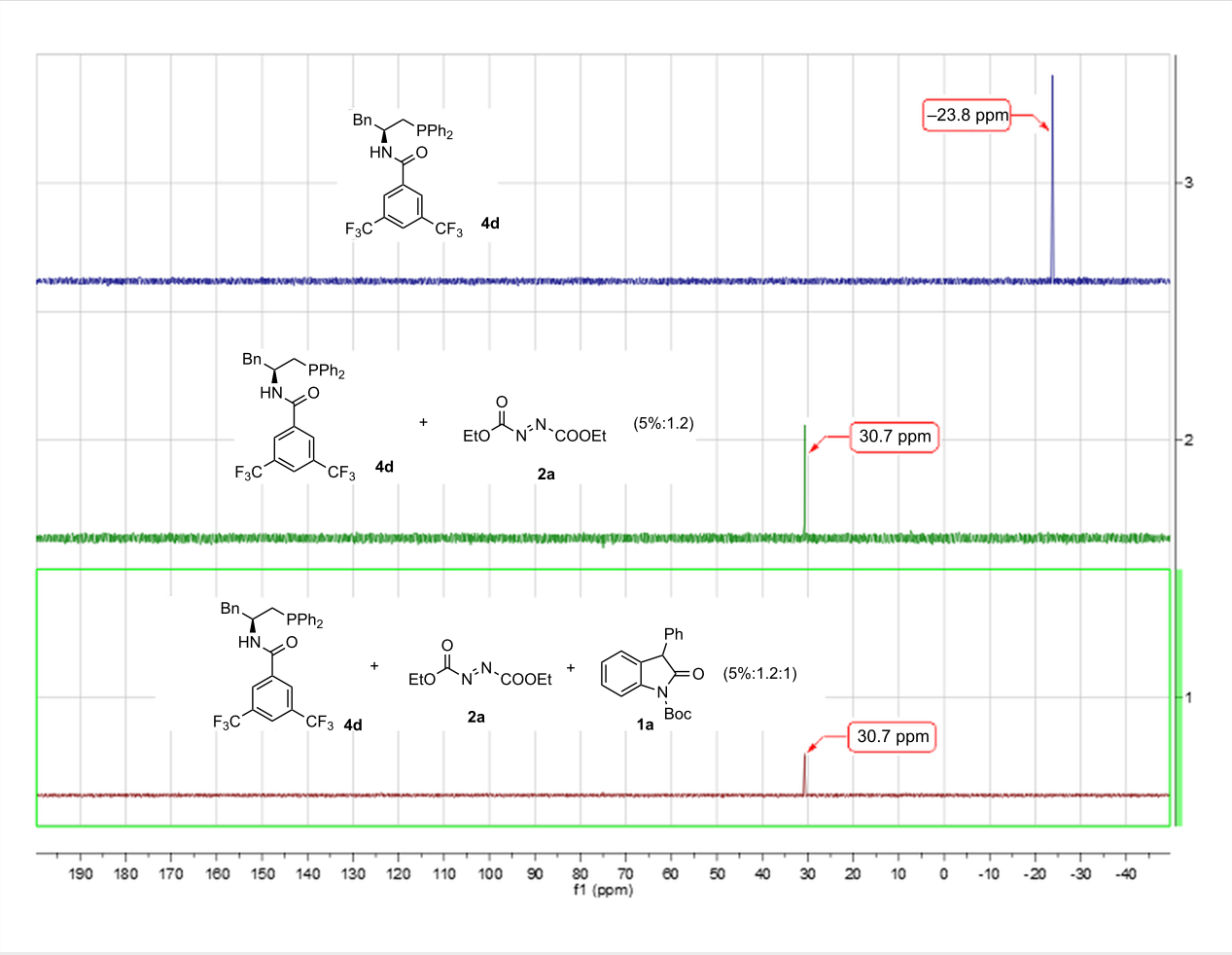


Figure 1: The ^{31}P NMR spectra research in CD_2Cl_2.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-72-S1.pdf]

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1*H*-Imidazol-4(5*H*)-ones and thiazol-4(5*H*)-ones as emerging pronucleophiles in asymmetric catalysis

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Review

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Abstract

Asymmetric catalysis represents a very powerful tool for the synthesis of enantiopure compounds. In this context the main focus has been directed not only to the search for new efficient chiral catalysts, but also to the development of efficient pronucleophiles. This review highlights the utility and first examples of 1*H*-imidazol-4(5*H*)-ones and thiazol-4(5*H*)-ones as pronucleophiles in catalytic asymmetric reactions.

Introduction

Asymmetric catalysis [1-3] constitutes a very powerful tool for the preparation of enantiomerically pure compounds [4]. Recent efforts in the field have been devoted to the development of new efficient chiral catalysts, both metal catalysts and organocatalysts, together with the search for appropriate (pro)nucleophiles and/or electrophiles. In this context, the enantioselective construction of tetrasubstituted stereocenters is another challenge [5-13]. Regarding reactions which involve proton transfer events, soft enolization [14-16] constitutes an efficient tool for the deprotonation of some carbonyl compounds [17,18]. In these cases, a relatively weak amine is generally used to reversibly deprotonate a relatively acidic substrate; however, to date, the carbonyl components for these reactions are mostly restricted to 1,3-diones, β-ketoesters, malonates, α-cyanoacetates, 3-substitued oxindoles and related systems. Generally, enolizable esters or carboxylic acid derivatives have been challenging in this strategy, because their p*K*a values (approximately 19 in DMSO) [19] are much higher, one exception being thioesters [20,21] and pyrazoleamides [22]. As an alternative, some specific heterocycles have been proposed as carboxylic acid surrogates. Examples of this type of heterocycles are oxazol-5-(4*H*)-ones (or azlactones) and their analogues (Figure 1a) and oxazol-4-(5*H*)-ones and their thiazolone and imidazolone analogues (Figure 1b).

These heterocycles show very interesting characteristics: i) easy deprotonation under soft enolization conditions (aromatic enolate formation); ii) the geometry of the resulting starting

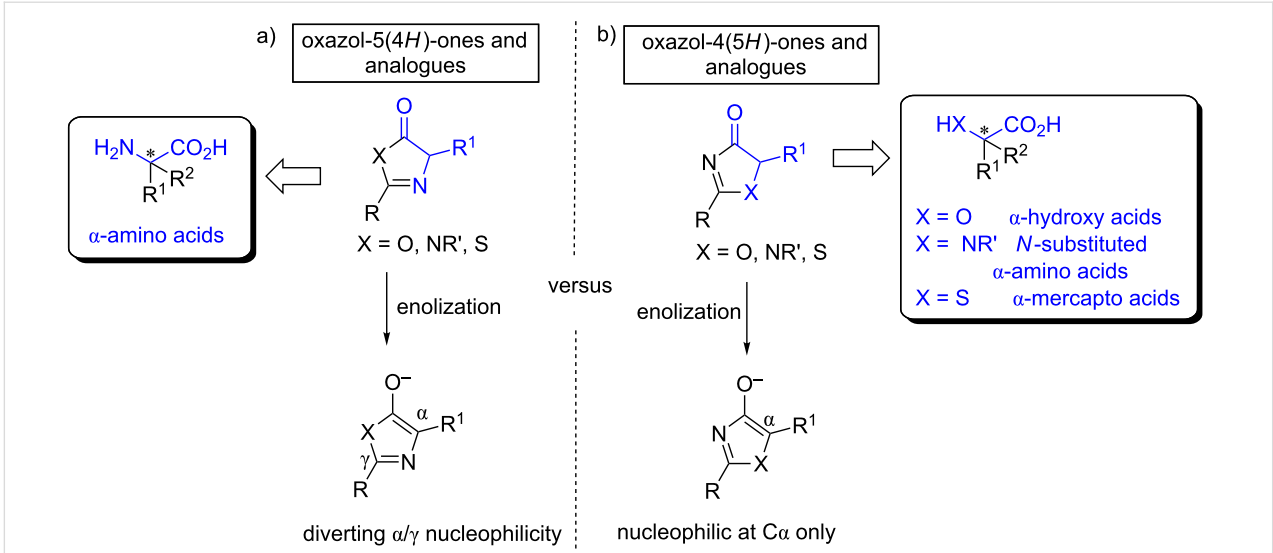


Figure 1: Some α-substituted heterocycles for asymmetric catalysis, their reactivity patterns against enolization, and resulting adducts after catalytic reaction and hydrolysis.

enolate or equivalent is fixed due to their cyclic nature, thus facilitating the control of the stereoselectivity; iii) they are substituted at the α-position of the carbonyl and therefore, after reaction with an electrophile, a tetrasubstituted stereocenter is created and, iv) the resulting adducts can be easily hydrolyzed to provide carboxylic acids or their derivatives carrying different functionalities.

The most common pronucleophiles of this type are oxazol-5-(4*H*)-ones or azlactones (Figure 1a, X = O), which have been thoroughly investigated and reviewed [23-25]. On the other hand, since the pionnering work by Trost in 2004 [26], several examples of the utility of the structurally related oxazol-4(5*H*)-ones (Figure 1b, X = O) have also been published, which involve mainly Michael additions (to enones [27,28], nitroalkenes [29,30], alkynones [31-33] and vinyl sulfones [34]), γ-additions to allenic ketones and esters [35,36], 1,6-additions to conjugated dienones [37], aldol/Mannich reactions [26,38-40], α-sulfenylation reactions [41] and alkylations [42,43]. More recently the nitrogen (1*H*-imidazol-4(5*H*)-ones, Figure 1b, X = NR') and sulfur (thiazol-4(5*H*)-ones, Figure 1b, X = S) analogues of these oxazol-4(5*H*)-ones have been demonstrated to be very interesting templates in asymmetric catalysis. In these cases the hydrolysis of the adducts coming from an asymmetric reaction can provide enantioenriched α-hydroxy acids (X = O), *N*-substituted α-amino acids (X = NR') or α-mercapto acids (X = S) depending on the nature of the starting heterocycle. This review describes the first examples and applications of 1*H*-imidazol-4(5*H*)-ones **1** and thiazol-4(5*H*)-ones **2** (Figure 2) as emerging pronucleophiles in asymmetric catalytic reactions.

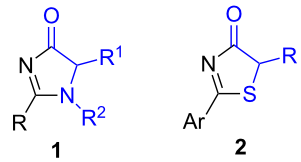


Figure 2: 1*H*-Imidazol-4(5*H*)-ones **1** and thiazol-4(5*H*)-ones **2**.

Review

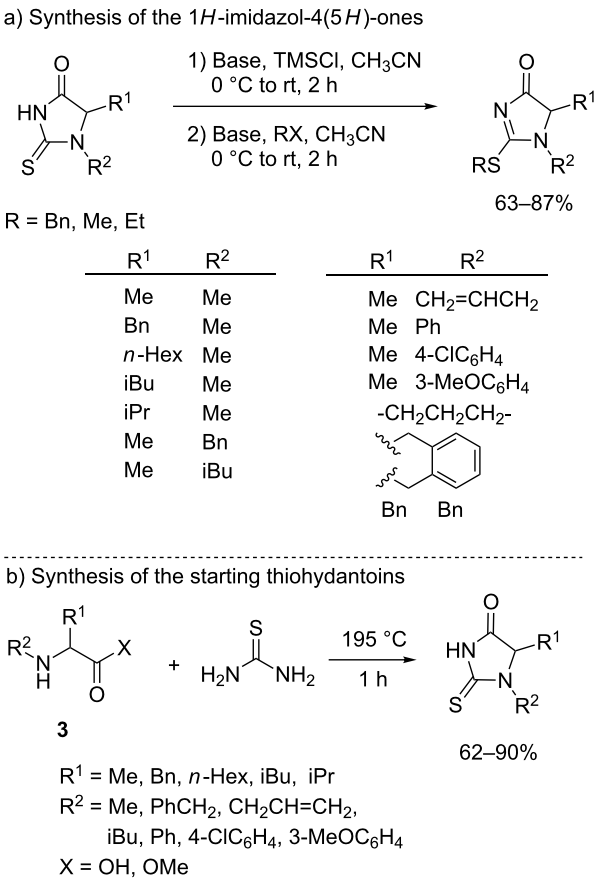
1 1*H*-Imidazol-4(5*H*)-ones **1**

α,α-Disubstituted (quaternary) amino acids are compounds and/or scaffolds of demanding continuous interest [44] and many stereoselective protocols have been developed for their syntheses [44-50]. In this field, particularly interesting are *N*-substituted derivatives, which are potentially good therapeutical candidates because of their high lipophilicity and membrane permeability [44,51]. A major catalytic entry to α,α-disubstituted (quaternary) amino acids is the α-functionalization of an appropriate template as, for instance, an α-imino ester or lactone, followed by hydrolysis [49,52,53]; but, however, very few of them provide *N*-substituted derivatives directly [54]. In this context, 1*H*-imidazol-4(5*H*)-ones **1** have been recently introduced as novel nucleophilic α-amino acid equivalents for the catalytic and asymmetric synthesis of *N*-alkyl, *N*-aryl and *N*-allyl α,α-disubstituted amino acids [55]. The main advantages of these pronucleophiles over the previous known templates are: i) the NR group can be installed in the heterocycle previous to the asymmetric reaction, ii) they are easily deprotonated under soft enolization conditions (aromatic enolate forma-

tion), and iii) unlike azlactones and analogous they do not show the Cα/Cγ selectivity problem [56-58].

1.1 Synthesis of 1*H*-imidazol-4(5*H*)-ones **1**

1*H*-Imidazol-4(5*H*)-ones **1** (R = SBn) are prepared by *S*-alkylation of the corresponding thiohydantoins [55,59] (Scheme 1a) prior trimethylsilyl enol ether formation which is necessary to avoid *O*-alkylation. The starting thiohydantoins, in turn, are obtained by heating a mixture of the corresponding *N*-substituted amino acid or its methyl ester **3** and thiourea at 195 °C [59] (Scheme 1b). Following this protocol different 1*H*-Imidazol-4(5*H*)-ones have been prepared in good yields.



Scheme 1: a) Synthesis of 2-thio-1*H*-imidazol-4(5*H*)-ones [55] and b) preparation of the starting thiohydantoins [59].

1.2 1*H*-Imidazol-4(5*H*)-ones **1** as pronucleophiles in organocatalyzed Michael addition reactions

2-Thio-1*H*-imidazol-4(5*H*)-ones **1** (R = SBn) have been reported to be effective equivalents of *N*-subtituted (alkyl, aryl, allyl) α-amino acids in conjugate addition reactions to both, nitroalkenes and α-silyloxy enones as Michael acceptors in reactions promoted by bifunctional Brønsted bases.

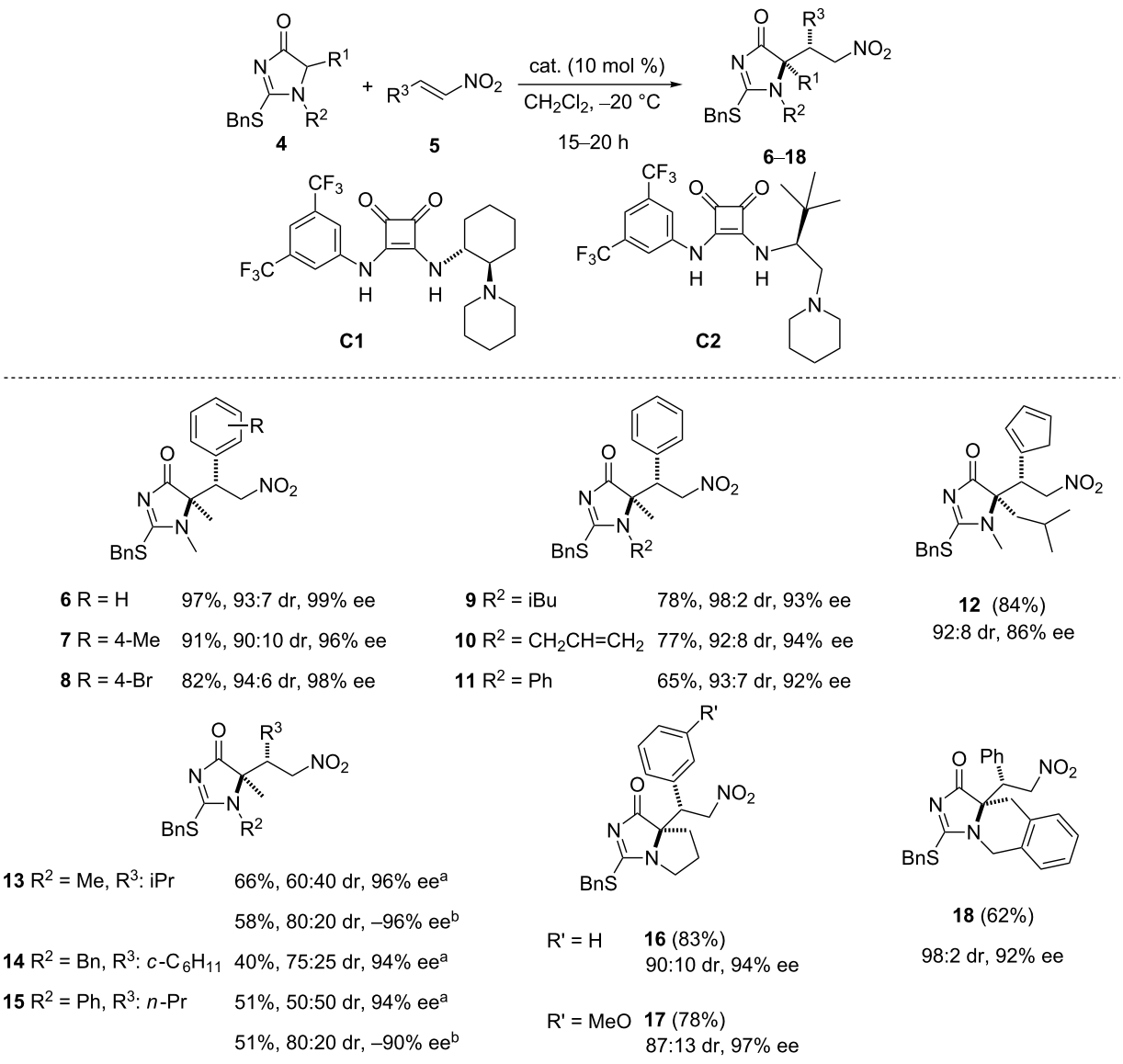
1.2.1 Nitroalkenes as acceptors. Investigation of the base-catalyzed Michael addition reaction of 2-thio-1*H*-imidazol-4(5*H*)-ones **4** to nitroalkenes **5** [55] revealed that cinchona alkaloids such as quinine, $(DHQ)_2Pyr$ or even thiourea tertiary amine catalysts were not efficient in terms of stereoselectivity. However, good results regarding both, yield and stereocontrol, were observed when the Rawal catalyst **C1** [60,61] was employed (Scheme 2).

Under the optimized conditions the reaction, as shown in Scheme 2, worked equally well regardless of the electronic character of the β-aryl substituent of nitroalkene **5** (compounds **6**–**8**). Different substituents either at the nitrogen atom of the starting imidazolone (compounds **9**–**11**) or at the 5-position (compound **12**) of the ring are also well tolerated. Reactions with β-alkyl nitroolefins in the presence of **C1** (Scheme 2, compounds **13**–**15**) proceeded with poor diastereocontrol but the results were improved by changing to catalyst **C2** [62]. Nonetheless, in both cases the enantioselectivity for the major diastereomer was excellent. Finally, and starting from the corresponding bicyclic imidazolones, quaternary proline and related derivatives (**16**–**18**), which are difficult to obtain through established catalytic methodologies [63-65], can also be efficiently synthesized.

On the other hand, it is worthy of note that thiohydantoins, which are structurally related to 2-thio-1*H*-imidazol-4(5*H*)-ones **1**, have been demonstrated to be either less reactive and/or less stereoselective in their addition reaction to nitrostyrene thus affording the corresponding Michael adducts with no diastereoselectivity and/or poor enantioselectivity (Scheme 3).

Useful applications of the Michael adducts coming from the Michael addition of imidazolones to nitroalkenes are shown by the transformations depicted in Scheme 4. Thus, nucleophilic displacement of the thioether group gives access to various types of heterocycles of interest in medicinal chemistry [66,67] (i.e., imidazolidinones **19** and **20**, 2-arylimidazolone **22**, 2-aminoimidazolone **23** and hydantoins **24**–**26**). On the other hand, acid hydrolysis of these adducts efficiently affords *N*-alkylamino acid derivatives, as for instance the *N*-methylamino amide **21**. Additionally, from the common adduct **26**, functionalized polycyclic hydantoins of type **27** and **28** can also be synthesized.

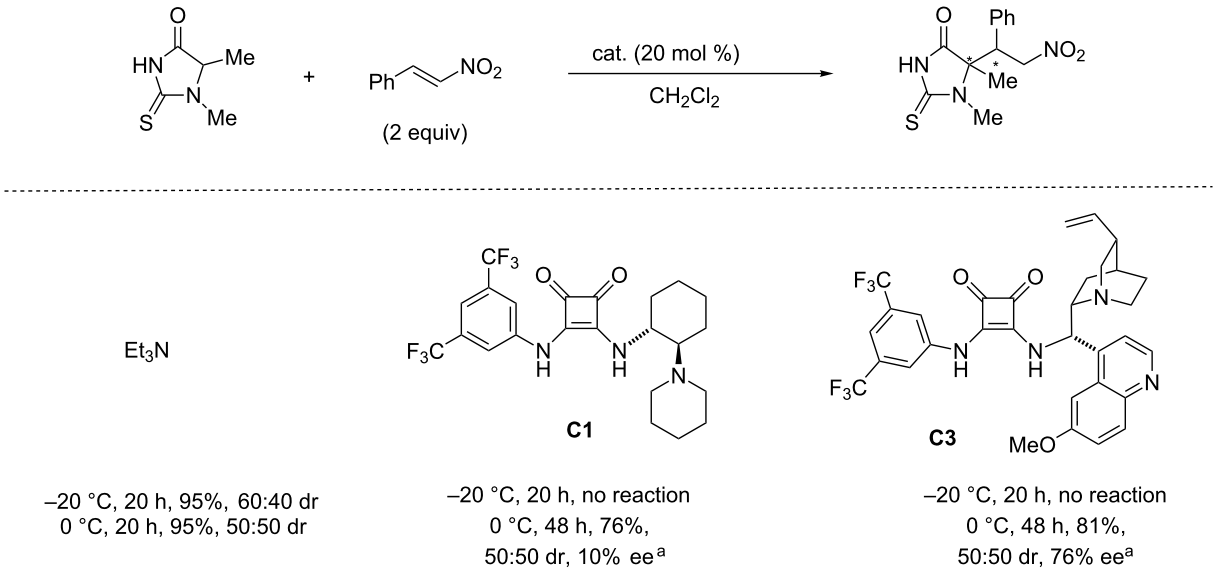
The authors proposed an heuristic model (Figure 3) to account for the experimentally encountered selectivity where the catalyst is proposed to act in a bifunctional way. In this proposal the imidazolone would be coordinated to the two NH bonds of the squaramide and the ortho-ArH in **C1**, whilst the nitroalkene would form a hydrogen bond by coordination to the protonated



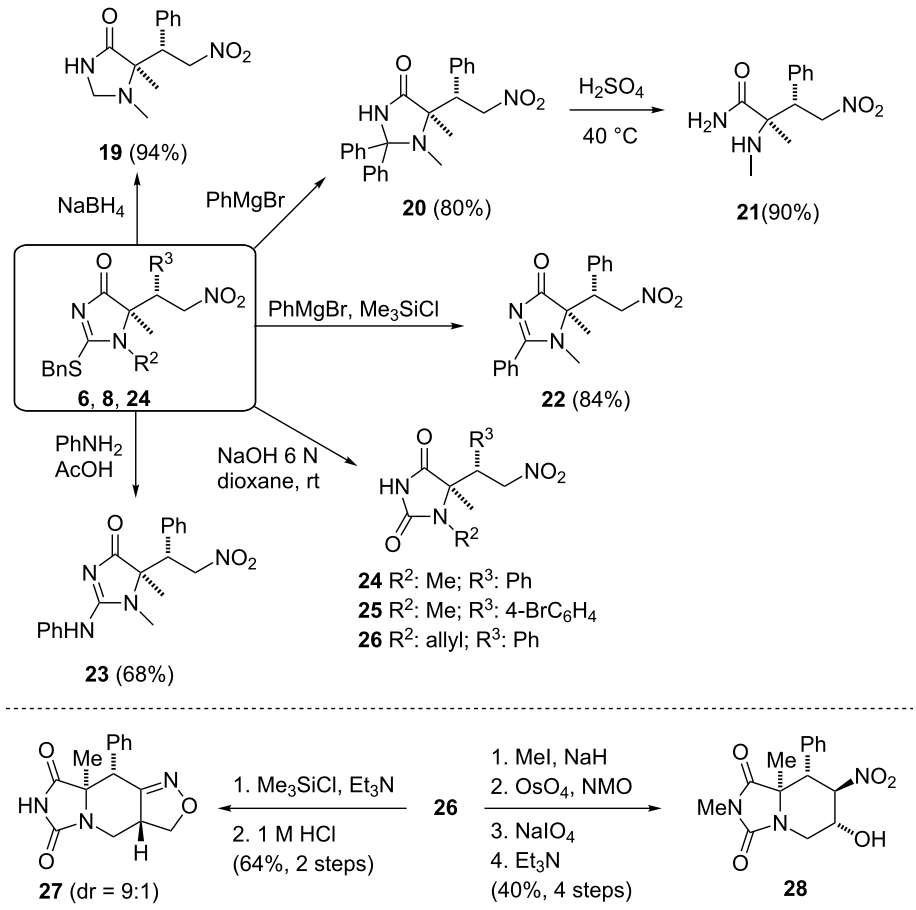
Scheme 2: Selected examples of the Michael addition of 2-thio-1*H*-imidazol-4(5*H*)-ones to nitroalkenes [55]. [a]Reactions run at 50 °C in CH_2Cl_2. [b]Using catalyst **C2**.

tertiary amine through the oxygen of the nitro group. This assumption was supported by the fact that the chemical shift of the *ortho*-ArH in **C1** varies considerably after the addition of 1 equivalent of imidazolone to a solution of **C1** in $CDCl_3$, whereas it doesn't change after the addition of nitrostyrene.

1.2.2 α-Silyloxyenones as acceptors. Among Michael acceptors, simple α,β-unsaturated esters and amides still are challenging substrates in direct Michael additions and have only been employed in few successful Michael reactions, mainly due to their inherent lower reactivity and the limitations associated to the activation/coordination of these compounds to a suitable chiral catalyst. Although recently it has been shown that the problem of this low reactivity may be addressed through the development of Brønsted base catalysts with increased basicity [68], most efforts still focus on the development of unsaturated ester/amide surrogates [69-71], which involve α,β-unsaturated imides, *N*-acyl heterocycles, α-oxophosphonates, α-ketoesters, 3-methyl-4-nitro-5-alkenylisoxazoles and α'-hydroxyenones. These latter substrates have proven to be very efficient platforms for bidentate coordination in metal catalysis and good precursors of carboxylic acids, ketones and aldehydes upon oxidative cleavage of the keto/diol moiety [72]. More recently, a comprehensive study on the first evidence of the utility of these acceptors in organocatalysis has been published [73]. This study shows that α'-oxyenones are very efficient key enoate equiva-



Scheme 3: Michael addition of thiohydantoins to nitrostyrene assisted by Et_3N and catalysts **C1** and **C3**. [a]Absolute configuration not determined.



Scheme 4: Elaboration of the Michael adducts coming from the Michael addition to nitroalkenes [55].

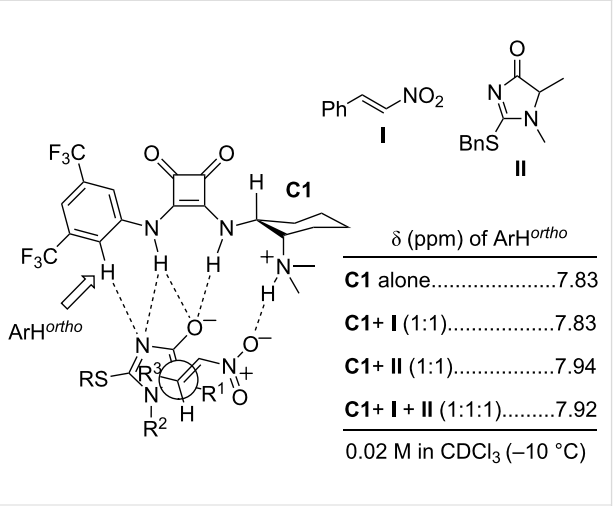


Figure 3: Proposed model for the Michael addition of 1*H*-imidazol4-(5*H*)-ones and selected ^{1}H NMR data which support it [55].

lents in Brønsted base-catalyzed asymmetric conjugate addition of a range of soft nucleophiles such as α-substituted oxindoles, cyanoesters, oxazolones, azlactones and thiazolones to afford the corresponding tetrasubstituted Michael adducts in high diastereo- and enantioselectivity. The efficiency of the previous 2-thio-imidazol-4(5*H*)-ones as pronucleophiles in Michael reactions has also been corroborated in the addition to these α-silyloxyenones as Michael acceptors [55].

First attempts to carry out the Michael addition reaction of imidazolones to simple unsaturated esters and ketones revealed that whilst these reactions worked sluggish, they proceeded efficiently when α-silyloxyenones were used as Michael acceptors. In these cases and, under the conditions shown in Scheme 5, reaction of the 1,5-dimethylimidazolone **4** ($R^1 = R^2 = Me$) in the presence of catalyst **C1** afforded, after desilylation, the Michael adduct **30** in good yield (74%) but in moderate enantioselectivity (−84%). Improved selectivity (91%) was observed using **C2** in the reaction with **4** ($R^1 = R^2 = Me$) and even better enantioselectivity was obtained with catalysts **C3** (94%) and **C4** (96%). Under these optimized conditions a survey of imidazolones reacted with enone **29** to produce adducts with yields within the range 71–83% and with very high enantioselectivity (Scheme 5).

The Michael adducts can also be transformed into different derivatives (Scheme 6), particularly into hydantoins **37**–**43** after hydrolysis of the corresponding adducts **30**–**32** [55]. Oxidative elaboration of the ketol unit in these compounds provides the corresponding carboxylic acids **40**/**41**, the aldehyde **42** and the ketone **43**. Therefore this methodology facilitates a novel entry to functionalized 5,5-disubstituted hydantoins, a well-recognized scaffold for drug discovery.

2 Thiazol-4(5*H*)-ones **2**

Thiazol-4(5*H*)-ones **2**, which exhibit interesting applications in medicinal and pharmaceutical areas [74-76], can be easily synthesized and can act as (pro)nucleophiles in asymmetric catalytic reactions. In 2011, Weib and Beckert et al. reported a ^{1}H NMR study of these compounds in solution that shows that they exist in equilibrium between two tautomeric forms [77], and therefore this could facilitate deprotonation at the 5-position to further react with various electrophiles. However, thiazol-4(5*H*)-ones have been until now rarely used in asymmetric catalysis, and only very recently four interesting examples describing their applications in this realm have been reported. On the other hand, rhodanines **44** and **45** (Scheme 7), heterocycles structurally related to thiazol-4(5*H*)-ones **2**, have also been very scarcely used as pronucleophiles in asymmetric catalysis. Only few examples have been reported, some of them involving the use of rhodanines of type **44** (Scheme 7a), which act directly as pronucleophiles against enones [78] (Scheme 7a,1), enals [79] (a,2) and azodicarboxylates [80] (a,3). In two other examples (Scheme 7b), however, rhodanines of type **45** have been employed to produce spirocyclic compounds. The first case is an enamine/Michael tandem reaction to unsaturated enones [81] (Scheme 7b,1) and the second one is the Diels–Alder reaction with 2,4-dienals which occurs via trienamine formation [82] (Scheme 7b,2).

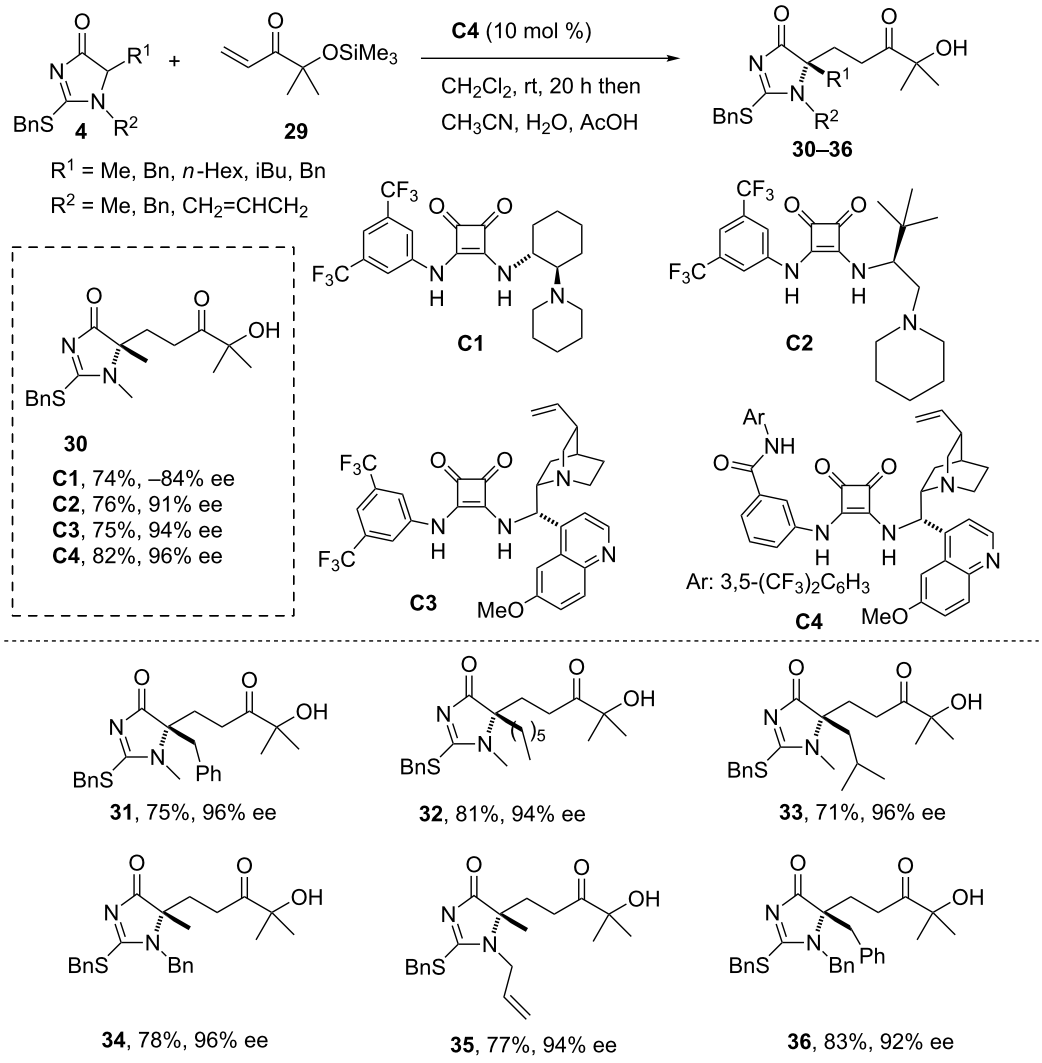
2.1 Synthesis of thiazol-4(5*H*)-ones **2**

Thiazol-4(5*H*)-ones **2** can be easily prepared starting from the corresponding α-mercaptocarboxylic acid and nitrile. Treatment of both with triethylamine in refluxing ethanol [83] provides the expected thiazol-4(5*H*)-ones as yellow/green solids in good yields. The starting α-mercaptocarboxylic acids can be prepared by reaction of the corresponding α-bromo derivatives with potassium thioacetate followed by treatment with ammonia in methanol [84].

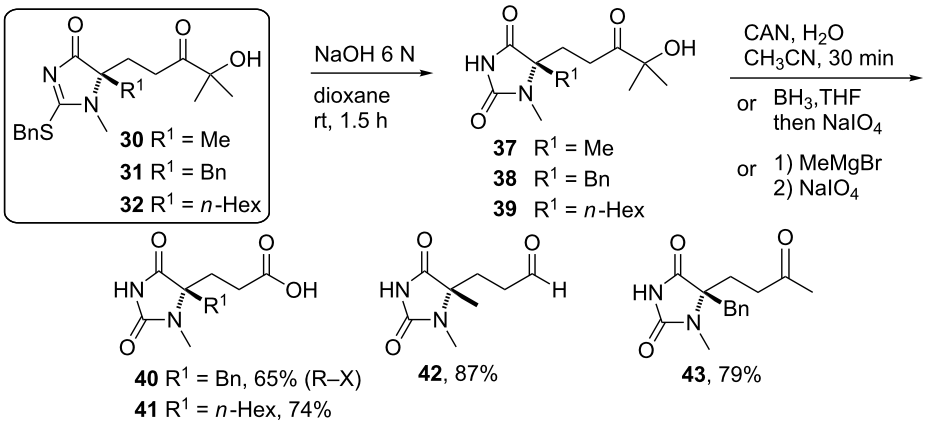
2.2 Thiazol-4(5*H*)-ones **2** as pronucleophiles in asymmetric catalytic reactions

The potential of thiazol-4(5*H*)-ones as pronucleophiles in asymmetric catalytic reactions has been investigated in the Michael addition reaction to nitroalkenes and α-silyloxyenones, phosphine-catalyzed γ-addition to allenoates and alkynoates, α-amination reactions and iridium-catalyzed allylic substitution reactions.

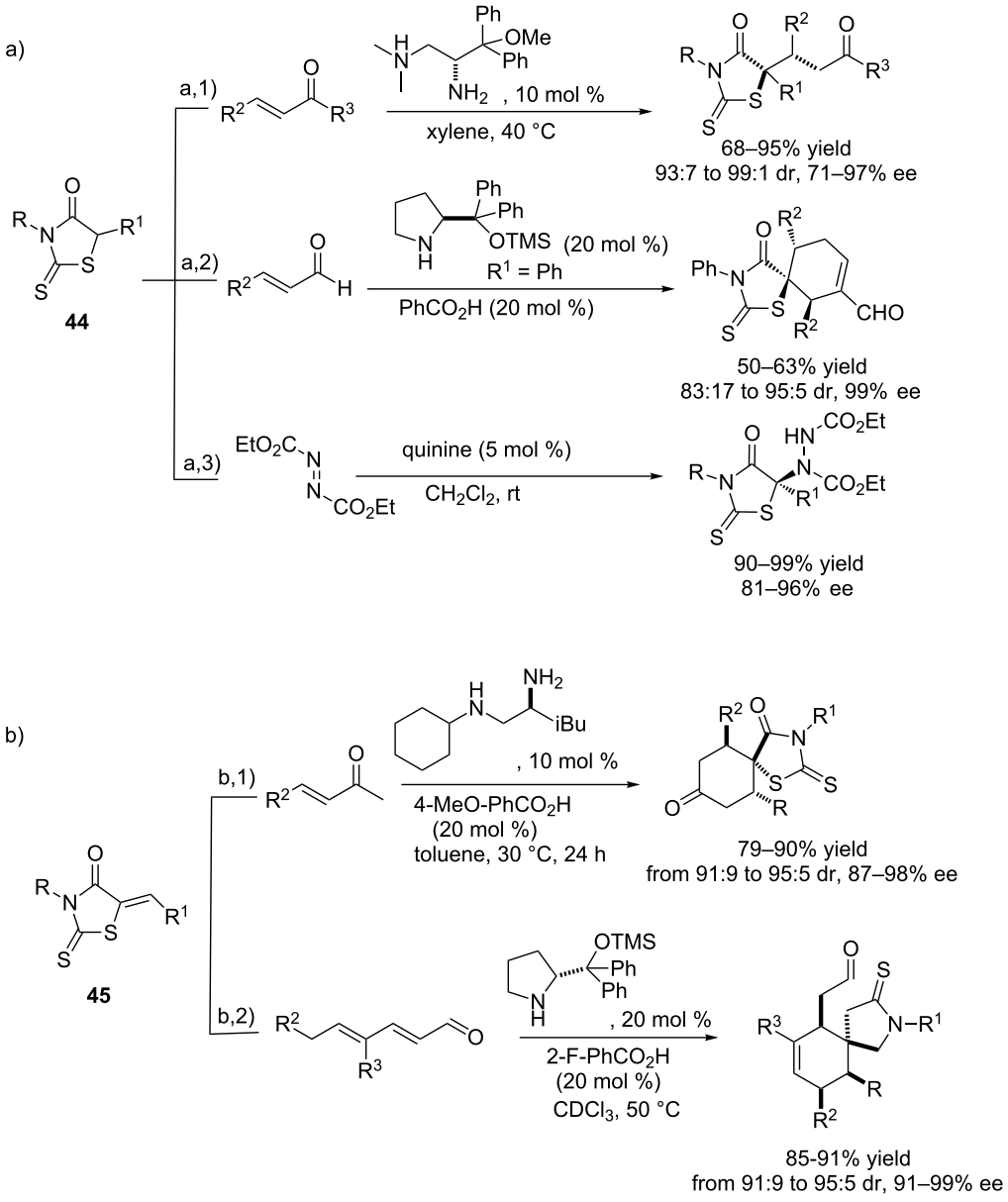
2.2.1 Michael addition reactions, nitroalkenes as acceptors. The first example of the utility of the thiazol-4(5*H*)-ones **2** as pronucleophiles in asymmetric catalysis was reported in 2013 in the Michael addition to nitroalkenes catalyzed by the bifunctional ureidopeptide-like Brønsted base **C5** (Scheme 8) [85].



Scheme 5: Michael addition 2-thio-1*H*-imidazol-4(5*H*)-ones to the α-silyloxyenone **29** [55].

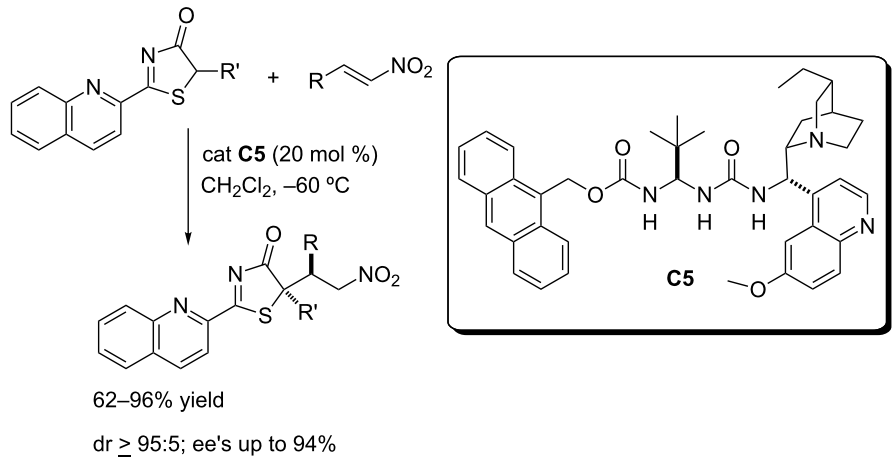


Scheme 6: Elaboration of the Michael adducts coming from the Michael addition to nitroolefins [55].



Scheme 7: Rhodanines in asymmetric catalytic reactions: a) Reaction with rhodanines of type **44** [78-80]; b) reactions with rhodanines of type **45** [81,82].

This catalyst belongs to a new subclass of bifunctional Brønsted bases, which was developed on the basis of Takemoto's model [86]. This model is featured by three different moieties: a basic site, a urea (thiourea) function and a 3,5-bis(trifluoromethyl)-phenyl group, all three elements being necessary for catalyst activity (Figure 4a) [87-89]. In 2010 Zhong proposed that the presence of the ortho C–H bond of the aryl group could be the key for success because it could participate together with the thiourea function in the activation of the electrophile [90]. This proposal was in 2012 supported by Schreiner [91] after an exhaustive study based on NMR/IR spectroscopy, mass spectrometry and theoretical DFT calculations. By taking into account these characteristics, the authors considered that the combination of ureidopetide's structure, which have been recognized by their ability to develop hydrogen bond interactions [92-95] with a Brønsted base could provide a new family of potentially efficient bifunctional catalysts (Figure 4b). The main features of these new catalysts are the presence of a urea moiety together with a *N*,*N*-diacylaminal unit, both in close proximity to an additional stereodirecting group.



Scheme 8: Michael addition of thiazol-4(5*H*)-ones to nitroolefins promoted by the ureidopeptide-like bifunctional Brønsted base catalyst **C5** [85].

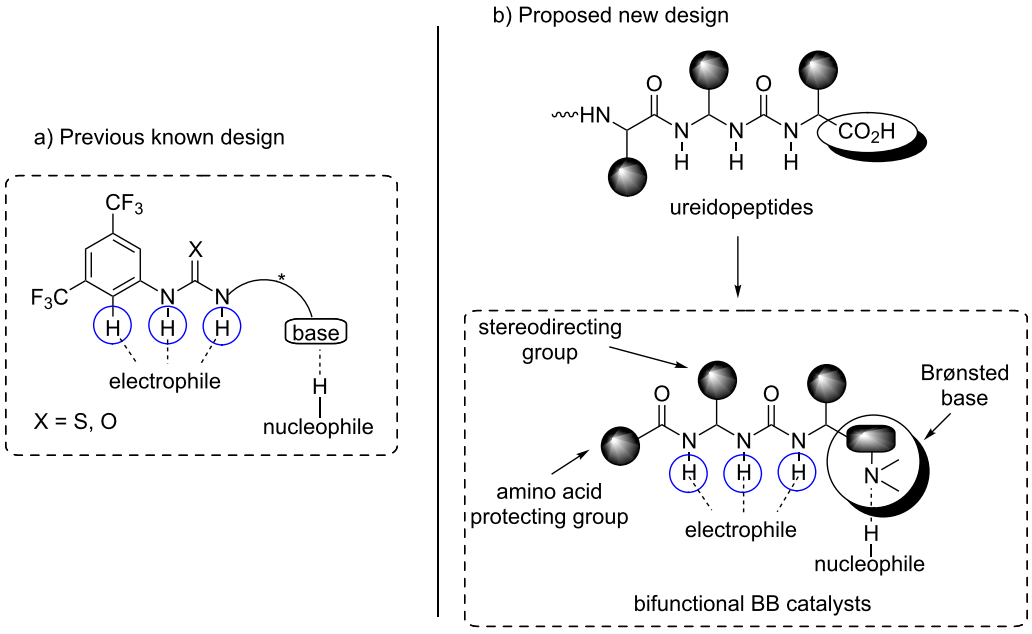
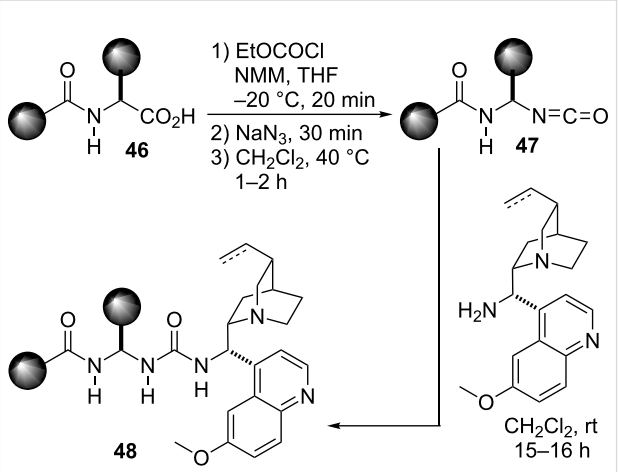


Figure 4: Ureidopeptide-like Brønsted bases: catalyst design. a) Previous known design. b) Proposed new design. BB: Brønsted base [85].

Following this design and starting from the corresponding *N*-protected α-amino acid **46** different catalysts were easily synthesized by the reaction of the respective intermediate isocyanates **47** [93] with 9-*epi*-9-amino-9-deoxyquinine or 9-*epi*-9-amino-9-deoxyhydroquinine (Scheme 9). These catalysts were tested in the reaction between 5-methylthiazolone **49** and nitrostyrene (Scheme 10) and after optimization catalyst **C5** was found to be the optimal for this transformation.

A representative selection of nitroalkenes was then evaluated in the presence of catalyst **C5** and, as the data in Scheme 10 show, those bearing β-aryl substituents with either electron-donating or electron-withdrawing groups produced the corresponding adducts in good enantio- and diastereoselectivities (compounds **53**–**59**). Even the most problematic β-alkyl nitroalkenes worked well affording the adducts in good stereoselectivity albeit in poor yields (Scheme 10, compounds **60**–**62**). The reaction was equally efficient with thiazolones carrying short and large alkyl chains (Scheme 10, compounds **63**–**66**).

An aspect of practical interest of this methodology is that whilst the majority of the procedures for the preparation of organosulfur compounds render thioether derivatives [96,97], this approach provides products with a free thiol group such as the

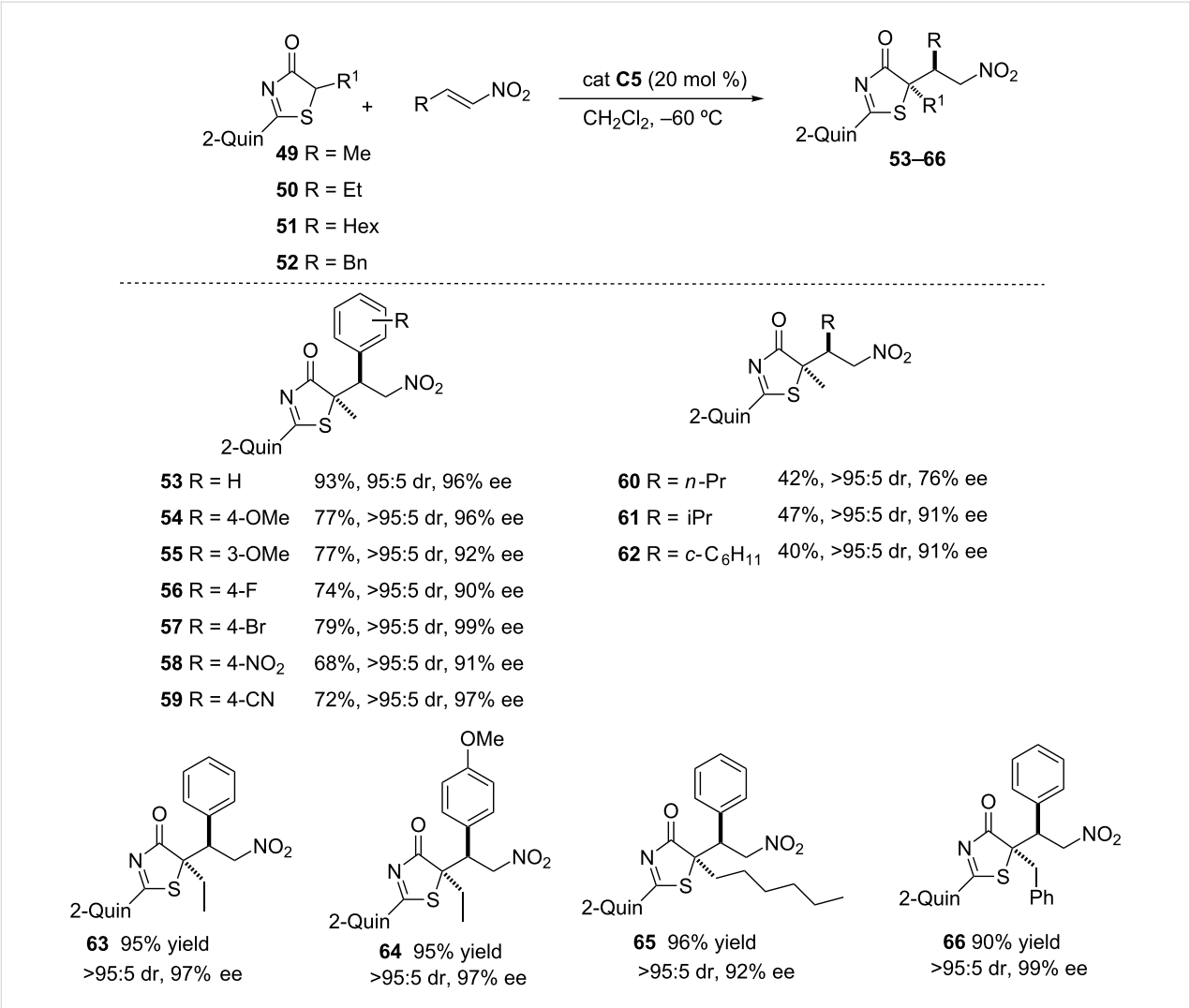


Scheme 9: Ureidopeptide-like Brønsted base bifunctional catalyst preparation. NMM = *N*-methylmorpholine, THF = tetrahydrofuran [85].

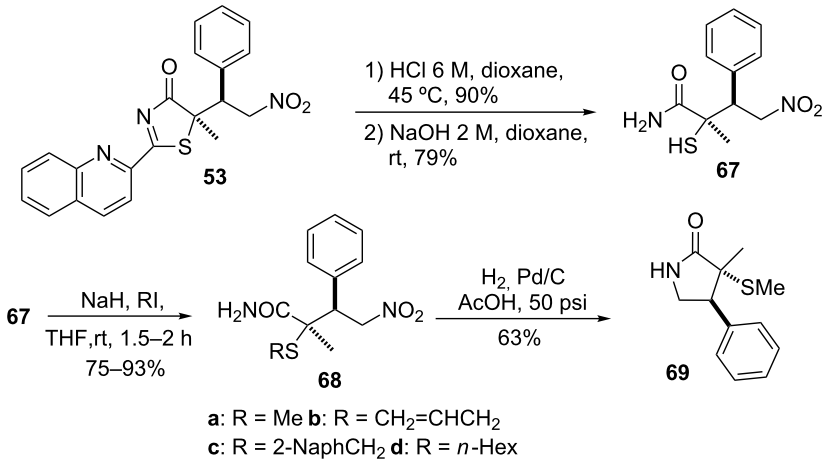
α-mercaptocarboxylic acid derivative **67** (Scheme 11). Additionally, these mercapto derivatives can also be *S*-alkylated by treatment with the corresponding halide in the presence of sodium hydride, giving thus access to thioether derivatives of type **68**, which can also be converted into γ-lactams such as **69**.

On the other hand, experiments carried out with pyridyl and quinoylthiazolone substrates reveal that in these cases selectivity is higher than with the phenyl and 2-naphthylthiazolones, respectively (Scheme 12, compound **70** versus **71** and **72** versus **73**). On this basis, the authors propose a bifunctional way of action of the catalyst, wherein the pyridine/quinoline nitrogen could coordinate to one of the free N–H hydrogen atoms of the catalyst.

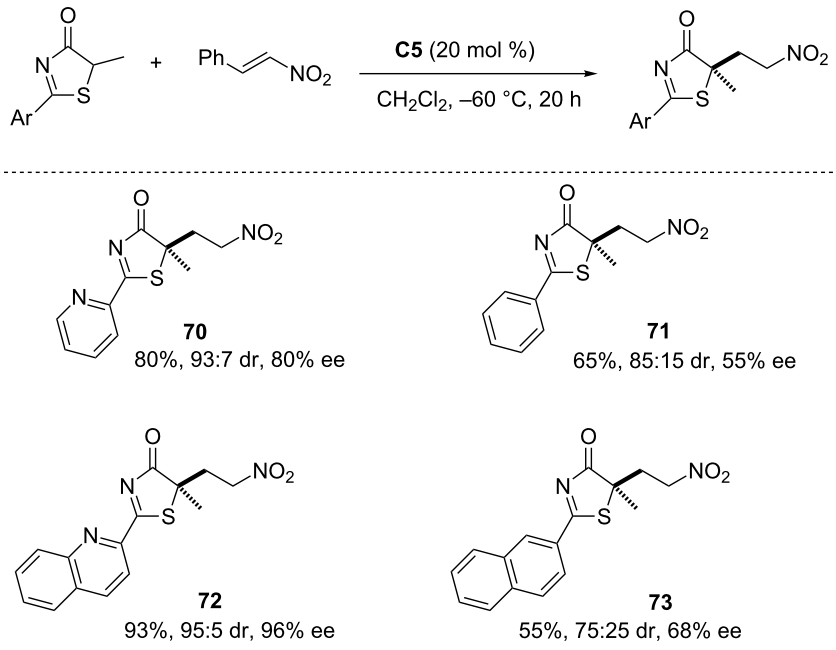
α'-Silyloxyenones as acceptors. As in the case of imidazolones, thiazolones also exhibit very poor reactivity in the



Scheme 10: Selected examples of the Michael addition of thiazolones to different nitroolefins promoted by catalyst **C5** [85].



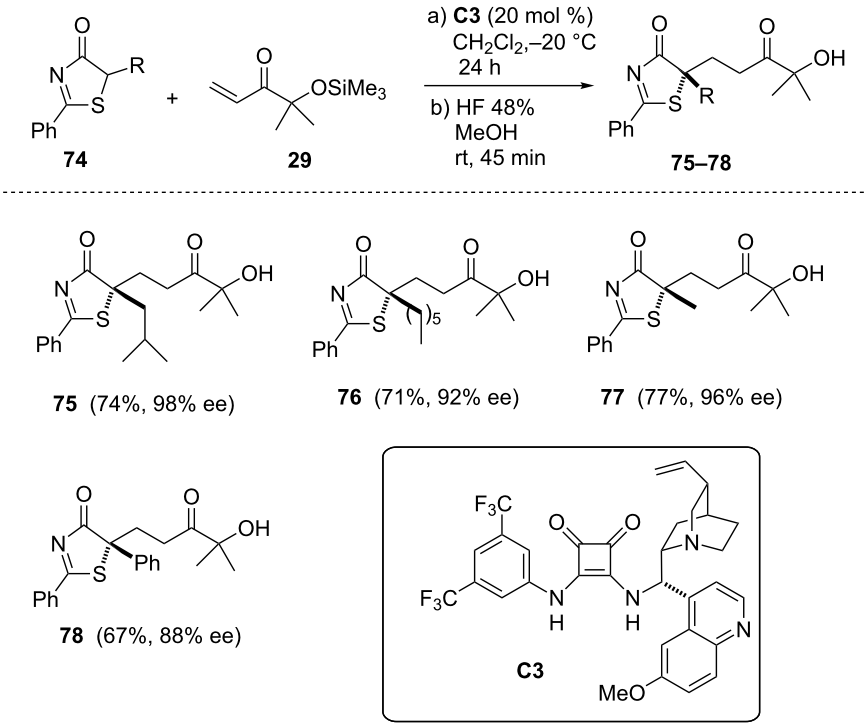
Scheme 11: Elaboration of the Michael adducts to α,α-disubstituted α-mercaptocarboxylic acid derivatives [85].



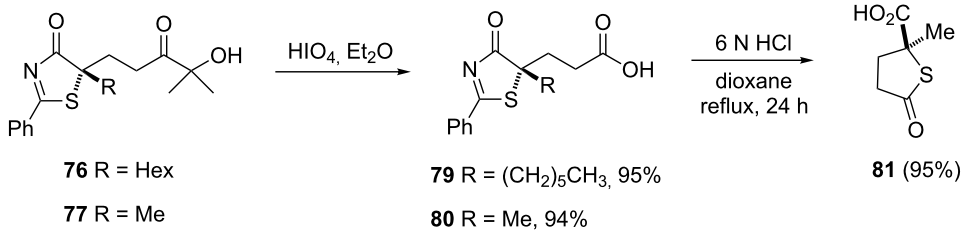
Scheme 12: Effect of the nitrogen atom at the aromatic substituent of the thiazolone on yield and stereoselectivity in the Michael addition to nitrostyrene [85].

Michael addition to methyl and *tert*-butyl acrylates. This problem could be circumvented by using α'-silyloxyenones as acrylate surrogates [73]. After catalyst screening and optimization of the reaction conditions the authors found that thiazolones **74** bearing either short, large or ramified alkyl chains at the heterocycle afforded the corresponding Michael adducts in good yields and excellent enantioselectivity in the presence of 20 mol % of catalyst **C3** (Scheme 13). Initial attempts to carry out the reactions with the α'-hydroxyenone provided the adducts in very poor enantioselectivity. This is a particular and interesting characteristic of these templates because the α-hydroxy group can be transformed into other oxy derivatives to better adapt to the most suitable substrate/catalyst interaction.

In addition, adducts **76** and **77** were easily transformed into the corresponding carboxylic acids **79** and **80** by treatment with periodic acid (Scheme 14) and thiolactone **81** by simple ring opening of the latter under mild acidic conditions.



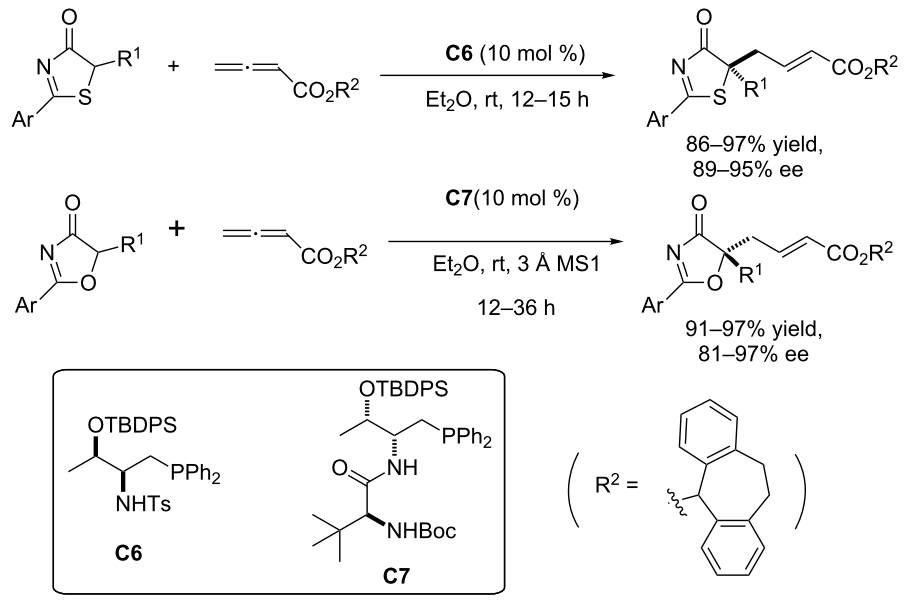
Scheme 13: Michael addition reaction of thiazol-4(5*H*)ones **74** to α'-silyloxyenone **29** [73].



Scheme 14: Elaboration of the thiazolone Michael adducts [73].

Phosphine-catalyzed γ-addition to allenoates and alkynoates. Chiral phosphine-mediated nucleophilic catalysis has attracted considerable attention in the recent years [98-101]. However, few examples of phosphine-mediated γ-addition reactions have been reported. Pioneering studies on γ-additions of pronucleophiles to allenoates or alkynoates were first published by the groups of Trost [102-104] and Lu [105] in the 1990s. However, asymmetric variants were not reported until more than a decade later. The group of Fu has recently described the enantioselective γ-addition of oxygen [106,107], carbon [108], sulfur [109], and nitrogen [110] pronucleophiles to γ-substituted allenoates and/or alkynoates in the presence of a C_2-symmetric chiral phosphine catalyst. Although γ-substituted allenes have been employed in many phosphine-mediated γ-additions, to date there was virtually no progress on the use of prochiral pronucleophiles in phosphine-mediated γ-additions until the group of Lu published in 2014 the addition of 3-substitued oxindoles [111]. More recently, Lu together with Lan also demonstrated the efficiency of oxazol-4(5*H*)-ones and thiazol-4(5*H*)-ones as pronucleophiles in the highly enantioselective phosphine-catalyzed asymmetric γ-addition to allenoates, which after elaboration of the resulting adducts, affords tertiary thioethers and alcohols [36] (Scheme 15).

Starting from readily available L-valine and L-threonine the authors first synthesized different phosphine catalysts and then screened in the γ-addition reaction of both, thiazol-4(5*H*)-ones and oxazol-4(5*H*)-ones. They found that whilst catalyst **C6** was

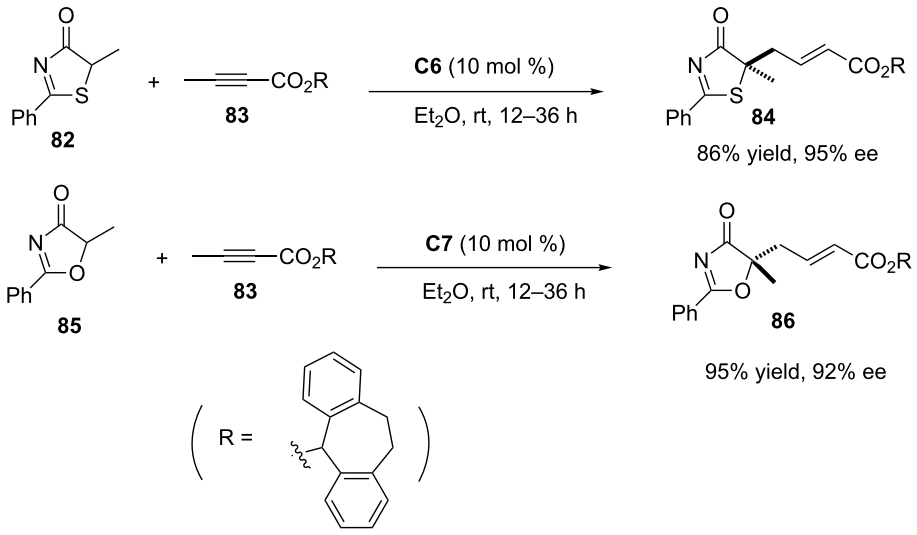


Scheme 15: Enantioselective γ-addition of oxazol-4(5*H*)-ones and thiazol-4(5*H*)-ones to allenoates promoted by **C6**/**C7** [36].

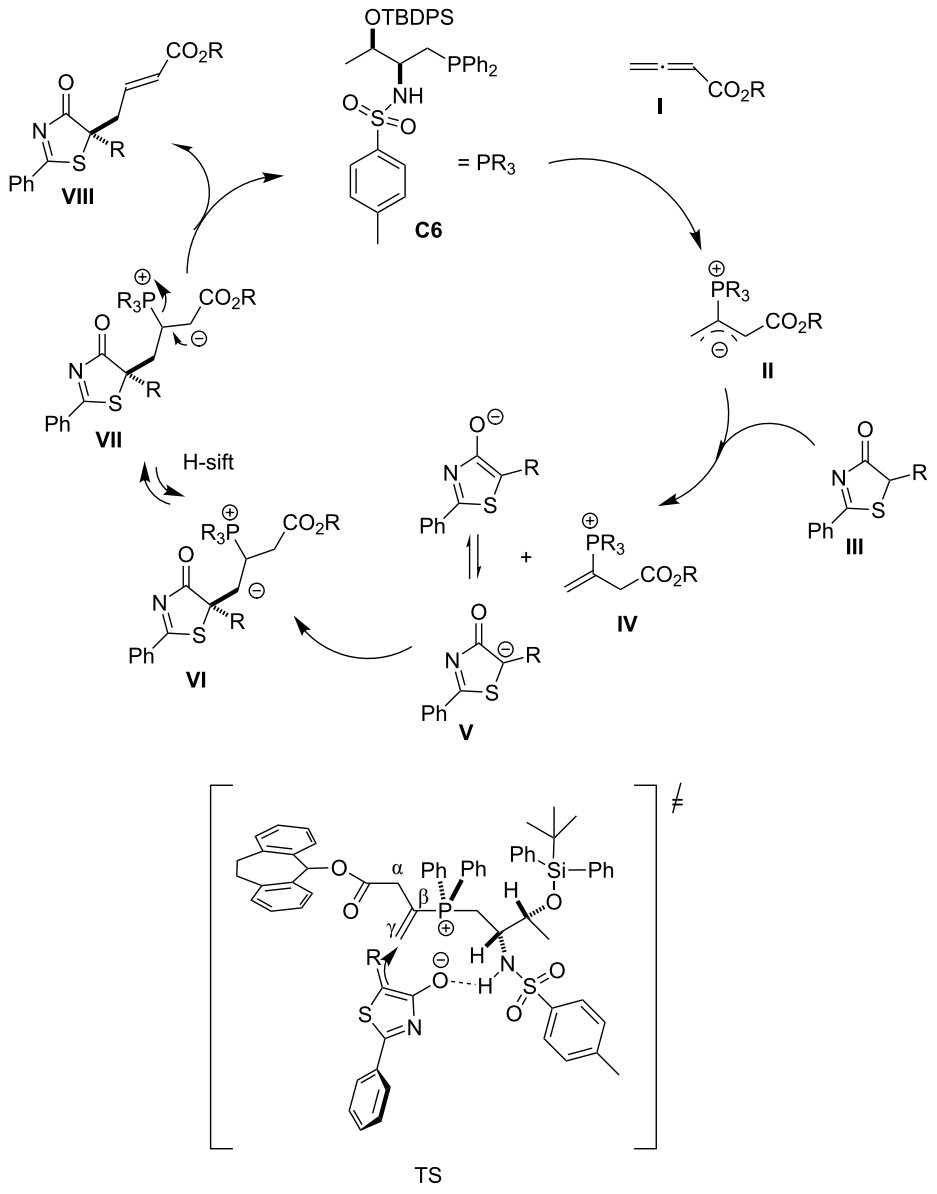
the best for the reaction with thiazol-4(5*H*)-ones, in the case of oxazol-4(5*H*)-ones, however, best results were provided by catalyst **C7**. The reaction conditions were further optimized by varying both, the solvent and the ester moiety of the allenoate. Examination of different allenoates revealed that the dibenzosuberyl ester provided the best results.

The scope of these catalysts was also proven in the reaction with alkyne substrates. For instance, both thiazol-4(5*H*)-one **82** and oxazol-4(5*H*)-one **85** react with alkynoate **83** to provide adducts **84** and **86**, respectively, with equal efficiency than allenoates (Scheme 16).

The authors propose the mechanism outlined in Scheme 17 on the basis of some DFT calculations. Accordingly, the first step is the γ-addition of the phosphine to the allenoate to produce intermediate **II**. Then this basic intermediate is proposed to deprotonate the starting thiazolone thus providing enolate **V**,



Scheme 16: Enantioselective γ-addition of thiazol-4(5*H*)-ones and oxazol-4(5*H*)-ones to alkynoate **83** promoted by **C6**/**C7** [36].

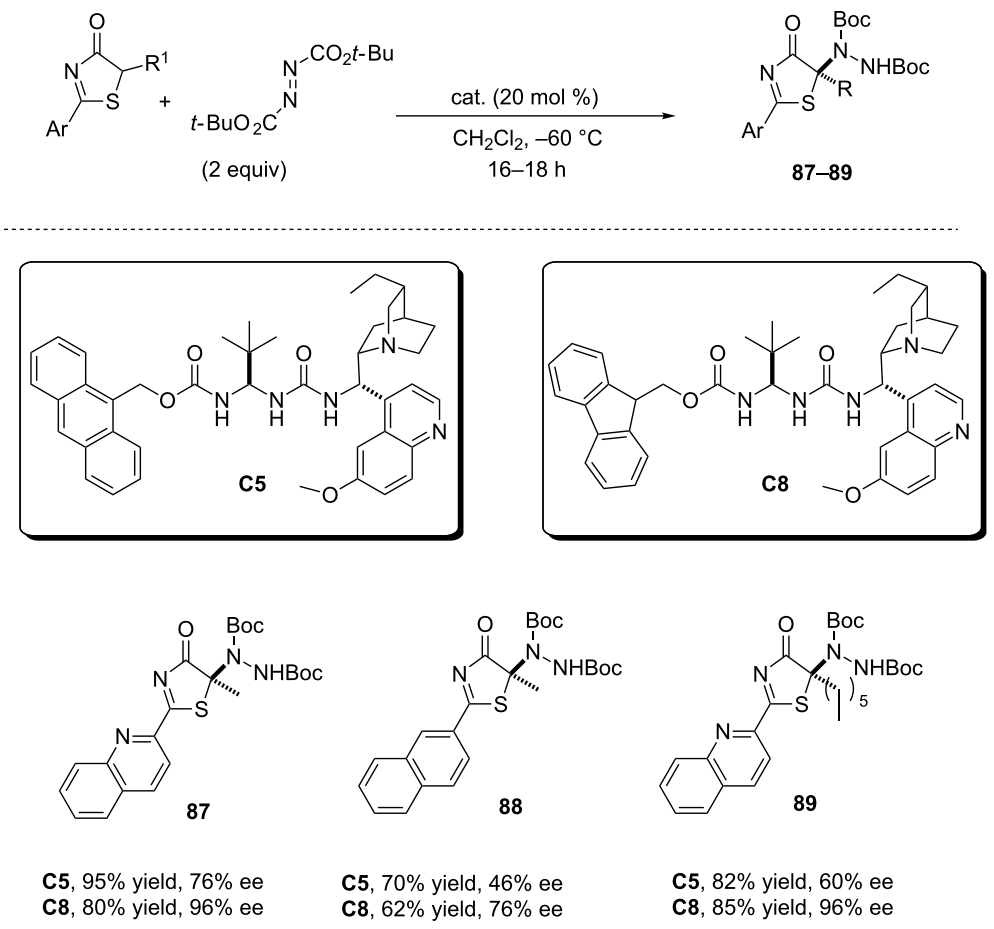


Scheme 17: Proposed mechanism for the **C6**-catalyzed γ-addition of thiazol-4(5*H*)-one to allenoates. Adapted from [36], copyright 2015 The Royal Society of Chemistry.

which subsequently adds to the γ-carbon of **IV** to afford intermediate **VI**. After proton shift, intermediate **VI** becomes intermediate **VII** and this eliminates the phosphine catalyst, which enters a new catalytic cycle, while providing the final product **VIII**. The authors propose a bifunctional behavior of the catalyst, wherein a hydrogen bonding interaction between the sulfonamide N–H and the thiazolone enolate controls its addition to the C–C double bond, which is the key step for asymmetric induction.

2.2.2 α-Amination reactions. Thiazolones **2** have also been investigated in the α-amination reaction with *tert*-butyl azodicarboxylate in the presence of the ureidopeptide like catalysts **C5** and **C8** (Scheme 18) [85]. In these cases better enantioselectivity was observed with catalyst **C8**, and thiazolones bearing the quinoyl moiety provided once again better stereochemical results than 2-naphthylthiazolones.

2.2.3 Iridium-catalyzed allylic substitution reactions. Allylic substitution reactions catalyzed by cyclometalated iridium phosphoramidite complexes constitute a powerful tool for the construction of C–C and C–heteroatom bonds [112] and have been used in many synthetic applications [113]. However one of the main limitations in the area is the lack of highly diastereo- and



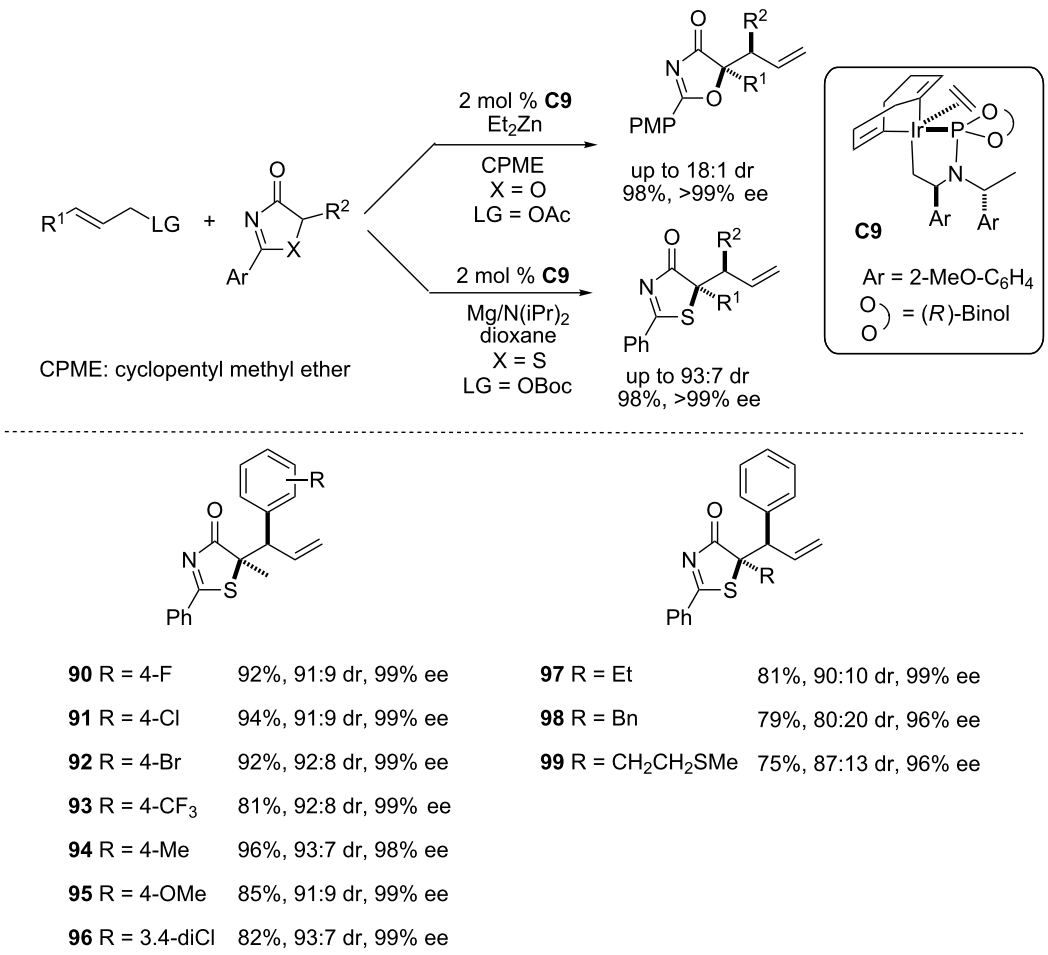
Scheme 18: Catalytic enantioselective α-amination of thiazolones promoted by ureidopeptide like catalysts **C5** and **C8** [85].

enantioselective protocols. In this context, particularly difficult has been to achieve high diastereoselectivity, and only a very narrow range of nucleophiles have been reported to be efficient in this regard (α,α-disubstituted aldehydes [114] and β-ketoesters [115] among others). With the aim of expanding the nucleophile scope of this transformation, in 2014 Hartwig et al. reported a highly diastereoselective iridium-catalyzed allylation substitution reaction of oxazol-4(5*H*)-ones and thiazol-4(5*H*)-ones to afford enantioenriched tertiary alcohols and thioethers (Scheme 19) [42]. In this case the diastereoselectivity is controlled by cations, in contrast to most of the described protocols wherein it is modulated by anions.

The authors found that whilst the best results for allylation of oxazol-4-(5*H*)-ones were achieved from zinc enolates, thiazol-4-(5*H*)-ones produced the best outcome when the magnesium enolate was used. After optimization it was shown that the reaction was efficient with different cinnamyl *tert*-butyl carbonates (Scheme 19) to afford compounds **90**–**99**in general with good yields, diastereomeric ratios and enantioselectivities. Aliphatic carbonates are also good substrates for this reaction but the corresponding adducts are obtained in lower diastereoselectivity. This work demonstrates that the selectivity of the reaction is dictated by the metallacyclic iridium complex and that the nature of the enolate counterion is significant to this respect.

Conclusion

In this short review we have summarized the published examples of the utility of 2-thio-1*H*-imidazol-4(5*H*)-ones and thiazol-4(5*H*)-ones as pronucleophiles in asymmetric catalytic reactions. The results show that they are efficient substrates in reactions which involve the creation of a tetrasubstituted stereogenic center. Further elaboration of adducts coming from these reactions gives access to *N*-substitued α-amino acids in the case of imidazolones and to tertiary thiols and thioethers in the case of thiazolones. In the future, other Brønsted base or bifunctional catalyst promoted reactions with these compounds can be envisaged.



Scheme 19: Iridium-catalized asymmetric allyllation of substituted oxazol-4(5*H*)-ones and thiazol-4(5*H*)-ones promoted by **C9**. PMP = *p*-methoxyphenyl [42].

Acknowledgements

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Towards the total synthesis of keramaphidin B

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Letter

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Abstract

The enantio- and diastereoselective Michael addition of a δ-valerolactone-derived pronucleophile to a substituted furanyl nitroolefin catalysed by a bifunctional cinchonine-derived thiourea has been used as the key stereocontrolling step in a new synthetic strategy to the heavily functionalised piperidine core of keramaphidin B.

Introduction

Keramaphidin B (**1**) is a marine alkaloid first isolated by Kobayashi in 1994 from the Okinawan marine sponge *Amphimedon* sp and has been shown to be cytotoxic against KB human epidermoid carcinoma cells (IC_{50} 0.28 μg/mL) and P388 murine leukemia cells (IC_{50} 0.28 μg/mL) [1]. It is a member of the manzamine alkaloids and has an exquisite molecular structure comprising a 6,6,6,11,13 pentacycle possessing 4 stereogenic centres including one quaternary centre (Figure 1). In 1992, two years before its isolation, Baldwin and Whitehead, in their landmark paper entitled 'On the Biosynthesis of Manzamines' postulated that keramaphidin B was a common intermediate in the biosynthesis of the manzamine alkaloids [2]. Several years later, Baldwin and co-workers synthesised keramaphidin B following a biomimetic pathway via an intramolecular Diels–Alder reaction as the late stage key step. After extensive purification, the authors were able to isolate keramaphidin B in just 0.3% yield, but nevertheless they provided evidence for the biosynthesis [3]. A year later, Baldwin et al. completed an alternative synthesis by performing an intermolecular Diels–Alder reaction and a double late stage RCM reaction to close the two macrocyclic rings; albeit the last stage afforded **1** in 1% yield after separation of various oligomeric byproducts [4].

Our group has had a long-standing research program dedicated towards the total syntheses of the manzamine alkaloids with a particular emphasis on the development of novel catalytic methods for simplifying their syntheses [5-10]. Owing to keramaphidin B's attractive structure combined with its interesting biological profile and the lack of an efficient method for its synthesis, we selected **1** as a suitable synthetic target. Our plan was to design and implement a new synthetic route that

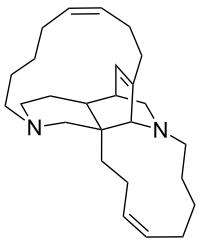


Figure 1: Keramaphidin B (**1**).

integrated some of our newly developed bifunctional organocatalytic reactions, as well as cascade technologies, to rapidly and stereoselectively build up the core of this fascinating molecule. Herein we wish to report our preliminary synthetic efforts towards the stereoselective synthesis of the heavily functionalised piperidine core of keramaphidin B (**1**).

Results and Discussion

Our overall synthetic strategy is presented in Figure 2. We envisaged that a late stage alkyne RCM reaction of **2** and *cis*-selective hydrogenation of the internal alkyne would present an efficient method for the synthesis of the 13-membered ring.

The synthesis of the 11-membered ring could be achieved by a *Z*-selective alkene RCM reaction [5] to afford spirocyclic bislactam **4** from metathesis precursor **5**. Bisalkene **5** could in turn be synthesised by an aminolysis/oxidation/olefination sequence of the terminal alcohol **6**, following traceless nitro group removal.

5-Nitropiperidin-2-one **6** in turn could be accessed by a nitro-Mannich lactamisation cascade reaction between Michael adduct **7**, formaldehyde and a suitable primary amine, following our well-established protocol [6-12]. The key quaternary stereocentre of keramaphidin B, we envisaged, would be installed through an enantio- and diastereoselective organocatalytic Michael addition [13-15] between pronucleophile **8** and the known substituted furanyl nitroolefin **9** under the control of a cinchona-derived bifunctional Brønsted base/H-bond donor organocatalyst developed in our group and others [16-19].

Bifunctional organocatalysed Michael addition studies

In our previous total syntheses of nakadomarin A [5,7,20] and manzamine A [10] the stereochemical configuration of the quaternary carbon was established by a diastereoselective Michael addition between a chiral, single enantiomer, cyclic β-amido ester and a nitroolefin, and, in the case of nakadomarin A the reaction could be rendered catalytic using a bifunctional cinchonine-derived urea catalyst. We reasoned that a similar catalytic approach could be used to fix the absolute stereo-

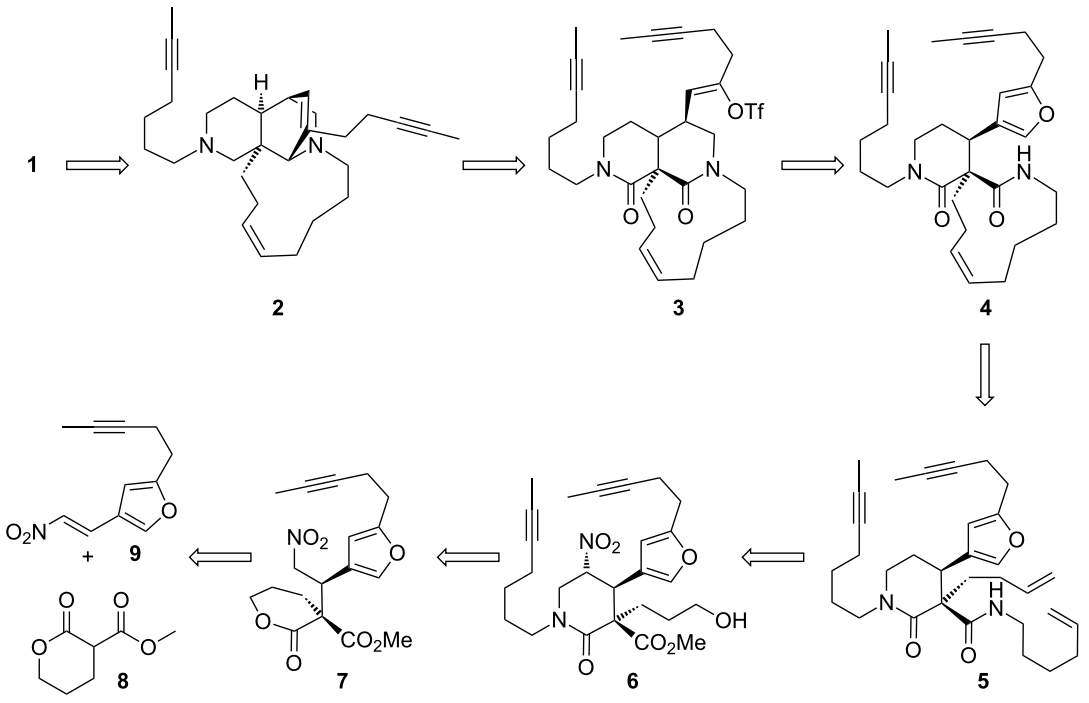


Figure 2: Retrosynthetic analysis of keramaphidin B.

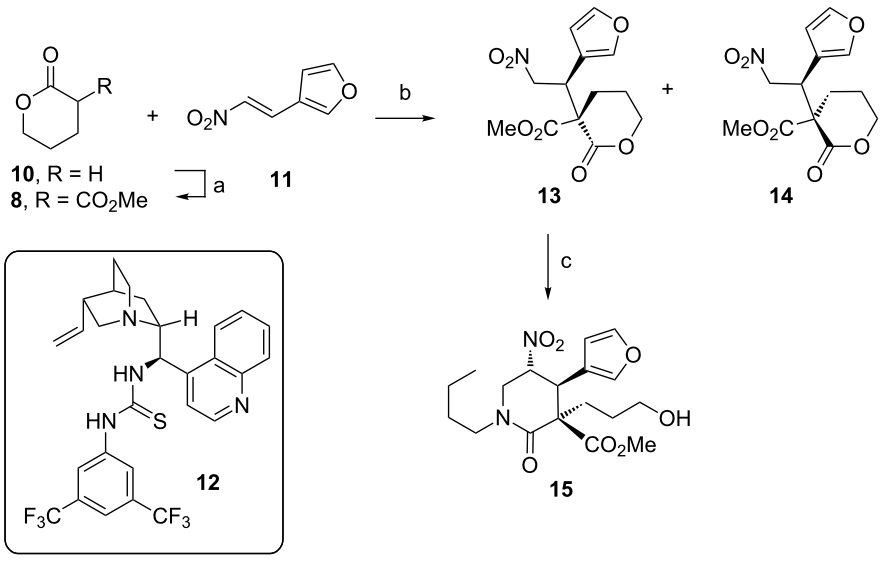
chemical configuration in the Michael addition reaction between δ-valerolactone pronucleophile **8** and nitro-olefin **9**, although a degree of uncertainty as to the relative stereochemical outcome of the catalyst-controlled Michael reaction remained present. Accordingly, we chose to probe reactivity and establish relative stereocontrol using a close model system comprising pronucleophile **8** and furanyl nitroolefin **11** (Scheme 1).

The δ-valerolactone pronucleophile **8** was synthesised by the enolate acylation of δ-valerolactone (**10**) with dimethyl carbonate, using LHMDS as the base, in 83% yield. The furanyl nitroolefin **11** was readily synthesised on multigram scale via a Henry condensation, according to literature procedures [20]. We were delighted to observe that the Michael addition reaction using our previously reported cinchonine-derived bifunctional thiourea catalyst **12** afforded the addition product **13** in high yield with good levels of diastereo- and enantioselectivity (95:5 dr, 90:10 er for the major diastereomer **13**). The relative stereochemical configuration of the minor diastereomeric product **14** was determined by single X-ray crystallographic analysis of *rac*-**14** (see Supporting Information File 1) and revealed that the major diastereomer **13** indeed possessed the necessary stereochemical configuration [21] for accessing keramaphidin B, assuming the chemoselectivity of the nitro-Mannich lactamisation favoured attack at the more reactive δ-lactone carbonyl instead of that of the methyl ester.

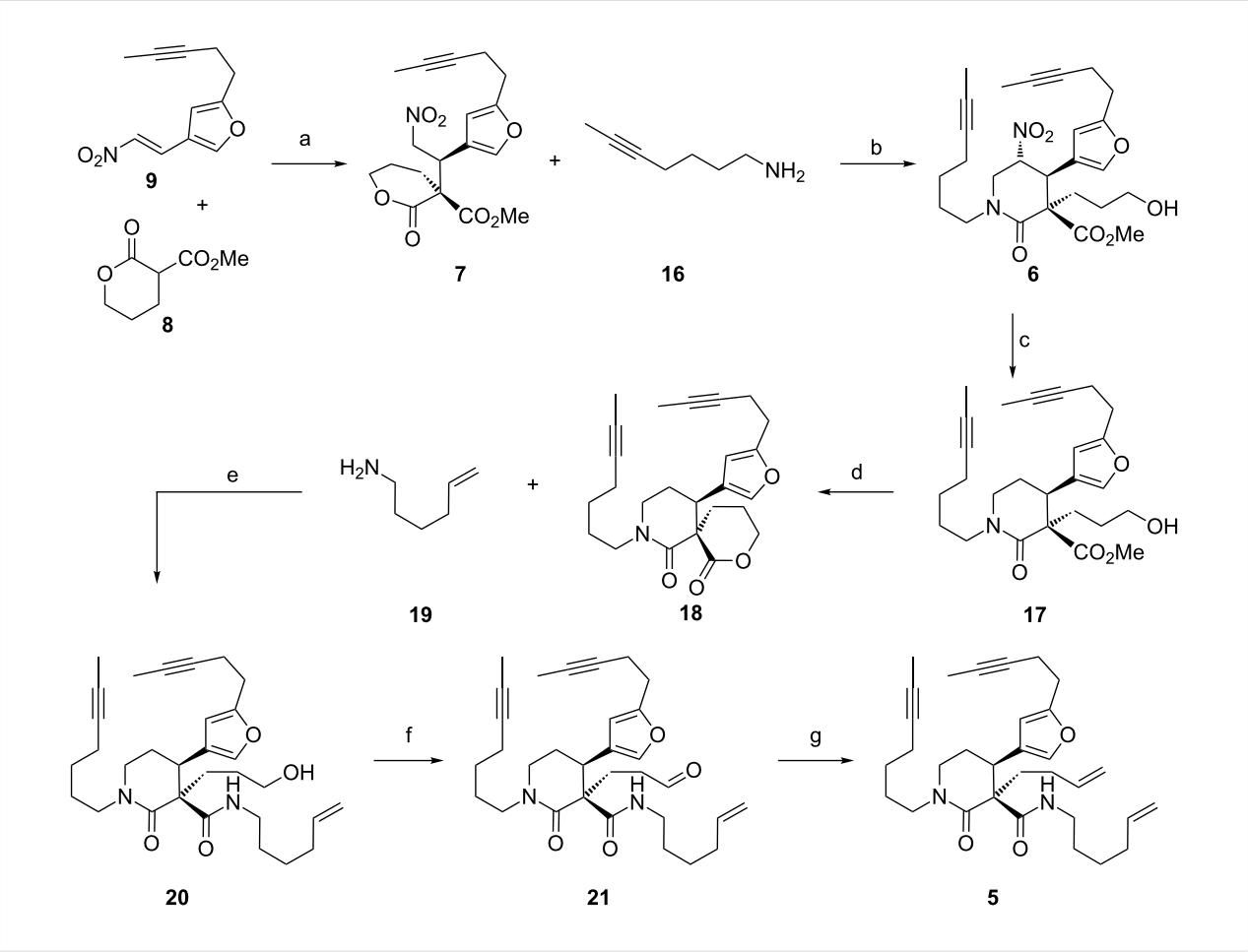
Pleasingly, this was indeed realised at the next stage; performing a nitro-Mannich lactamisation cascade on **13** with formaldehyde and butylamine in methanol afforded lactam **15** in 63% yield, possessing the hydroxypropyl chain attached to the quaternary stereocentre, poised for further functionalisation.

Having established that the cinchonine-derived bifunctional Brønsted base/thiourea organocatalyst **12** was effective for installing two stereocentres including the quaternary carbon in a model system, we next performed the reaction using the substituted furanyl nitroolefin **9** (Scheme 2).

The organocatalysed Michael addition of **8** with substituted furanyl nitroolefin **9** [20] under the control of bifunctional organocatalyst **12** proceeded efficiently and, although the reaction time was slightly increased relative to the model system, identical levels of diastereo- and enantiocontrol were observed in the formation of **7** (92% yield). Treatment of the major diastereomeric product **7** with hept-5-yn-1-amine (**16**) and formaldehyde in boiling methanol afforded the lactam **6** in 56% yield as a single diastereomer in 91:9 er. Having played a key role in the Michael addition reaction and the nitro-Mannich lactamisation cascade, at this stage the nitro functionality had fully served its purpose. Accordingly, traceless reductive cleavage of the nitro group [22] using tributyltin hydride and AIBN was carried out to afford piperidin-2-one **17** in 71% yield. Lactonisation under Lewis acidic conditions afforded spirocyclic malonamate **18** possessing the correct relative stereochemistry for keramaphidin B, in 84% yield. Aminolysis under neat conditions with hex-5-en-1-amine (**19**) gave the primary alcohol **20** (67% yield), which was subsequently subject-



Scheme 1: Enantio- and diastereoselective bifunctional thiourea **12** organocatalysed Michael addition. (a) $CO(OMe)_2$, LHMDS, THF, −78 °C to rt, 83%; (b) 20 mol % **12**, toluene, −20 °C, 24 h, 95:5 dr (**13**:**14**), 90:10 er for **13**, 99% yield; (c) butylamine, aq formaldehyde, MeOH, reflux, 1 h, 63%.



Scheme 2: Synthesis of bis alkene **5**. (a) **12** (20 mol %), toluene, −20 °C, 36 h, 95:5 dr, 92% yield; (b) aq HCHO, MeOH, reflux, 70 °C, 1 h, >95:5 dr, 91:9 er, 56% yield; (c) AIBN, Bu_3SnH, toluene, reflux, 0.33 h, 71% yield; (d) $Ti(OiPr)_4$, toluene, 50 °C, 2 h, 84% yield; (e) **19** (neat), 130 °C, 24 h, 67% yield; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 0.5 h, 88% yield; (g) $Cp_2Ti(CH_3)_2$, THF/toluene, reflux, 0.33 h, 42% yield.

ed to a Swern oxidation to yield the aldehyde **21** in 88% yield. Finally, treatment of the aldehyde with Petasis reagent afforded the target bisalkene RCM precursor **5** in a satisfactory 42% yield.

Conclusion

In conclusion we have utilized a bifunctional cinchona-derived thiourea organocatalyst **12** for governing the key Michael addition towards the synthesis of keramaphidin B. The catalyst imparted high levels of enantio- and diastereocontrol at the newly formed contiguous tertiary and quaternary stereocentres. The stereochemical integrity of the newly formed stereogenic centres was not compromised during a subsequent three-step nitro-Mannich lactamisation cascade, aminolysis and lactonisation sequence. Further manipulation of the pendant functional groups allowed the synthesis of target compound **5** bearing two alkynes and two terminal alkenes for successive RCM reactions to construct the 11- and 13-membered rings of keramaphidin B. RCM precursor **5** – possessing all of the necessary masked functionality already installed about a piperidin-2-one framework – represents an advanced intermediate for the potential future synthesis of keramaphidin B, and our work towards this goal will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental procedures, analytical data, copies of NMR spectra and single X-ray crystal diffraction data of **14**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-104-S1.pdf]

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Enantioselective addition of diphenyl phosphonate to ketimines derived from isatins catalyzed by binaphthyl-modified organocatalysts

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Letter

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Abstract

Chiral binaphthyl-modified squaramide-catalyzed enantioselective addition of diphenyl phosphonate to ketimines derived from isatins has been achieved. This method affords practical and efficient access to chiral 3-amino-3-phosphonyl-substituted oxindole derivatives in high yields with excellent enantioselectivities (up to 99% ee).

Introduction

α-Aminophosphonate derivatives are important compounds as structural mimics of natural α-amino acids [1-3]. Chiral α-aminophosphonates have been shown a wide range of biological activities including antibacterial [4] and anticancer properties [5], enzyme inhibition [6], peptide mimetic function [7], and herbicidal properties [8]. Since the biological activity of α-aminophosphonate derivatives is dependent upon the chirality of the α-position to the phosphorus atom, asymmetric synthesis of α-aminophosphonates has received considerable attention, and numerous catalytic enantioselective methods using chiral catalysts have been reported [9-13].

Oxindole and its derivatives can be exploited as important synthons to synthesize various alkaloid natural products and biologically active compounds [14-16]. In particular, 3,3-disubstituted oxindoles bearing a quaternary stereogenic center at the C3-position have been reported to be biologically active against a variety of targets [17-19]. Consequently, the asymmetric synthesis of 3,3-disubstituted oxindole derivatives has received significant research attention over the past few decades [20-22]. General approaches for the synthesis of chiral 3-substituted-3-aminooxindole derivatives include the amination of various 3-monosubstituted oxindoles [23-27] and the nucleophilic addition to ketimines derived from isatin derivatives [28-35]. Recently, there were a few reports on the synthesis of chiral 3-amino-3-phosphonyl-substituted oxindole derivatives by the catalytic enantioselective hydrophosphonation of ketimines [36,37]. The previous synthetic procedures suffered from

several drawbacks, such as a high catalyst loading, long reaction time, and low temperature required for good enantioselectivity. Thus, new approaches for the organocatalytic enantioselective addition of diphenyl phosphonate to isatin imines are highly desired.

In connection with our ongoing research program on the design and application in asymmetric catalysis of organocatalysts [38-45], we have reported the catalytic asymmetric decarboxylative aldol addition reaction of isatins with benzoylacetic acids catalyzed by chiral binaphthyl-based squaramide [46]. Here we wish to report the enantioselective addition reaction of diphenyl phosphonate to ketimines derived from isatins catalyzed by binaphthyl-modified bifunctional organocatalysts (Figure 1).

Results and Discussion

To determine suitable reaction conditions for the organocatalytic enantioselective addition reaction of diphenyl phosphonate to ketimines derived from isatins, we initially investigated a reaction system with ketimine **1a** derived from *N*-allylisatin and diphenyl phosphonate (**2**) with organocatalyst in the presence of 4 Å molecular sieves. We first surveyed the effect of the structure of bifunctional organocatalysts **I**–**VI** (Figure 1) on enantioselectivity in ethyl acetate at room temperature (Table 1, entries 1–6). Catalyst **III**, which is a binaphthyl-modified squaramide bifunctional organocatalyst, was the best catalyst for this enantioselective addition reaction (90% ee, Table 1, entry 3). In order to improve the selectivity, different solvents were tested in the presence of 10 mol % of catalyst **III** together with ketimine **1a** and diphenyl phosphonate (**2**). We obtained excellent results in ethyl acetate (85% yield, 90% ee, Table 1, entry 3), while a slight decrease in enationselectivities was observed when dichloromethane, chloroform, tetrahydrofuran, toluene, and methanol were used as the solvent (Table 1, entries 7–11). Under low catalyst loading of 2.5 mol %, this enantioselective addition reaction proceeded successfully to give **3a** without compromising the reactivity and enantioselectivity (Table 1, entries 3 and 12–14). Finally, lowering the reaction temperature to 0 °C with catalyst **III** improved the enantioselectivity (93% ee, Table 1, entry 15). Performing the reaction without 4 Å molecular sieves generated a lower yield (Table 1, entry 16).

With the optimized conditions in hand, we proceeded to investigate the scope of the enantioselective addition of diphenyl phosphonate (**2**) with various ketimines **1** in the presence of 2.5 mol % of binaphthyl-modified squaramide-tertiary amine catalyst **III** in ethyl acetate at 0 °C (Table 2). The corresponding addition products **3a**–**l** were formed in high yields (74–94%) with excellent enantioselectivities (up to 99% ee). The reaction of diphenyl phosphonate (**2**) with *N*-allylated and

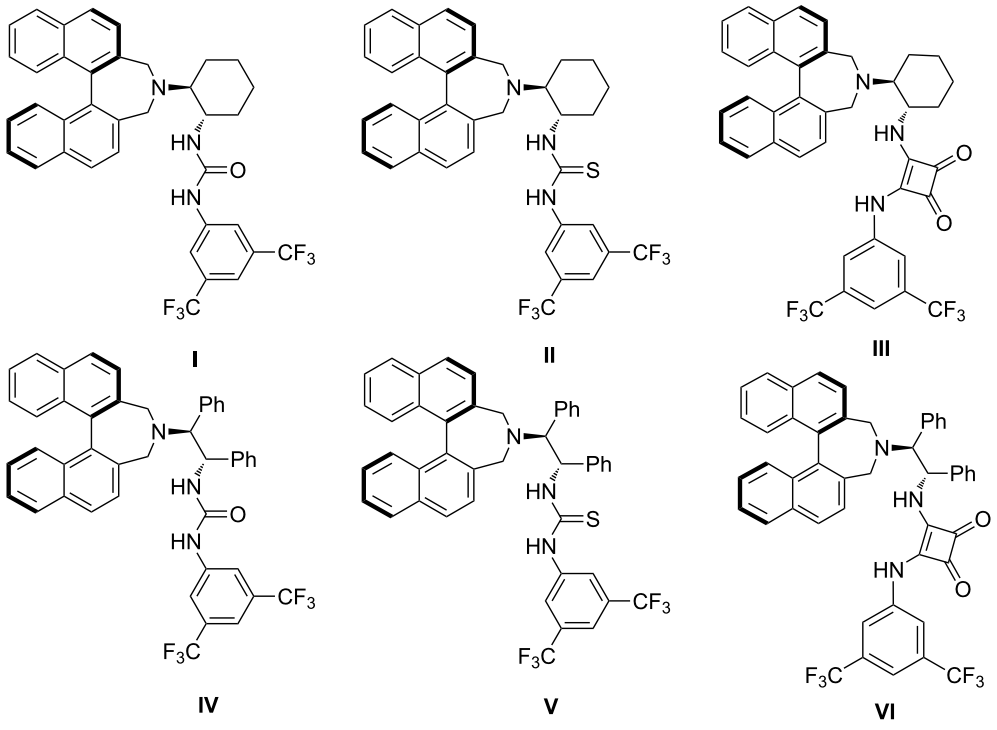
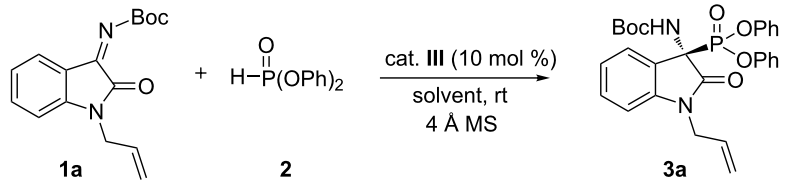


Figure 1: Structure of chiral bifunctional organocatalysts.

Table 1: Optimization of the reaction conditions. [a]

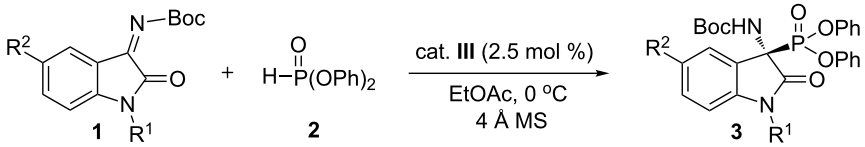


1a 2 3a

entry	cat.	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**I**	EtOAc	9	**3a**, 85	73
2	**II**	EtOAc	11	**3a**, 94	62
3	**III**	EtOAc	9	**3a**, 85	90
4	**IV**	EtOAc	12	**3a**, 85	54
5	**V**	EtOAc	12	**3a**, 85	78
6	**VI**	EtOAc	9	**3a**, 95	74
7	**III**	CH_2Cl_2	3	**3a**, 92	87
8	**III**	$CHCl_3$	7	**3a**, 82	80
9	**III**	THF	3	**3a**, 88	85
10	**III**	PhMe	6	**3a**, 75	87
11	**III**	MeOH	8	**3a**, 54	84
12[d]	**III**	EtOAc	16	**3a**, 82	90
13[e]	**III**	EtOAc	19	**3a**, 80	90
14[f]	**III**	EtOAc	25	**3a**, 76	81
15[e,g]	**III**	EtOAc	21	**3a**, 80	93
16[e,h]	**III**	EtOAc	21	**3a**, 58	93

[a]Reaction conditions: ketimine (**1a**, 0.3 mmol), diphenyl phosphonate (**2**, 0.45 mmol), catalyst (0.03 mmol), solvent (3.0 mL) in the presence of 150 mg molecular sieves. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using Chiralpak IB column. [d]5 mol % catalyst loading. [e]2.5 mol % catalyst loading. [f]1.3 mol % catalyst loading. [g]Reaction was performed at 0 °C. [h]Reaction was performed without 4 Å molecular sieves.

Table 2: Substrate scope.[a]



1 2 3

entry	**1** (R^1, R^2)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a** (R^1 = $CH_2CH{=}CH_2$, R^2 = H)	21	**3a**, 80	93
2	**1b** (R^1 = $CH_2CH{=}CH_2$, R^2 = F)	15	**3b**, 94	94
3	**1c** (R^1 = $CH_2CH{=}CH_2$, R^2 = Cl)	12	**3c**, 90	94
4	**1d** (R^1 = $CH_2CH{=}CH_2$, R^2 = Br)	19	**3d**, 84	97
5	**1e** (R^1 = $CH_2C(CH_3){=}CH_2$, R^2 = Cl)	48	**3e**, 84	99
6	**1f** (R^1 = $CH_2CH{=}CHCH_3$, R^2 = Cl)	47	**3f**, 70	88
7	**1g** (R^1 = $CH_2C_6H_5$, R^2 = H)	21	**3g**, 87	99
8	**1h** (R^1 = $CH_2C_6H_5$, R^2 = F)	20	**3h**, 88	99
9	**1i** (R^1 = $CH_2C_6H_5$, R^2 = Cl)	16	**3i**, 78	98
10	**1j** (R^1 = $CH_2C_6H_5$, R^2 = Br)	32	**3j**, 84	99
11	**1k** (R^1 = $CH_2C_6H_5$, R^2 = OMe)	48	**3k**, 79	99
12	**1l** (R^1 = H, R^2 = Cl)	31	**3l**, 74	73
13	**1m** (R^1 = Boc, R^2 = H)	48	**3m**, 45	26

[a]Reaction conditions: ketimines (**1**, 0.3 mmol), diphenyl phosphonate (**2**, 0.45 mmol), catalyst (**III**, 7.5 μmol), EtOAc (3.0 mL) at 0 °C in the presence of 150 mg molecular sieve. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using Chiralpak IA (for **3f**), IB (for **3a**), IC (for **3b–e**, **3g–j**), and AD-H (for **3k**, **3l**) columns.

5-halo-*N*-allylated isatin imines provided adducts **3a**–**d** in good yields (80–94%) with excellent enantioselectivities (93–97% ee, Table 2, entry 1–4). The addition of diphenyl phosphonate (**2**) to 5-chloro-*N*-substituted isatin imines **1e** and **1f** provided 3-amino-3-phosphonyl-substituted oxindole derivatives **3e** and **3f** in high yields (84% and 70%) with good enantioselectivities (99% ee and 88% ee, Table 2, entries 5 and 6). *N*-Benzylisatin imine **1g** and 5-halogen-*N*-benzylisatin imines **1h**–**j** reacted well with diphenyl phosphonate (**2**), giving 3-amino-3-phosphonyl-substituted oxindole derivatives **3g**–**j** in high yields (78–88%) with excellent enantioselectivities (98–99% ee) (Table 2, entries 7–10). Ketimine **1k** containing an electron donating group gave the desired product **3k** in high yield (79%) with excellent enantioselectivity (99% ee, Table 2, entry 11). The nucleophilic addition of diphenyl phosphonate (**2**) to ketimine **2l** derived from *N*-unprotected isatin was also studied. The adduct **3l** was isolated in 74% yield with 73% ee (Table 2, entry 12). Unfortunately, the reaction of diphenyl phosphonate (**2**) with *N*-Boc-ketimine **2m** provided adduct **3m** with low yield and enantioselectivity (Table 2, entry 13). The absolute configuration of adducts **3** was determined to be *R* by comparison of the specific rotations and HPLC properties with literature values [36.37].

The stereochemical outcome in the above addition reaction was rationalized by a proposed stereochemical model. We propose that ketimine **1** is activated by the squaramide moiety through hydrogen bonding, and diphenyl phosphonate (**2**) is activated by the basic nitrogen atom in the tertiary amine of catalyst **III**. Then, diphenyl phosphonate (**2**) attacks the *re*-face of the carbon in ketimine **1** as shown in Figure 2.

To further demonstrate the synthetic potential of this method, we performed the addition reaction at the gram scale. As shown in Scheme 1, when ketimine **1a** was treated with diphenyl phosphonate (**2**) in the presence of 2.5 mol % of catalyst **III** at 0 °C, the desired product **3a** was obtained in 81% yield and 93% ee (Scheme 1).

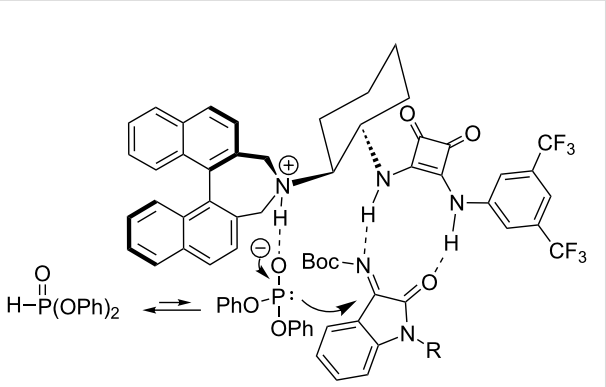


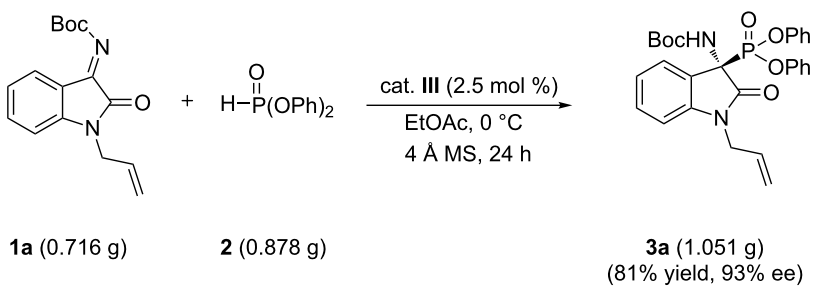
Figure 2: Proposed stereochemical model.

Conclusion

In conclusion, we have developed a practical and efficient catalytic enantioselective addition reaction of diphenyl phosphonate (**2**) with various ketimines **1** derived from isatins. This transformation is catalyzed by binaphthyl-modified squaramide catalyst **III** with low catalyst loading (2.5 mol %). Chiral 3-amino-3-phosphonyl-substituted oxindole derivatives were obtained in high yields and excellent enantioselectivities were observed (up to 99% ee). This reaction affords valuable and easy access to chiral 3-amino-3-phosphonyl-substituted oxindole derivatives.

Experimental

General procedure for the enantioselective addition of diphenyl phosphonate (2) to ketimines derived from isatins 1: To a solution of ketimine **1** (0.3 mmol), diphenyl phosphonate (**2**, 0.45 mmol), and 4 Å molecular sieves (150 mg) in ethyl acetate (3 mL), the catalyst (**III**, 7.5 μmol) was added at 0 °C. The reaction mixture was stirred for 12–48 h. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc–hexane) to afford the corresponding adducts **3**.



Scheme 1: Gram scale addition of ketimine **1a** and diphenyl phosphonate (**2**).

Supporting Information

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-149-S1.pdf]

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