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Asymmetric Iminium Ion Catalysis with a Novel Bifunctional Primary Amine Thiourea: Controlling Adjacent Quaternary and Tertiary Stereocenters

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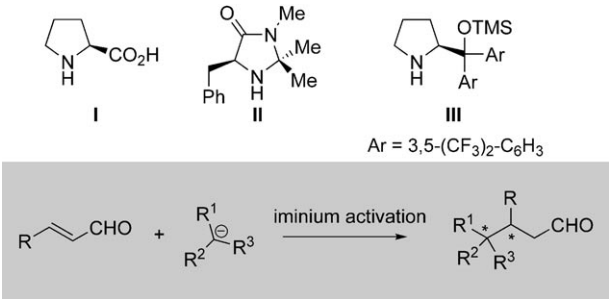
Dedicated to the Centenary of the Italian Chemical Society

The development of novel and highly enantioselective transformations is one of the most exciting goals for organic chemists involved in the competitive and stimulating field of asymmetric organocatalysis.[1] In this area, the remarkable advances in the application of chiral secondary amine catalysts (asymmetric aminocatalysis)[2a,b] are linked with the accessibility of divergent carbonyl activation modes, through either nucleophilic enamine[2c] or dienamine[2e] intermediates, electrophilic iminium ions[2d] or even radical[2f] intermediates. In particular, the incredibly high efficiency and generality demonstrated by some "privileged" organocatalysts such as proline[3a] (**I**) or the synthetic MacMillan imidazolidinones[2d] (**II**) and the silyl-protected diarylprolinols catalysts[3b] (**III**) (Scheme 1) have consolidated asymmetric aminocatalysis as a reliable and powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds.[2] These general and readily available catalysts represent an important starting point for the investigations of new asymmetric processes because they often avoid the need for multiple screening processes of catalysts to determine the optimal reaction conditions. However, because aminocatalysis may face problems of increasing complexity and diversity, the privileged catalysts might not always be the best candidates to solve some specific and challenging tasks (Scheme 1). In this context, the stereocontrolled conjugate addition of prochiral trisubstituted carbon nucleophiles to α,β-unsaturated aldehydes through iminium activation still represents a daunting synthetic challenge[4] because the privileged catalysts generally allow the formation of products with high enantioselectivity but with poor diastereocontrol.[5]



Scheme 1. The privileged catalysts **I**, **II**, and **III**. Illustration of the challenging task of creating adjacent stereocenters by iminium ion catalysis.

Herein, we describe the development of a new bifunctional chiral primary amine thiourea catalyst and its application in the first asymmetric conjugate addition of oxindoles to enals. A bifunctional catalyst was chosen because it was thought that only concomitant and synergistic activation of both the reacting partners may enforce high diastereocontrol during C–C bond formation. The high levels of both enantio- and diastereoselectivity achieved demonstrate the ability of the catalyst to provide a solution to the challenging problem of generating valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters.[6] Moreover, we demonstrated for the first time that chiral primary amine thiourea catalysts, which during the last two years have been successfully applied in many enamine-based asymmetric transformations expanding the synthetic potential of aminocatalysis,[7] can also be effective for iminium ion activation of α,β-unsaturated aldehydes.

For exploratory studies, we selected the reaction between 3-methyl oxindole (**1a**) and cinnamaldehyde (**2a**), a combination of simple and readily available starting materials that

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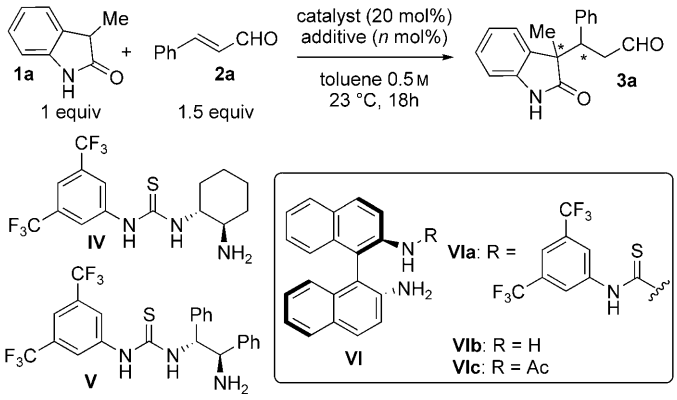
would readily give access to structurally complex oxindole **3a** with a quaternary stereogenic center at C3 (Table 1).[8,9] Chiral 3,3-disubstituted oxindole frameworks are attractive targets in organic synthesis because of their promising biological activities,[9a,b] as well as their wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals.[9b,c] The use of the privileged secondary amines **I** and **II** as iminium catalysts of this challenging reaction afforded poor results, whereas the silyl-protected diarylprolinol **III** provided very high enantioselectivity, although an almost 1:1 mixture of the two diastereomers was formed (Table 1, entries 1–3). This evidence supports the lack of substrate-controlled stereoselectivity in the process.

We speculated that a key factor to improve the stereocontrol of the process might be to use a bifunctional catalyst capable of synergistically arranging and activating both of the reagents. The ability of primary amine thiourea catalysts to induce high stereocontrol through a cooperative mechanism in a variety of enamine-based transformations has been recently established.[7] This fact, together with the potential application of this catalyst architecture in iminium activation,[10] even of simple α,β-unsaturated aldehydes,[11] led us to perform an extensive screen of chiral primary amines incorporating a thiourea framework, which led to the identification of **VIa** as a promising iminium catalyst. The newly synthesized catalyst **VIa**, readily accessible through a one-step synthesis from commercially available compounds,[12] induced a high level of stereocontrol with good catalytic activity (Table 1, entry 6). The poor catalytic performance and the very low selectivity observed with **VIb** and **VIc** suggested a critical role of the thiourea moiety during the stereoselective C–C bond-forming step (Table 1, entries 7 and 8). Further optimization experiments (see the Supporting Information for details) revealed that the nature and the amount of the acidic additive were crucial parameters to obtain high levels of stereoselectivity and reaction efficiency. By using 50 mol% of benzoic acid,[13] the catalyst loading was reduced to 10 mol%, while still maintaining high diastereo- and enantiocontrol, and significant reactivity (Table 1, entry 10).

As summarized in Table 2, under the optimized conditions, the conjugate addition of oxindoles to enals catalyzed by 10 mol% of **VIa** displays a broad scope.

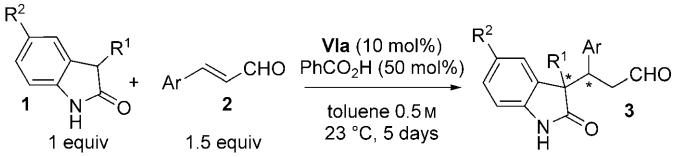
Table 1. Optimization studies.[a]



Entry	Catalyst	Additive [mol%]	Conv[b] [%]	dr[c] [%]	*ee*[d] [%]
1	**I**	none	<5	–	–
2	**II**	DCA (20)	53	1.1:1	5
3[e]	**III**	pNO_2-$C_6H_4CO_2H$ (20)	>95	1.1:1	92
4	**IV**	pNO_2-$C_6H_4CO_2H$ (20)	>95	1:1	7
5	**V**	pNO_2-$C_6H_4CO_2H$ (20)	84	1:1	2
6	**VIa**	pNO_2-$C_6H_4CO_2H$ (20)	55	4.5:1	84
7	**VIb**	pNO_2-$C_6H_4CO_2H$ (40)	<5	–	–
8	**VIc**	pNO_2-$C_6H_4CO_2H$ (20)	20	1.2:1	40
9	**VIa**	$PhCO_2H$ (20)	51	6:1	90
10[f]	**VIa**	$PhCO_2H$ (50)	35	7:1	90

[a] For studies on additional additives and reaction conditions, see the Supporting Information. DCA: dichloroacetic acid. [b] Conversion, determined by ^{1}H NMR spectroscopy analysis of the crude mixture. [c] Diastereomeric ratio (dr), determined by ^{1}H NMR spectroscopy analysis of the crude mixture. [d] Enantiomeric excess (*ee*), determined by chiral HPLC analysis. [e] Reaction carried out at −10 °C in AcOEt as the solvent for 66 h. [f] 10 mol% of **VIa** was used.

Table 2. Diastereo- and enantioselective conjugate addition of oxindoles to enals catalyzed by **VIa**.[a]



Entry	R^1, R^2	Ar	**3**	Yield[b] [%]	dr[c] [%]	*ee*[d] [%]
1	Me, H	Ph	**a**	71	7:1	90
2	Bn, H	Ph	**b**	73[e] (59)	7:1	92 (>99)
3[f]	Bu, H	Ph	**c**	65	5:1	73
4	Bn, Me	Ph	**d**	55	5:1	81
5	Me, H	p-NO_2-C_6H_4	**e**	70 (56)	7.5:1	88 (>99)
6[f]	Bn, H	p-NO_2-C_6H_4	**f**	47[e]	11.5:1	93
7	Bn, H	p-Cl-C_6H_4	**g**	85[e] (77)	5.7:1	85 (97)
8[f]	Bn, H	p-CN-C_6H_4	**h**	56	12:1	83
9[f]	Me, H	naphthyl	**i**	71	13.2:1	80
10[f]	Bn, H	naphthyl	**j**	55[e] (49)	>19:1	89 (>99)

[a] Unless noted, the reactions were carried out on a 0.2 mmol scale with 1.5 equiv of **2** and $[\mathbf{1}]_0 = 0.5$ M in toluene for 5 days in the presence of 10 mol% of **VIa** and 50 mol% of $PhCO_2H$. [b] Isolated yield (sum of diastereomers). The yield of the single major diastereomer obtained after a single crystallization is given in brackets. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis. The values in parenthesis are the *ee* values obtained after a single crystallization. [e] Yield refers to the single major diastereoisomer obtained after chromatography. [f] The *ee* value determined on the corresponding alcohols after reduction with $NaBH_4$.

High enantioselectivity and useful levels of diastereoselectivity were obtained with different combinations of substituted oxindoles and a variety of aldehydes.[14] These results

are in sharp contrast with the very low dr values (from 1:1 to 2:1) obtained in the same process by using **III** as the iminium catalyst (see the Supporting Information for details). The best diastereocontrol was observed for enals that have a naphthyl β substituent (up to 19:1 dr; Table 2, entries 9 and 10) and by using oxindole that has a benzyl substituent.

Importantly, in many cases the main diastereomer can be isolated by column chromatography (Table 2, entries 2, 5–7, and 10). This observation, taken together with the possibility of obtaining a single diastereomer in almost enantiopure form after a single crystallization (Table 2, entries 2, 5, 7, and 10), renders this novel catalytic system a useful synthetic route to valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters.

The relative and absolute configuration of compound **3e** was determined to be 3*S*,3′*R* by anomalous dispersion X-ray crystallography of the corresponding tosylated alcohol **4**, obtained by simple aldehyde reduction (Figure 1).[15]

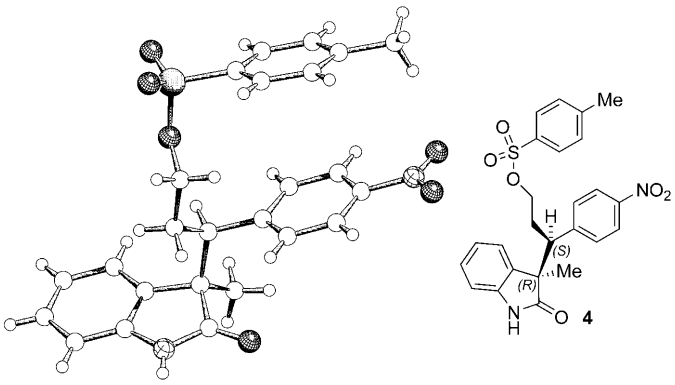


Figure 1. X-ray structure of toluene-4-sulfonic acid **4**.

Generally, the stereoselective one-step construction of highly congested products, such as **3**, is dependent on the capability of the catalyst to activate and orient the Michael donor and the acceptor simultaneously by means of a network of hydrogen-bonding interactions. Modifications of the catalyst scaffold revealed that the presence of the primary amine[16] and the thiourea group play an active role during the catalysis (compare entries 6–8 in Table 1). To gain some insight into the substrate–catalyst interactions, we ran the reaction by using catalyst **VIa** in combination with 50 mol% of $PhCO_2H$, **2a** and the *N*-methyl oxindole as the nucleophile.[17] The very poor reactivity and selectivity observed (less than 10% conversion after 5 days; 1.4:1 d.r.) strongly suggest a direct interaction of the amidic nitrogen in the nucleophilic component with the catalyst. On these grounds, a plausible bifunctional activation mode of the chiral primary amine thiourea **VIa** can be envisaged, in which the thiourea moiety activates the oxindole, stabilizing its enol form, and the primary amine activates the unsaturated aldehyde through iminium ion formation.[18]

In summary, for the first time, a chiral primary amine thiourea catalyst has been successfully applied for the iminium ion activation of α,β-unsaturated aldehydes. In addition to expanding the applicability of this class of bifunctional organocatalysts beyond enamine catalysis, the present study provides a straightforward solution to the challenging problem of generating valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters; a daunting challenge in asymmetric aminocatalysis. The bifunctional activation mode of the novel organocatalyst **VIa** allows the development of a previously elusive asymmetric conjugate addition of oxindoles to enals. Studies towards a more detailed mechanistic understanding are ongoing, aimed at further expanding the efficiency and scope of the novel chiral primary amine thiourea in iminium catalysis.

Experimental Section

All of the reactions were carried out in undistilled toluene without any precautions to exclude water. In a test tube equipped with a magnetic stirring bar, catalyst **VIa** (0.02 mmol, 11.1 mg, 10 mol%) was dissolved in toluene (400 μL). After addition of benzoic acid (0.1 mmol, 12.2 mg, 50 mol%), the solution was stirred for 5 min at room temperature. The α,β-unsaturated aldehyde **2** (0.3 mmol, 1.5 equiv) was added to the mixture and after being stirred for 10 min, the oxindole derivative **1** (0.20 mmol, 1 equiv) was added in one portion, the tube was capped with a rubber stopper, and stirring was continued at 23 °C for the indicated time (generally 5 days). The crude reaction mixture was diluted with dichloromethane/AcOEt (1:1; 1 mL) and flushed through a short plug of silica gel by using the same mixture as the eluent. The solvent was removed in vacuo, and the residue was purified by flash chromatography to yield the desired compound **3**.

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Keywords: asymmetric catalysis · chirality · conjugate addition · primary amine · thioureas

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[12] Both enantiomers of **VIa** are easily accessible from a single-step synthesis, see the Supporting Information.

[13] It is likely that the acid serves to facilitate catalyst turnover by promoting iminium formation/imine hydrolysis; for similar effects with primary amine thiourea catalysts in enamine catalysis, see references [7b,c].

[14] Enals with alkyl β substituents afforded poor results; for example, crotonaldehyde (2.3:1 dr; 24% *ee*); the presence of a chlorine on the oxindole scaffold ($R^2 = Cl$) led to a decreased stereoselectivity in the reaction with **2a** (1.5:1 dr; 11% *ee*).

[15] CCDC-710802 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[16] Replacement of the primary amine moiety with a tertiary one (NMe_2) in the catalyst scaffold led to a complete loss of catalytic activity and this evidence ruled out possible activation of the nucleophile through chiral Brønsted base catalysis.

[17] The employment of the *N*-Boc protected oxindole under the best reaction conditions afforded low stereocontrol, albeit with improved reactivity (18 h; >95% conversion; 2:1 dr; 67% *ee*).

[18] The presence of the primary amine is crucial for the catalytic activity, see reference [16]; at this stage of the investigations a plausible Brønsted acid activation of unsaturated aldehydes cannot be ruled out.

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