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Highly enantioselective Michael addition of 2-oxindoles to vinyl selenone in RTILs catalyzed by a *Cinchona* alkaloid-based thiourea†

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A highly enantioselective Michael addition of 2-oxindoles (1) to vinyl selenone (2) in RTILs catalyzed by a *Cinchona* alkaloid-based thiourea has been developed in high yields (80–91%) with excellent enantioselectivities (up to 95% ee).

Recently, the applications of room-temperature ionic liquids (RTILs) as green and alternative media[1] and organocatalytic enantioselective reactions for organic synthesis[2] have attracted considerable attention. The organocatalysts employed in the RTIL-mediated enantioselective reaction, highly interesting and promising in organic synthesis, were only focused on proline and its derivatives under the covalent catalysis through an enamine intermediate.[3] However, very few examples were reported on the RTIL-mediated enantioselective reaction catalyzed by *Cinchona* alkaloid-type catalysts. As a chiral phase-transfer catalyst, a quaternary ammonium salt derived from quinine was used in the asymmetric Michael reaction and epoxidation of chalcones in RTILs, but relatively low enantioselectivities (42–68% ee) were obtained.[4] The relatively low enantioselectivity was attributed to a different catalytic mode, non-covalent organocatalysis.[2a] During the course of the reaction the generated chiral ion-pair intermediate might be interfered by achiral anions of the ionic liquid *via* ion exchange.[5] To obtain high enantioselectivities in ionic liquids *via* the mode of non-covalent catalysis is still a great challenge. In order to achieve high enantioselectivity, it is necessary to enhance the non-covalent interaction between chiral catalysts and substrates to generate a tighter chiral ion-pair intermediate and restrain ion exchange with the achiral anion of the ionic liquid used.

Oxindoles bearing a quaternary carbon stereocenter at the 3-position of the indole ring constitute a ubiquitous structural motif in a variety of natural products and biologically active drug candidates.[6] The asymmetric Michael reaction of 2-oxindoles is a straightforward approach to the biological motif.[7] Compared with sulfur analogues, selenones are well recognized as precursors in organic synthesis, because the selenonyl group is considered as a good leaving group, offering an opportunity to accomplish further derivatizations for the synthesis of biologically active compounds.[8] However, to the best of our knowledge, only one example of enantioselective Michael addition employing the α,β-unsaturated selenone as the acceptor was reported.[9]

Herein, we would like to report an enantioselective Michael addition of 2-oxindoles to vinyl selenone in RTILs catalyzed by a *Cinchona* alkaloid-based thiourea in high yields with excellent enantioselectivities.

Initially, the reaction of 2-oxindole **1a** with vinylselenone **2** was carried out in RTIL [bpy][BF_4] in the presence of *Cinchona* alkaloid catalysts (**3a–e**) (10 mol%) (Fig. 1) at room temperature. The stereointroduction *via* only a single hydrogen bonding donor either at C9 (**3a** and **3e**) or C6′ (**3b**)[10] gave the product **4a** in low yields with poor enantioselectivities (Table 1, entries 1, 2 and 5). The enantioselectivity could not be improved by increasing the hindrance at C9 (**3c** and **3d**) (entries 3 and 4). When Takemoto's catalyst **3f**,[11] bearing

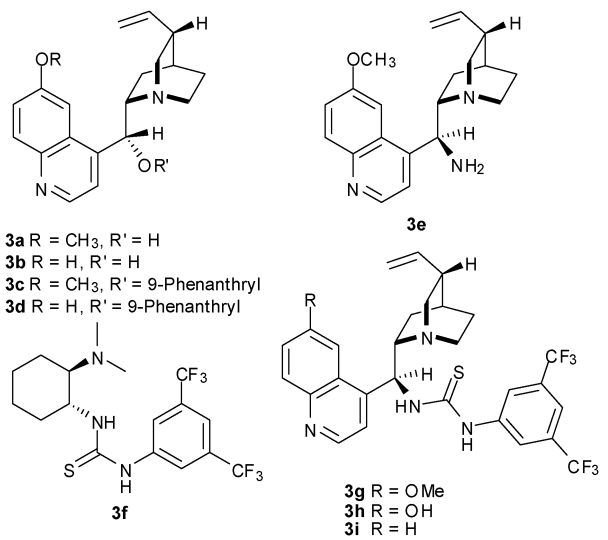

Fig. 1 Catalysts for the Michael addition of oxindoles with vinyl selenone.

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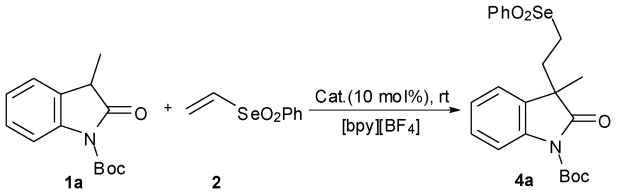
Table 1 Catalyst screening for the reaction of **1a** with **2**[a]



Entry	Catalyst	Reaction time/h	Yield[b] (%)	ee[c] (%)
1	**3a**	48	19	22
2	**3b**	48	35	12
3	**3c**	48	13	0
4	**3d**	48	56	46
5	**3e**	48	25	−2[d]
6	**3f**	4	65	68
7	**3g**	4	77	−91[d]
8	**3h**	4	86	−91[d]
9	**3i**	4	88	−95[d]

[a] Reaction conditions: 0.2 mmol **1a** with 1 equiv. of **2**, using 10 mol% of catalyst **3** in 0.5 mL [bpy][BF_4]. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The opposite enantiomer was obtained.

a thiourea moiety possessing two hydrogen bonding donors, was used, only moderate yield and enantioseletivity were obtained (entry 6). The combination of the *Cinchona* alkaloid moiety with the thiourea unit formed catalysts **3g–i**,[12] which could enhance the hydrogen-bonding interaction and the steric effect with substrates, leading to high enantioselectivities. To our delight, the yield and enantioselectivity of the product **4a** were increased noticeably under the catalysis of *Cinchona* alkaloid-based thioureas (entries 7–9). With the decrease of the hindrance at C6′, the catalyst **3i** provided the highest yield and enantioselectivity (entry 9, yield 88%, ee 95%).

Subsequently, various ionic liquids were used as reaction media in the reaction of **1a** with **2** (Table 2). Although in the imidazole-type ionic liquids, [bmim][BF_4] and [bdmim][BF_4], the reaction offered high enantioselectivities, relatively lower yields were unsatisfactory (entries 1 and 2). Thus, pyridine-type ionic liquids were selected as the reaction media. It was found that [bpy][BF_4] provided the best result for the asymmetric Michael addition of **1a** with **2**. The anions of ionic liquids influenced the enantioselectivity of the product strongly. [bpy][NO_3] gave a very poor enantioselectivity (9% ee) despite giving a good yield (87%) of **4a** (entry 3). Furthermore, when [bpy][OTf] was employed, no reaction was observed (entry 4). The relatively loose anion–cation interaction of ILs may be more prone to interference with the chiral ion-pair intermediate.[5b] When [$c_6$py][BF_4] and [$c_8$py][BF_4] bearing a longer alkyl chain were used (entries 5 and 6) and when the catalyst loading and concentration of substrates in [bpy][BF_4] were varied (entries 7–10), the enantioselectivity of the reaction was not improved noticeably.

Under the optimum conditions various 2-oxindoles (Table 3) with 3-alkyl substituents including methyl, ethyl, *n*-propyl, naphthylmethyl and benzyl groups were employed in the asymmetric Michael addition reaction catalyzed by **3i** in [bpy][BF_4], affording the corresponding adducts **4a–f** in 84–91% yields with up to 95% ee (entries 1–6). All 3-benzyl-2-oxindoles bearing the functional group either at *ortho*-, *meta*- or *para*-position on the aromatic ring of the benzyl group gave the corresponding products (**4g–k**) in high to excellent yields and enantioselectivities (entries 7–11).

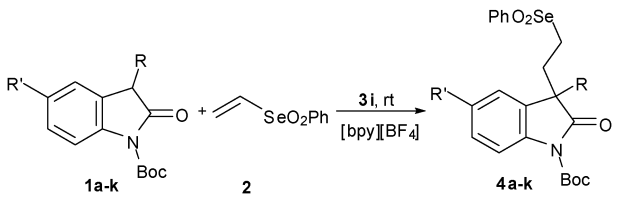
The absolute configuration of the main enantiomer of **4a** was deduced as (*R*) by X-ray single-crystal analysis of **4a** (see ESI†). Based on the results listed above, a possible model of dual activation of the nucleophile and the electrophile was proposed (Fig. 2). Catalyst **3i** serves as the bifunctional chiral organocatalyst: the thiourea moiety activates selenone **2** by double hydrogen bonding, while the quinuclidine moiety deprotonates the C3 methine proton leading to the generation

Table 2 RTIL screening for the reaction of **1a** with **2**[a]

Entry	RTIL	Yield[b] (%)	ee[c] (%)
1	[bmim][BF_4]	80	92
2	[bdmim][BF_4]	77	95
3	[bpy][NO_3]	87	9
4	[bpy][OTf]	nr[d]	
5	[$c_6$py][BF_4]	87	91
6	[$c_8$py][BF_4]	78	90
7[e]	[bpy][BF_4]	77	93
8[f]	[bpy][BF_4]	28	93
9[g]	[bpy][BF_4]	86	92
10[h]	[bpy][BF_4]	88	90

[a] Reaction performed at a 0.2 mmol scale **1a** with 1 equiv. of **2**, 10 mol% of catalyst **3i** in the indicated solvent (0.5 mL) for 4 h. [b] Isolated yield after FC. [c] Determined by chiral HPLC analysis. [d] No reaction. [e] 5 mol% cat. [f] 1 mol% cat., reaction time: 4 d. [g] 2 mL IL was used. [h] 0.2 ml IL was used.

Table 3 Organocatalytic Michael reactions of oxindoles with **2** in RTIL



Entry[a]	R	R′	Products	Yield[b] (%)	ee[c] (%)
1	Me	H	**4a**	88	95
2	Me	Me	**4b**	84	91
3	Et	H	**4c**	86	94
4	*n*-Pr	H	**4d**	86	88
5	Bn	H	**4e**	91	88
6	1-Naphthylmethyl	H	**4f**	86	88
7	2-Me$C_6H_4CH_2$	H	**4g**	86	91
8	3-Me$C_6H_4CH_2$	H	**4h**	90	91
9	4-Me$C_6H_4CH_2$	H	**4i**	86	85
10	2-MeO$C_6H_4CH_2$	H	**4j**	80	90
11	3-MeO$C_6H_4CH_2$	H	**4k**	80	90

[a] Reaction conditions: 0.2 mmol **1** with 1 equiv. of **2**, 10 mol% catalyst **3i** in [bpy][BF_4] (0.5 mL) at room temperature for 4 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

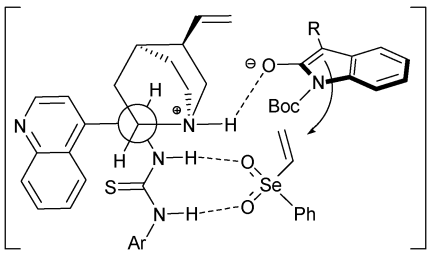
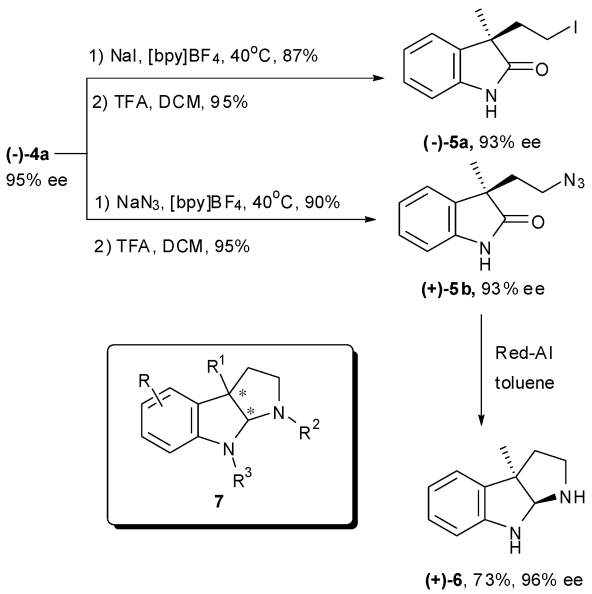


Fig. 2 Proposed transition state of the Michael reaction of 2-oxindole with vinyl selenone promoted by catalyst **3i**.



Scheme 1 Applications of the methodology.

of the enolate-anion intermediate of the 2-oxindole.[13] The approach of an activated α,β-unsaturated selenone to the enolate anion from the *Re*-face resulted in the formation of a *R*-selective product.

The products **4** could readily undergo nucleophilic substitution reaction with NaN_3 and NaI. For example, starting from (−)-**4a** (95% ee), the substitution products **5a** and **5b** were obtained in 83% and 86% overall yields both with 93% ee, respectively (Scheme 1). Followed by reduction and cyclization, (+)-**5b** was further transformed to pyrroloindoline (+)-**6** in overall yield 73% with 96% ee. It is noteworthy that many optically active compounds with a pyrroloindoline unit (**7**), such as (−)-physostigmine, show wide biological activities and have been clinically used as medicines.[14]

In summary, we have developed a novel organocatalytic enantioselective Michael addition of 2-oxindoles to vinyl selenone, which was promoted by a *Cinchona* alkaloid-based thiourea in RTILs. High to excellent yields and enantioselectivities were obtained. The developed approach could readily access chiral pyrroloindoline-type compounds. The investigation of the Michael addition to other nucleophiles in RTILs is underway in our lab.

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