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Organocatalytic Asymmetric Conjugate Addition of 3-Alkyl-Substituted Oxindoles to Vinyl Ketones

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Oxindole structures are widely present in a large number of natural and biologically active molecules.[1] Particularly, oxindole scaffolds bearing a quaternary stereocenter at the 3-position are a versatile common motif found in a variety of biologically and pharmaceutically active natural products and utilized as building blocks for indole alkaloid synthesis.[2] Several methods for their asymmetric formation and transformation are of considerable interest. Among the established strategies for the synthesis of chiral 3,3-disubstituted oxindoles, a transition metal-catalyzed asymmetric reaction has been intensively studied.[3] Recently, organocatalytic enantioselective conjugate addition reactions of oxindoles with enals, nitroalkenes, and vinyl sulfones have been reported.[4] Several groups have reported an enantioselective conjugate addition reaction of 3-aryloxindoles to vinyl ketones catalyzed by organocatalysts, phase-transfer catalyst, and chiral calcium phosphate.[5] Although there have been reports for the catalytic enantioselective conjugate addition reaction of 3-aryl-substituted oxindoles to vinyl ketones,[5] a few examples for the catalytic enantioselective conjugate addition reaction of 3-alkyl-substituted oxindoles to cyclic enones were reported using chiral primary or secondary amine catalysts.[6] Therefore, the development of alternative catalysts for the catalytic enantioselective conjugate addition reaction of 3-alkyl-substituted oxindoles to vinyl ketones would be highly desirable.

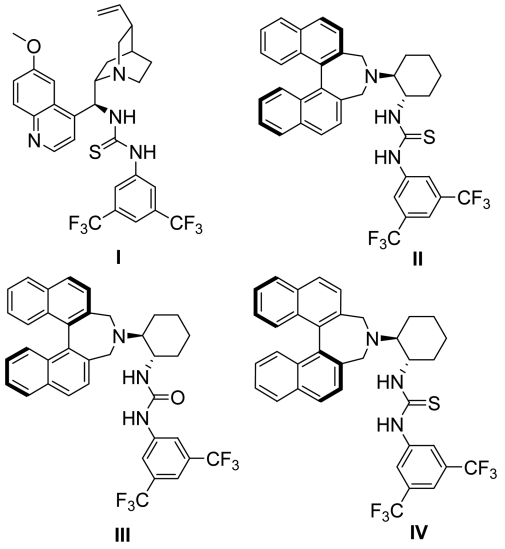
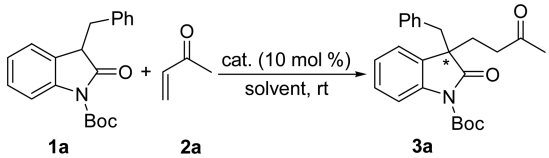


Figure 1. Structures of various chiral organocatalysts.

As part of the research program toward the development of synthetic methods for the catalytic carbon-carbon bond formations,[7] we recently reported the organocatalytic conjugate addition reaction to α,β-unsaturated carbonyl compounds[8] and the other Michael acceptors.[9] In this communications, we wish to describe the enantioselective conjugate addition reaction of prochiral 3-alkyl-substituted oxindoles with vinyl ketones catalyzed by binaphthyl-modified bifunctional organocatalysts bearing both central and axial chiral elements.

In an attempt to validate the feasibility of the organocatalytic enantioselective conjugate addition reaction of 3-substituted oxindoles, we first investigated the reaction system with 3-benzyl oxindole **1a** with methyl vinyl ketone (**2a**) in the presence of 10 mol % of catalyst in toluene at room temperature. We examined the impact of the structure of catalysts **I-IV** on enantioselectivities (Table 1, entries 1-4). Quinine-derived thiourea catalyst **I** was ineffective (Table 1, entriry 1). While binaphthyl-modified chiral bifunctional organocatalysts **II-III** bearing both central and axial chiral

Table 1. Optimization of the reaction conditions



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

Entry	Cat.	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
1	**I**	PhMe	12	89	3
2	**II**	PhMe	11	87	91
3	**III**	PhMe	15	90	77
4	**IV**	PhMe	13	80	19
5	**II**	CH_2Cl_2	9	74	83
6	**II**	THF	9	76	87
7	**II**	CH_3CN	9	88	79
8	**II**	*p*-xylene	18	89	87
9[c]	**II**	PhMe	9	75	95
10[d]	**II**	PhMe	9	82	97
11[e]	**II**	PhMe	20	78	97
12[d,f]	**II**	PhMe	9	81	97
13[g]	**II**	PhMe	10	65	84

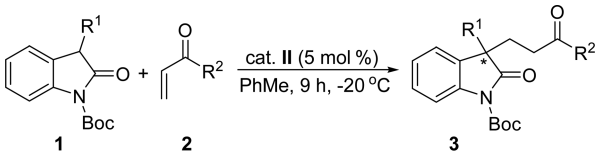
[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using Chiralpak IA column. [c]This reaction was carried out at 0 °C. [d]at −20 °C. [e]at −40 °C. [f]5 mol % of catalyst loading. [g]1 mol % of catalyst loading.

elements effectively promoted the addition reaction in high yield with moderate to high enantioselectivity (77-91% ee, entries 3-4). Catalyst **II** gave the desired product **3a** with high enantioselectivity (91%, entry 2), whereas diastereomeric catalyst **IV** afforded product **3a** in lower enantioselectivity (19% ee, entry 4). This result demonstrated that the central and axial chiral elements in chiral amine-thiourea catalyst **II** are matched, enhancing the stereochemical control, whereas diastereomeric catalyst **IV** is mismatched. Among the solvents probed, the best results (87% yield and 91% ee) were achieved when the reaction was conducted in toluene (Table 1, entry 2). Lowering the temperature to 0, −20, and −40 °C with catalyst **II** increased enantioselectivities up to 97% ee (entries 2, 9-11). The present catalytic system tolerates catalyst loading down to 5 mol % without compromising both the yield and enantioselectivity (entries 10 and 12).

To examine the generality of the catalytic enantioselective conjugate addition reaction of 3-alkyl-substituted oxindoles with vinyl ketones in the presence of catalyst **II**, we studied the addition of various 3-benzyl oxindoles **1a-1e** to vinyl ketones **2**. As can be seen in Table 2, the corresponding products **3a-3f** were obtained in high yields (80-92%) and excellent enantioselectivities (91-97%, entries 1-6). Unfortunately, conjugate addition reaction of 3-alkyl-substituted oxindoles **1f-1h** to vinyl ketones **2** gave the desired products **3** in moderate enantioselectivity (52-67% ee, entries 7-9).

In conclusion, we have developed a highly efficient catalytic enantioselective conjugate addition reactions of both 3-alkyl-substituted oxindoles to vinyl ketones using binaphthyl-modified bifunctional catalyst **II**. The desired Michael products were obtained in good to high yields, and excellent enantioselectivities (up to 97% ee) were observed for 3-benzyl oxindoles examined in this work. Further study of these bifunctional organocatalysts in other asymmetric reactions is being under investigated.

Table 2. Variation of 3-alkyl-substituted oxindoles



Entry	**1**, R^1	**2**, R^2	Yield (%)[a]	ee (%)[b]
1	**1a**, $PhCH_2$	**2a**, Me	**3a**, 81	97
2	**1b**, *p*-$MeOC_6H_4CH_2$	**2a**, Me	**3b**, 89	91
3	**1c**, *p*-$FC_6H_4CH_2$	**2a**, Me	**3c**, 88	93
4	**1d**, *p*-$ClC_6H_4CH_2$	**2a**, Me	**3d**, 92	97
5	**1e**, *p*-$BrC_6H_4CH_2$	**2a**, Me	**3e**, 90	97
6	**1a**, $PhCH_2$	**2b**, Et	**3f**, 80	97
7	**1f**, *i*-Bu	**2a**, Me	**3g**, 85	67
8	**1g**, Me	**2a**, Me	**3h**, 76	59
9	**1h**, CH_2=$CHCH_2$	**2a**, Me	**3i**, 78	52

[a]Isolated yield. [b]Enantiomeric excess of **3** was determined by HPLC analysis using Chiralpak IA (for **3a-3e**, **3g**, and **3i**), IB (for **3f**), IC (for **3h**) columns.

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