Highly Enantioselective Conjugate Addition of 3-Substituted Oxindoles to Vinyl Sulfone Catalyzed by Binaphthyl-Modified Tertiary Amines

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Abstract: The enantioselective conjugate addition reaction of 3-substituted oxindoles with 1,1-bis(benzenesulfonyl)ethylene by binaphthyl-modified bifunctional organocatalysts was investigated. The corresponding Michael adducts, containing a quaternary center at C3 position of the oxindoles, were generally obtained in high yields with excellent enantioselectivities (up to 99% ee).

Key words: oxindole, vinyl sulfone, conjugate addition, bifunctional organocatalysis, asymmetric catalysis

Oxindole structures exist in a large number of natural products and bioactive molecules.[1] In particular, oxindole derivatives bearing a C3 quaternary carbon stereocenter are a versatile structural motif found in a variety of biologically and pharmaceutically active natural products and utilized as building blocks for indole alkaloid synthesis.[2] Therefore, several methods for their asymmetric formation and transformation are of considerable interest. Discovering diverse electrophiles to react with 3-substituted oxindoles for the synthesis of diversely structured 3,3-disubstituted oxindoles is still strongly desired. Among the established strategies for the synthesis of chiral 3,3-disubstituted oxindoles, the transition-metal-catalyzed asymmetric reaction has been intensively studied.[3] Recently, organocatalytic enantioselective conjugate addition reactions of oxindoles with enals and nitroalkenes have been reported.[4] The Lu group reported the stereoselective conjugate addition of 3-substituted oxindoles to 1,1-bis(benzenesulfonyl)ethylene,[5,6] which is a valuable and unique acceptor in conjugate addition and subsequent desulfonation, might provide a viable approach for the construction of optically enriched 3,3-alkyl-/aryl-disubstituted oxindoles.[7]

As part of the research program related to the development of synthetic methods for the catalytic carbon–carbon bond formations,[8] we recently reported the organocatalytic conjugate addition reaction to α,β-unsaturated carbonyl compounds[9] and the other Michael acceptors.[10]

We envisioned that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a H-bonding motif could constitute a new class of bifunctional organocatalyst. The rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element.

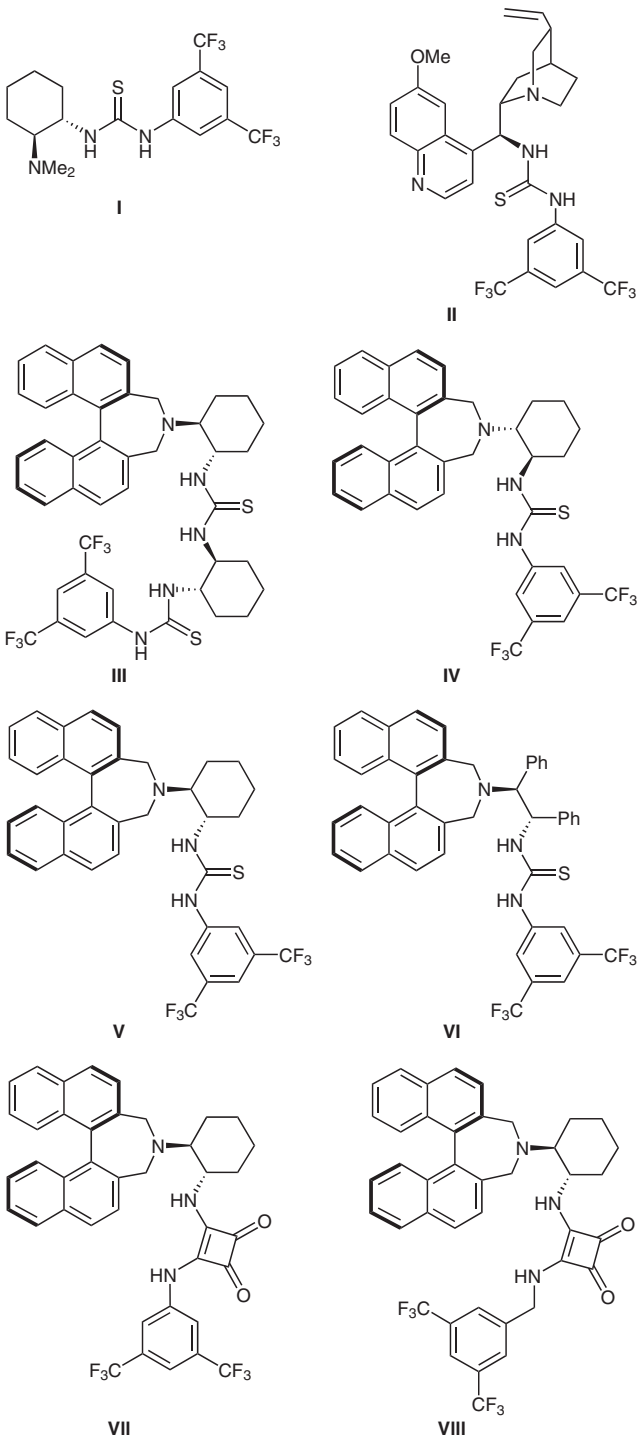

Figure 1 Structures of various chiral bifunctional organocatalysts

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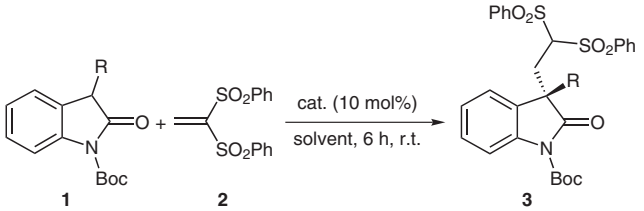
In this letter, we wish to describe the enantioselective conjugate addition reaction of prochiral 3-substituted oxindoles with 1,1-bis(benzenesulfonyl)ethylene catalyzed by binaphthyl-modified bifunctional organocatalysts bearing both central and axial chiral elements.

Table 1 Optimization of the Reaction Conditions



1 2 3

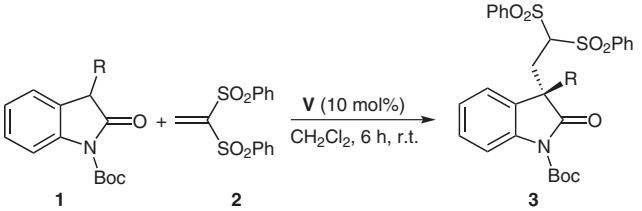
Entry	1 R	Cat.	Solvent	Yield (%)[a]	ee (%)[b]
1	**1a** Bn	**I**	CH_2Cl_2	88	19
2	**1a** Bn	**II**	CH_2Cl_2	90	–35
3	**1a** Bn	**III**	CH_2Cl_2	91	83
4	**1a** Bn	**IV**	CH_2Cl_2	83	–9
5	**1a** Bn	**V**	CH_2Cl_2	89	97
6	**1a** Bn	**VI**	CH_2Cl_2	90	95
7	**1a** Bn	**VII**	CH_2Cl_2	92	61
8	**1a** Bn	**VIII**	CH_2Cl_2	82	81
9	**1f** Ph	**III**	CH_2Cl_2	88	88
10	**1f** Ph	**V**	CH_2Cl_2	89	81
11	**1f** Ph	**VI**	CH_2Cl_2	90	90
12	**1f** Ph	**VIII**	CH_2Cl_2	90	95
13	**1f** Ph	**VIII**	EtOH	87	60
14	**1f** Ph	**VIII**	Et_2O	80	61
15	**1f** Ph	**VIII**	PhMe	88	89

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using Chiralpak IA column.

In an attempt to validate the feasibility of the organocatalytic enantioselective conjugate addition reaction of 3-substituted oxindoles, we initially investigated the reaction system with 3-benzyl oxindole **1a** with 1,1-bis(benzenesulfonyl)ethylene (**2**) in the presence of 10 mol% of catalyst in dichloromethane at room temperature. We first examined the impact of the structure of catalysts **I**–**VIII** (Figure 1) on enantioselectivities (Table 1, entries 1–8). Takemoto's catalyst **I** and quinine-derived thiourea catalyst **II** were ineffective (Table 1, entries 1 and 2). While binaphthyl-modified chiral bifunctional organocatalysts **III**–**VIII** bearing both central and axial chiral elements effectively promoted the addition in high yield with high enantioselectivity (61–97% ee). Catalyst **V** gave the desired product **3a** with high enantioselectivity (97%, Table 1, entry 5), whereas diastereomeric catalyst **IV** afforded product **3a** in lower enantioselectivity (–9% ee, Table 1, entry 4), as well as a reversal absolute configuration. These results demonstrated that the central and axial chiral elements in chiral amine-thiourea catalyst **V** are matched, enhancing the stereochemical control, whereas the two chiral elements in catalyst **IV** are mismatched. When 3-phenyloxindole **1f** was used as substrate in the presence of catalyst **V** in dichloromethane, the corresponding Michael adduct **3f** was obtained in 89% yield, but moderate selectivity (81% ee, Table 1, entry 10). To improve the enantioselectivity for 3-phenyl oxindole **1f**, the catalytic effects of other catalysts **III**, **IV**, and **VIII**[11] on the conjugate addition of 3-phenyloxindole **1f** to 1,1-bis(benzenesulfonyl)ethylene (**2**) were examined under several solvents (Table 1, entries 9 and 11–15). Binaphthyl-modified squaramide catalyst **VIII** turn out to be an excellent catalyst (95% ee, Table 1, entry 12). Based on the exploratory studies, we decided to select binaphthyl-modified thiourea catalyst **V** for 3-alkyl-substituted oxindoles and binaphthyl-modified squaramide catalyst **VIII** for 3-aryl oxindoles for further optimization of reaction conditions. Absolute configuration of **3** was determined by comparison of the optical rotation and chiral HPLC data with the literature values.[7]

To examine the generality of the catalytic enantioselective conjugate addition reaction of 3-alkyl-substituted oxindoles with vinyl sulfone in the presence of a binaphthyl-modified thiourea–tertiary amine catalyst **V**, we studied the addition of various 3-alkyl-substituted oxindoles **1a**–**e** to 1,1-bis(benzenesulfonyl)ethylene (**2**). As can be seen in Table 2, the corresponding products **3a**–**e** were obtained in high yields (80–92%) and excellent enantioselectivities (91–97%). We then examined the catalytic enantioselective conjugate addition reaction of 3-aryl-substituted oxindoles **1f**–**l** with 1,1-naphthyl-modified squaramide catalyst **VIII**.[12] As shown in Table 3, high to excellent

Table 2 Variation of 3-Alkyl-Substituted Oxindoles



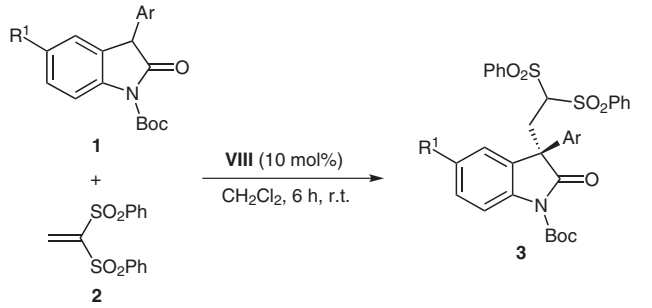
1 2 3

Entry	1 R	Yield (%)[a]	ee (%)[b]
1	**1a** Bn	**3a** 89	97
2	**1b** 4-$MeC_6H_4CH_2$	**3b** 80	91
3	**1c** Me	**3c** 90	91
4	**1d** Et	**3d** 92	91
5	**1e** *i*-Bu	**3e** 90	93

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using Chiralpak IA (for **3a**,**e**), AD-H (for **3c**–**d**), IC (for **3b**) columns.

yields (80–95%) and excellent enantioselectivities (up to 99%) were observed for different substitution patterns on the aryl group at C3. Both electron-withdrawing and electron-donating substrates on the C3 aryl group gave excellent results.

Table 3 Variation of 3-Aryl-Substituted Oxindoles



Entry	**1** Ar, R^1	Yield (%)[a]	ee (%)[b]
1	**1f** Ph, H	**3f** 90	95
2	**1g** 3-MeC_6H_4, H	**3g** 95	97
3	**1h** 4-MeC_6H_4, H	**3h** 80	91
4	**1i** 3-$MeOC_6H_4$, H	**3i** 89	99
5	**1j** 4-FC_6H_4, H	**3j** 91	93
6	**1k** Ph, Me	**3k** 90	95
7	**1l** Ph, F	**3l** 92	85

[a] Isolated yield.
[b] Enantiomeric excess of **3f–l** was determined by HPLC analysis using Chiralcel OD-H (for **3f–j**) and Chiralpak IB (for **3k–l**) columns.

In conclusion, we have developed a highly efficient catalytic enantioselective conjugate addition reactions of both 3-alkyl- and 3-aryl-substituted oxindoles **1a–l** to 1,1-bis(benzenesulfonyl)ethylene (**2**) using binaphthyl-modified bifunctional catalysts **V** and **VIII**. The desired Michael products were obtained in good to high yields, and excellent enantioselectivities (up to 99% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the preparation of synthesis of medicinally useful chiral 3,3-disubstituted oxindoles. Further study of these bifunctional organocatalysts in other asymmetric reactions is under investigation.

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(12) **Typical Procedure for the Conjugate Addition Reaction of 3-Phenyl Oxindole 1f with Vinyl Sulfone 2**

To a solution of 3-phenyl oxindole **1f** (0.3 mmol, 92 mg) and catalyst **VIII** (0.03 mmol, 21.4 mg) in CH_2Cl_2 (1.2 mL) was added 1,1-bis(benzenesulfonyl)ethylene (**2**, 0.45 mmol, 138.7 mg). Reaction mixture was stirred for 6 h at r.t., concentrated, and purified by flash column chromatography (EtOAc–hexane = 1:5) to afford the Michael adduct (**3f**, 168 mg, 90%).

(*R*)-*tert*-Butyl 3-[2,2-bis(phenylsulfonyl)ethyl]-2-oxo-3-phenylindoline-1-carboxylate (3f)

$[\alpha]_D^{27}$ 26.0 (*c* 0.4, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.07–7.97 (m, 3 H), 7.77–7.67 (m, 3 H), 7.64–7.46 (m, 6 H), 7.38–7.16 (m, 7 H), 4.45–4.41 (m, 1 H), 3.40–3.29 (m, 2 H), 1.59 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2, 149.2, 141.2, 140.8, 138.0, 134.7, 134.4, 131.0, 129.3, 128.9, 128.8, 128.0, 126.7, 125.7, 124.6, 116.3, 84.3, 80.6, 55.2, 32.1, 28.0. HPLC [*n*-hexane–*i*-PrOH (90:10), 254 nm, 0.5 mL/min] Chiralcel OD-H column, t_R = 18.8 min (major), t_R = 23.9 (minor), 95% ee.