Asymmetric Catalysis

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Stereocontrolled Creation of All-Carbon Quaternary Stereocenters by Organocatalytic Conjugate Addition of Oxindoles to Vinyl Sulfone**

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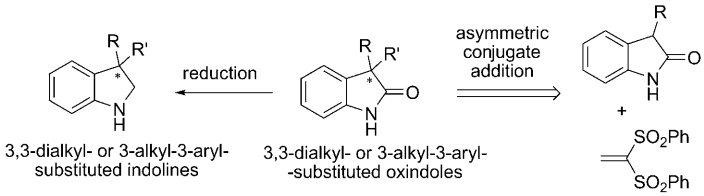
Oxindole motifs are widely present in natural products and bioactive molecules.[1] In particular, oxindole compounds bearing a quaternary stereogenic center[2] at the 3-position are extremely useful. In this context, various synthetic strategies have been devised in recent years for the asymmetric synthesis of 3,3-disubstituted oxindole derivatives. Most approaches, including fluorination,[3] hydroxylation,[4] amination,[5] aldol and Mannich reactions,[6] allylic alkylation,[7] and conjugate addition,[8] employ 3-substituted oxindoles as nucleophiles. The research groups of Vedejs and Fu have achieved the synthesis of 3-acylated oxindoles[9] bearing a quaternary stereocenter through a rearrangement mediated by a chiral nucleophilic catalyst. In spite of the aforementioned synthetic advances, organocatalytic approaches to access chiral 3,3-dialkyl-substituted or 3-alkyl-3-aryl-disubstituted oxindole derivatives are very limited.[10] It is thus highly desirable to develop asymmetric synthetic methods for the preparation of such medicinally useful and synthetically challenging molecules.

Vinyl sulfones are valuable and unique acceptors in conjugate addition.[11] Recently, our research group and others[12] have reported a wide range of asymmetric organocatalytic conjugate additions, which employed vinyl sulfones as acceptors. We envisioned that an organocatalytic conjugate addition of 3-aryl- or 3-alkyl-substituted oxindole to 1,1-bis(benzenesulfonyl)ethylene, and subsequent desulfonation, might provide a viable approach for the construction of optically enriched 3,3-alkyl/aryl-disubstituted oxindoles. Moreover, facile reduction of the carbonyl moiety of oxindoles allows easy access to 3,3-disubstituted indolines, which are known to be extremely important structural elements in many biologically active compounds and natural products (Scheme 1).[13] Herein, we document the first highly stereoselective conjugate addition of 3-aryl- or 3-alkyl-substituted oxindoles to 1,1-bis(benzenesulfonyl)ethylene, thus leading to an enantioselective preparation of 3-alkyl-3-aryl-disubstituted or 3,3-dialkyl-substituted oxindoles and indolines bearing an all-carbon quaternary stereogenic center.



Scheme 1. Construction of 3,3-dialkyl-substituted or 3-alkyl-3-aryl-disubstituted oxindoles and indolines. R = aryl or alkyl, R′ = alkyl.

To effect a stereoselective conjugate addition of oxindoles to vinyl sulfone, a bifunctional tertiary amine catalyst with a properly installed Brønsted acid moiety is an obvious choice. We began our investigation by examining a number of bifunctional tertiary amine catalysts in the conjugate addition of oxindole **1a** to vinyl sulfone **2** (Table 1). Quinidine **4** gave disappointing results (Table 1, entry 1), 6′-demethylated quinidine[14] **5** and quinidine-derived sulfonamide[15] **6** were found to be poor catalysts (Table 1, entries 2 and 3). Quinidine-derived tertiary amine thiourea catalyst **7**[16] turned out to be an excellent catalyst (Table 1, entry 4). Other thioureas, such as tryptophan-derived **8**[16i] and Takemoto's catalyst **9**[16a] were ineffective (Table 1, entries 5 and 6). By lowering the reaction temperature to −78 °C, we were able to obtain the desired adduct in 97 % yield and with 94 % *ee* (Table 1, entry 7). The absolute configurations of the adducts were assigned based on X-ray crystallographic analysis of a single crystal of **3b**.[17] It should be noted that the Boc protecting group on the nitrogen atom is crucial for the observed enantioselectivity, as the same reaction catalyzed by **7** employing oxindole **1b** gave racemic product, thus suggesting the important role of the *N*-Boc group in asymmetric induction.

The generality of the conjugate addition was subsequently investigated. A wide range of 2-aryl-substituted oxindoles were employed as acceptors, and very high yields and excellent enantioselectivities were attainable in all the examples examined (Table 2, entries 1–10). However, when 3-benzyloxindole was used, the corresponding adduct **3m** was obtained in 76 % yield, but only with 28 % *ee* (Table 2, entry 11).[18]

It is not surprising that conjugate addition catalyzed by **7** was not applicable to 3-alkyl-substituted substrates. In fact, all the examples reported in the literature only worked well either for 3-aryl- or 3-alkyl-substituted oxindoles.[3–8] To achieve high enantioselectivity in the projected conjugate addition, it is essential for the catalyst to interact with oxindole and vinyl sulfone simultaneously in a cooperative

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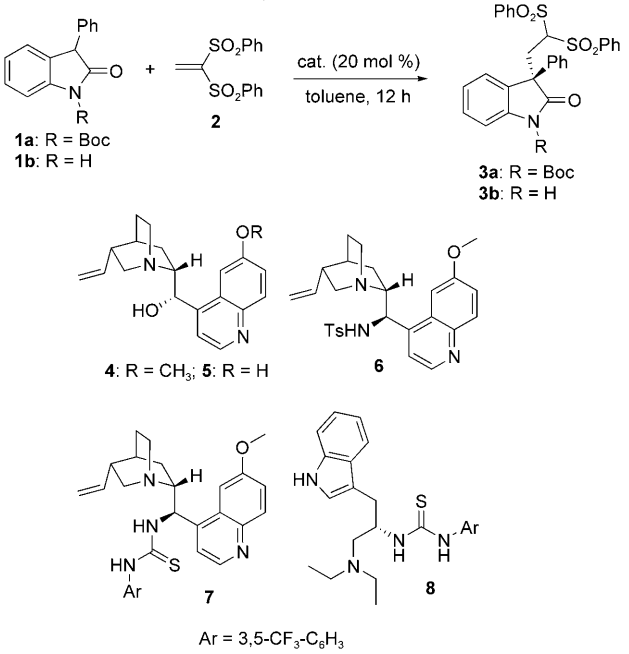
Table 1: Screening of catalysts in the conjugate addition of 3-phenyl-substituted oxindole **1a** to vinyl sulfone **2**.[a]



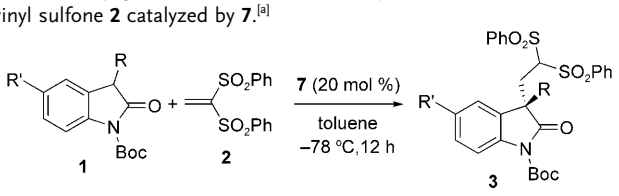
Entry	Catalyst	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**4**	−20	91	20
2	**5**	−20	90	2
3	**6**	−20	88	12
4	**7**	−20	95	81
5	**8**	−20	92	28
6	**9**	−20	88	38
7	**7**	−78	97	94

[a] Reactions were performed with **1a** (0.06 mmol), **2** (0.05 mmol), and the catalyst (0.01 mmol) in toluene (0.4 mL) at the specified temperature. See the Supporting Information for solvent screening. [b] Yield of the isolated product. [c] Determined by HPLC analysis with a chiral stationary phase. Boc = *tert*-butoxycarbonyl.

manner; hence, we reasoned that multifunctional catalysts may be the key. Utilizing the existing bifunctional catalyst scaffolds, simple insertion of a chiral building block can result in novel trifunctional catalysts (Scheme 2). Recently, primary amino acid based synthetic methods have found wide applications in asymmetric synthesis.[19] To further expand the uses of primary amino acids in asymmetric catalysis, we decided to derive novel trifunctional catalysts by incorporating primary amino acid moieties into the bifunctional cinchona alkaloids, and thus a number of cinchonidine-derived trifunctional catalysts **10** were prepared.

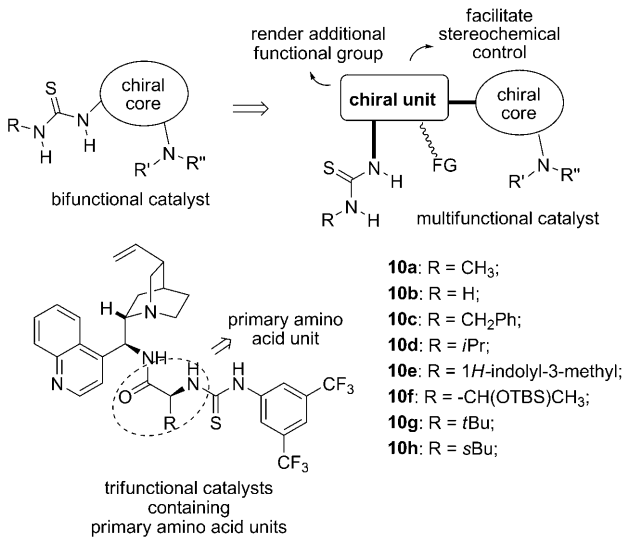
The catalytic effects of the trifunctional catalysts **10** on the conjugate addition of 3-benzyl-substituted oxindole **1n** to vinyl sulfone **2** were examined (Table 3). Catalysts with small substituents were not very effective (Table 3, entries 1 and 2), however, high enantioselectivity was achieved with the phenylalanine-containing catalyst **10c** (Table 3, entry 3). Tryptophan-containing catalyst **10e** was better than the catalyst with a phenylalanine moiety (Table 3, entry 5). We were pleased to find that **10d**, with a valine moiety incorporated, afforded the desired adduct in 81% yield and 90% *ee* (Table 3, entry 4). Further tuning of the steric

Table 2: Conjugate additions of various 3-aryl-substituted oxindoles **1** to vinyl sulfone **2** catalyzed by **7**.[a]



Entry	Product **3**: R/R′	Yield [%][b]	*ee* [%][c]
1	**3c**: *p*-MeC$_6$H$_4$/H	92	90
2	**3d**: *m*-MeC$_6$H$_4$/H	97	90
3	**3e**: *o*-MeC$_6$H$_4$/H	93	91
4	**3f**: *p*-OMeC$_6$H$_4$/H	95	91
5	**3g**: *o*-OMeC$_6$H$_4$/H	94	99
6	**3h**: *p*-FC$_6$H$_4$/H	97	94
7	**3i**: *p*-PhC$_6$H$_4$/H	98	96
8	**3j**: 2-naphthyl/H	95	93
9	**3k**: Ph/CH$_3$	95	90
10	**3l**: Ph/F	94	93
11	**3m**: Bn/H	76	28

[a] Reactions were performed with oxindole (0.5 mmol), **2** (0.05 mmol), and **7** (0.01 mmol) in anhydrous toluene (0.4 mL) at −78 °C for 12 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. Bn = benzyl.

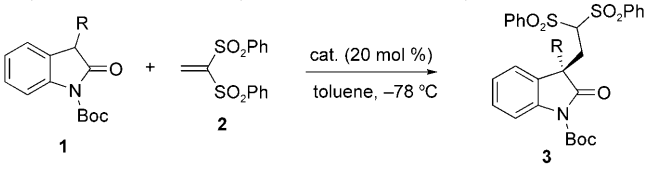


Scheme 2. Novel trifunctional catalysts containing an amino acid unit. FG = functional group, TBS = *tert*-butyldimethylsilyl.

hindrance at the amino acid side chain did not result in better catalysts (Table 3, entries 6–8). These results suggested that the steric hindrance at the R site in **10** may be important to enable the thiourea moiety to adopt a relatively constrained conformation; however, a group that is too sterically hindered could be detrimental as the chiral pocket in **10** is rather crowded. Conjugate addition to vinyl sulfone **2** mediated by the trifunctional catalyst **10d** is applicable to different 3-alkyl-substituted oxindoles, and high yields and good to excellent enantioselectivities were generally attainable (Table 3, entries 9–14).

3-Alkyl-3-aryl-disubstituted oxindoles and indolines are useful synthetic intermediates and they are also important in biological sciences and medicinal chemistry.[13c,20] The method

Table 3: Conjugate addition of various 3-alkyl-substituted oxindoles to vinyl sulfone **2** mediated by novel trifunctional catalysts.[a]



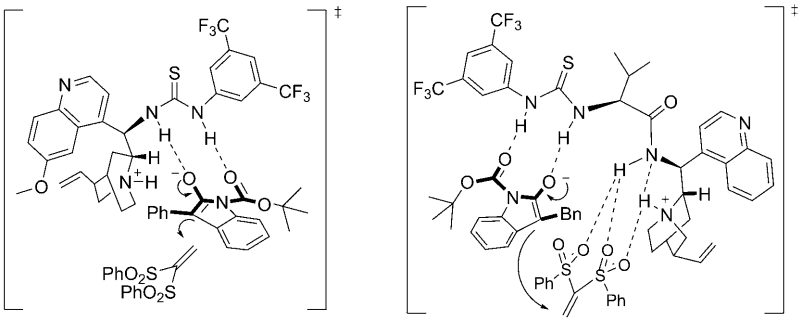
Entry	Cat.	Product **3**: R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**10a**	**3n**: $PhCH_2$	48	76	41
2	**10b**	**3n**: $PhCH_2$	48	72	37
3	**10c**	**3n**: $PhCH_2$	48	77	70
4	**10d**	**3n**: $PhCH_2$	48	81	90
5	**10e**	**3n**: $PhCH_2$	48	67	81
6	**10f**	**3n**: $PhCH_2$	48	54	37
7	**10g**	**3n**: $PhCH_2$	48	67	87
8	**10h**	**3n**: $PhCH_2$	48	64	75
9	**10d**	**3o**: 4-$FC_6H_4CH_2$	60	85	91
10	**10d**	**3p**: 4-$OMeC_6H_4CH_2$	48	88	90
11	**10d**	**3q**: *n*-C_3H_7	60	84	77
12	**10d**	**3r**: *n*-C_4H_9	60	76	80
13	**10d**	**3s**: *n*-C_6H_{13}	72	80	77
14	**10d**	**3t**: *n*-$C_{11}H_{23}$	96	72	80

[a] Reactions were performed with oxindole (0.06 mmol), **2** (0.05 mmol), and the catalyst (0.01 mmol) in toluene (0.4 mL) at −78 °C. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

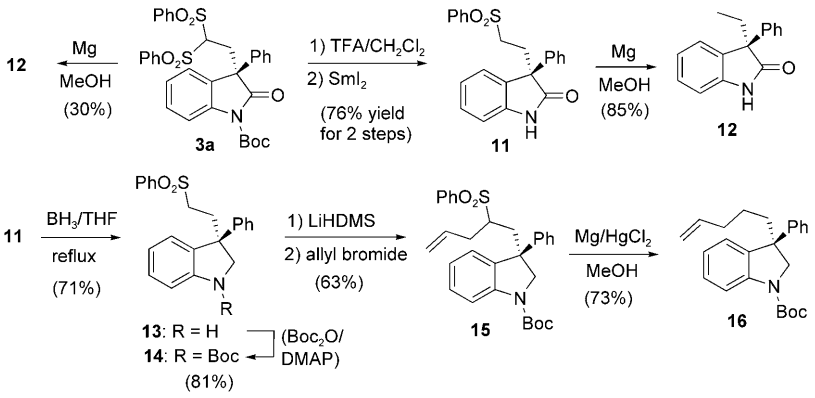
described here represents an efficient approach to synthesize such scaffolds (Scheme 3). Treatment of adduct **3a** with magnesium/methanol gave the desired desulfonated product **12** in low yield, together with retro-Michael side products. To provide a practical solution, a two-step synthetic sequence was then devised. Selective removal of one aryl sulfone group was achieved by treating the reaction mixture with samarium diiodide, and the subsequent desulfonation with magnesium/methanol yielded 3-alkyl-3-aryl-disubstituted oxindole **12**.[10b] Reduction of oxindole **11** afforded the corresponding indoline **13**. Compound **14** is an excellent intermediate for further structural elaboration. For example, allylation of **14,** and subsequent desulfonation led to the formation of indoline **16** with an all-carbon quaternary center at the 3-position, which represents an important class of compounds in the development of therapeutic agents for central nervous system diseases.[21]

Although the mechanisms of reactions reported here remain to be clarified, plausible transition-state models are proposed (Scheme 4). For 3-aryl-substituted oxindoles, tertiary amine thiourea **7** catalyzes the reaction in a bifunctional mode, and it appears that aromatic interactions may be involved when the vinyl sulfone reagent approaches the oxindole substrate. In the conjugate addition of 3-alkyl oxindoles, we hypothesize that the amide group facilitates the orientation of vinyl sulfone **2**, most likely through multiple hydrogen-bonding interactions.[22]

In conclusion, we have disclosed highly enantioselective organocatalytic conjugate additions of both 3-aryl- and 3-alkyl-disubstituted oxindoles to 1,1-bis(benzenesulfonyl)-ethylene. In particular, we introduced for the first time a class of trifunctional thiourea catalysts containing natural amino acid residues, which offered excellent stereocontrol in the reactions of 3-alkyl oxindole substrates. Thus, by using the synthetic method developed as a key step, enantioselective synthesis of medicinally important 3-alkyl-3-aryl-disubstituted oxindoles and indolines with an all-carbon quaternary stereogenic center were realized. Investigations aimed at fully understanding the reaction mechanisms and applications of novel trifunctional catalysts of type **10** in other asymmetric organic reactions are currently ongoing.



Scheme 4. Plausible reaction mechanisms.



Scheme 3. Synthesis of 3-alkyl-3-aryl-disubstituted oxindole and indoline. DMAP = 4-dimethylaminopyridine, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

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[17] CCDC 789891 (**3b**) 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.
[18] Other catalysts were also examined for the same reaction, and the results are: catalyst **5**, 67% yield, 10% ee; catalyst **6**, 72% yield, 30% ee; catalyst **8**, 74% yield, 37% ee; catalyst **9**, 76% yield, 41% *ee*.
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