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Enantioselective Organocatalyzed Sulfenylation of 3-Substituted Oxindoles

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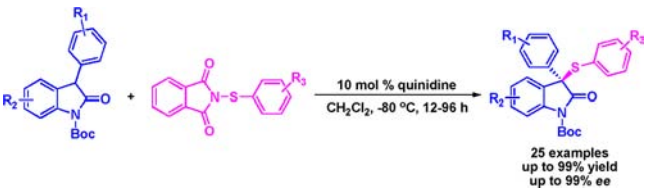
ABSTRACT



A highly enantioselective sulfenylation reaction with respect to 3-substituted oxindoles and electrophilic sulfur reagents by a quinidine catalyst was investigated.

Organocatalysis is described as a powerful, environmentally friendly methodology for the enantioselective construction of valuable synthetic building blocks and have gained a prominent position in organic chemistry.[1] Although rapid progress in the development of small molecular catalysis has been realized, practical and efficient asymmetric approaches remain in high demand. An aspect of an ideal asymmetric reaction is performing with an adequately facile catalyst to yield quantitative, enantiomerically pure products. Thus, some commercially available and inexpensive natural products, such as Cinchona alkaloids and their derivatives, have emerged as privileged catalysts in asymmetric synthesis.[2]

Oxindoles and their derivatives have received extensive attention, since the structural motif of this type of compound, which has the construction of a quaternary chiral center, is a prominent feature in many biologically and pharmaceutically active natural products.[3] Thus, various synthetic approaches, including the aldol reaction,[4] Mannich reaction,[5] Henry reaction,[6] allylic alkylation,[7] and Michael addition[8] with 3-substituted oxindoles as nucleophiles, have been developed in recent years for the asymmetric synthesis of this challenging structural core.[9] Moreover, the presence of enolizable C−H bonds in 3-substituted oxindoles also allows the possibility of reactions with different classes of heteroatom type electrophiles leading

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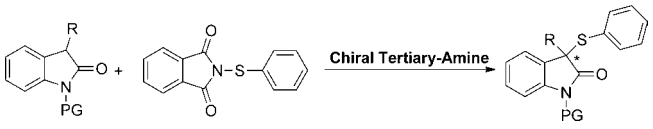
Scheme 1. Strategy of Chiral Tertiary-Amine Catalyzed Asymmetric Sulfenylations of 3-Substituted Oxindoles



to the formation of carbon−heteroatom bonds of oxindoles. A number of asymmetric strategies for the constructed heteroquaternary stereocenter of oxindole type compounds, including fluorination,[10] chlorination,[11] hydroxylation,[12] and amination,[13] have been successfully established. To sum up, enantioselective formation of a variety of chemical bonds (i.e., C−C, C−O, C−N, C−Cl, C−F) with a chiral tetrasubstituted stereocenter at the C3-position of oxindole have been accomplished.

It is well-known that enantiomerically pure sulfur-containing compounds constitute an important class of chiral ligands, auxiliaries, and synthetic intermediates in organic chemistry.[14] Moreover, many chiral S-containing molecules also exhibit pharmaceutical activities. As a result, several groups have successfully accomplished the asymmetric sulfenylation of aldehydes[15] and ketones[16] with different

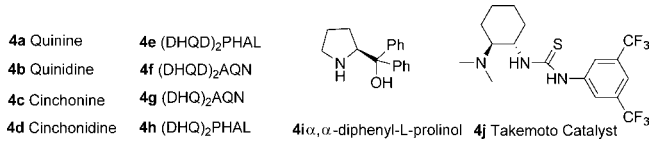


Figure 1. Examined catalysts.

electrophilic sulfur reagents in recent years. On the other hand, asymmetric conjugated addition reactions, in which thiols or thioacetic acids were used as donors, were also studied as a valuable method for the preparation of chiral S-containing compounds.[17] Although impressive advances have been made in this area, searching for efficient, especially simple catalysts that could achieve high enantioselectivity and extending the substrate scope are still desirable and challenging. Very recently, Feng et al. reported a chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ complex and a Brønsted base catalyzed asymmetric sulfenylation of unprotected 3-substituted oxindoles.[18] To our knowledge to date, no organocatalytic processes are available for the preparation of chiral 3-substituted 3-sulfenylindol-2-ones, in which the motif is the key structure of bioactive oxindole type products.[19−21] As part of our ongoing program on asymmetric organocatalysis,[22] we have recently found that various 3-substituted 3-sulfenylindol-2-ones can be obtained in high yield and good to excellent enantioselectivity with a very simple Cinchona alkaloids catalyst (Scheme 1). Herein we wish to report our preliminary results on this subject.

We envision that the application of enolizable 3-substituted oxindoles and electrophilic sulfur reagents in the presence of a chiral tertiary-amine organic catalyst will generate 3-substituted 3-sulfenylindol-2-ones (Scheme 1).

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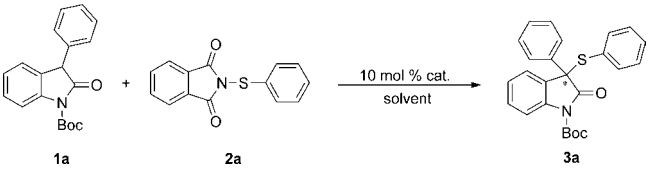
To demonstrate the working hypothesis, we carried out a model reaction of 3-phenyl-N-Boc oxindole (**1a**) with *N*-(phenylthio)phthalimide (**2a**) in dichloromethane at 20 °C with a 10 mol % loading of quinine (**4a**, Figure 1). A high yield and good enantioselectivity for sulfenylation product **3a** was obtained (Table 1, entry 1). Other Cinchona alkaloids and their derivatives (**4b**−**4h**, Figure 1) were then evaluated (Table 1, entries 2−8). To our delight, the examined catalysts exhibited high catalytic activities, and the sulfenylation products were isolated with very good yields (97−99%). However, the enantioselectivities varied significantly. Among the catalysts tested, quinidine (**4b**) was found to give the optimal enantioselectivity (99% yield and 82% *ee*, entry 2 in Table 1). Two other types of amine catalysts, including α,α-diphenyl-L-prolinol **4i** and bifuctional tertiary-amine thiourea **4j**, were inferior to **4b** in terms of enantioselectivity (Table 1, entries 9 and 10).

We then focused on the optimization of a **4b** catalyzed sulfenylation of 3-phenyl-N-Boc oxindole to improve the reaction efficiency. All of the solvents afforded the desired products in quantitative yield. Moderate stereoselectivities were obtained for toluene, benzene, ether, and THF (Table 1, entries 13−16, 54−68% *ee*). It was observed that chloric solvents were favored for this reaction (Table 1, entries 2, 11−12, 74−82% *ee*). Further studies indicated that lowering the reaction temperature can promote the enantioselectivity (Table 1, entry 17). Gratifyingly, diluting the reaction system also displays an increase in the *ee* value of sulfenylation product **3a** to 97% *ee* (Table 1, entry 18). Collectively, the best result with respect to yield and stereoselectivity was obtained by performing the reaction with 10 mol % quinidine at −80 °C under a 0.05 M concentration in CH_2Cl_2.

With the optimal protocol in hand, we then turned our attention toward the scope of the reaction. We first examined the reactions of a range of 3-aryl oxindoles **1a**−**1k** with **2a** under the optimized conditions. As shown in Table 2, oxindoles with 3-aryl groups bearing either an electron-withdrawing or -donating moiety could be converted into the desired products with excellent yields (83−99%) and enantioselectivities (90−99% *ee*) (Table 2, entries 1−11). A slightly lower stereoselectivity was obtained with *meta*-methoxy-substituted 3-aryl-N-Boc oxindole **1g** (Table 2, entries 7). The reaction of 5-position substituted oxindole **1i**−**1k** also worked very well to give the desired sulfenylation products **3i**−**3k** with 91−99% yield and 94−97% *ee* (Table 2, entries 9−11).

We also investigated the effect of differently substituted sulfenylation reagents on the currently studied sulfenylation reaction. When 3-substituted-N-Boc oxindoles **1a** and **1d** were chosen as the substrates, sulfur reagents (**2a**−**2e**) with

Table 1. Screening of the Reaction Conditions for the Sulfenylation of 3-Phenyl-*N*-Boc Oxindole (**1a**)[a]

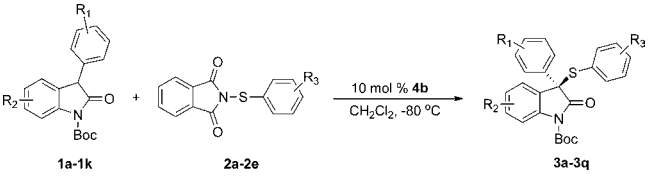


1a **2a** **3a**

entry	cat.	solvent	yield[b] (%)	*ee*[c] (%)
1	**4a**	CH_2Cl_2	99	−77[f]
2	**4b**	CH_2Cl_2	99	82
3	**4c**	CH_2Cl_2	99	53
4	**4d**	CH_2Cl_2	99	−46[f]
5	**4e**	CH_2Cl_2	98	−31[f]
6	**4f**	CH_2Cl_2	99	−60[f]
7	**4g**	CH_2Cl_2	98	8
8	**4h**	CH_2Cl_2	97	48
9	**4i**	CH_2Cl_2	99	−44[f]
10	**4j**	CH_2Cl_2	99	43
11	**4b**	$CHCl_3$	99	81
12	**4b**	CH_2ClCH_2Cl	99	74
13	**4b**	toluene	99	68
14	**4b**	benzene	99	54
15	**4b**	ether	99	56
16	**4b**	THF	99	60
17[d]	**4b**	CH_2Cl_2	99	94
18[e]	**4b**	CH_2Cl_2	99	97

[a] The general reaction was carried out on a 0.1 mmol scale in 1 mL of solvent with 20 min, and the molar ratio of **1a**/**2a** is 1/1.2. [b] Isolated yield after chromatography. [c] Determined by chiral HPLC. [d] The reaction was carried out under general conditions at −80 °C in 12 h. [e] The reaction was carried out under general conditions in 2 mL of CH_2Cl_2 at −80 °C in 12 h. [f] The major product is the enantiomer of the one obtained in the rest of the entries.

Table 2. Substrate Scope of 3-Aryl Oxindoles[a]



1a-1k **2a-2e** **3a-3q**

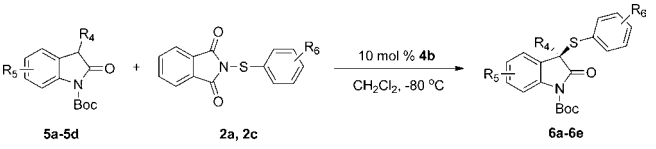
entry	R_1	R_2	R_3	time (h)	yield[b] (%)	*ee*[c] (%)
1	**1a**: H	H	**2a**: H	12	**3a**: 99	97
2	**1b**: 4-CH_3	H	**2a**: H	18	**3b**: 99	97
3	**1c**: 4-*n*Bu	H	**2a**: H	12	**3c**: 99	95
4	**1d**: 3,5-2CH_3	H	**2a**: H	12	**3d**: 99	98
5	**1e**: 4-F	H	**2a**: H	18	**3e**: 85	97
6	**1f**: 4-CH_3O	H	**2a**: H	24	**3f**: 99	99
7	**1g**: 3-CH_3O	H	**2a**: H	48	**3g**: 99	90
8	**1h**: 4-C_2H_5O	H	**2a**: H	24	**3h**: 83	98
9	**1i**: H	5-CH_3O	**2a**: H	36	**3i**: 99	97
10	**1j**: H	5-F	**2a**: H	24	**3j**: 91	94
11	**1k**: H	5-Br	**2a**: H	24	**3k**: 93	94
12	**1d**: 3,5-2CH_3	H	**2b**: 4-F	24	**3l**: 99	97
13	**1a**: H	H	**2c**: 4-Cl	12	**3m**: 98	95
14	**1d**: 3,5-2CH_3	H	**2c**: 4-Cl	12	**3n**: 98	99
15	**1d**: 3,5-2CH_3	H	**2d**: 4-CH_3	24	**3o**: 99	97
16	**1a**: H	H	**2e**: 4-CH_3O	24	**3p**: 99	95
17	**1d**: 3,5-2CH_3	H	**2e**: 4-CH_3O	24	**3q**: 95	97

[a] The reaction was carried out on a 0.1 mmol scale in 2 mL of CH_2Cl_2 at −80 °C, and the molar ratio of **1**/**2** is 1/1.2. [b] Isolated yield after chromatography. [c] Determined by chiral HPLC.

an electron-rich or -deficient group on the aromatic ring can afford the optically active 3,3′-disubstituted sulfenylated oxindoles (**3l**−**3q**) with excellent yields (95−99%) and enantioselectivities (95−99% *ee*) (Table 2, entries 12−17).

3-Alkyl-N-Boc oxindoles were also applied as nucleophiles (Table 3). Compared with 3-aryl-N-Boc oxindoles, a longer reaction time and higher concentration of the system were indispensable to accelerate the asymmetric sulfenylation. As a result, the examined 3-alkyl oxindoles **5a**−**5d** can smoothly react with **2a** (or **2c**) to afford the corresponding sulfenylated products **6a**−**6e** with very good yields (93−99%) and variable enantioselectivities (72−94% *ee*).

Table 3. Substrate Scope of 3-Alkyl Oxindoles[a]



entry	R_4	R_5	$macR_6$	time (h)	yield[b] (%)	*ee*[c] (%)
1	**5a**: CH_3	H	**2a**: H	60	**6a**: 91	94
2	**5b**: C_2H_5	H	**2a**: H	48	**6b**: 99	91
3	**5c**: Bn	H	**2a**: H	48	**6d**: 93	72
4	**5d**: CH_3	4-CH_3O	**2a**: H	60	**6e**: 99	91
5	**5b**: C_2H_5	H	**2c**: 4-CH_3	96	**6f**: 96	79

[a] The reaction was carried out on a 0.1 mmol scale in 1 mL of CH_2Cl_2 at −80 °C, and the molar ratio of **1**/**2** is 1/1.2. [b] Isolated yield after chromatography. [c] Determined by chiral HPLC.

The absolute configuration of adducts **3** was determined by X-ray crystallographic analysis of **3k** (Figure 2; for details see Supporting Information).[23] Absolute configurations of other products can therefore be determined by analogy.

Furthermore, three different 3-methyl *N*-substituted oxindoles (**7a**−**7c**) were also included in the examination. As expected, the result was not positive, affording the corresponding adducts **8a**−**8c** in very low enantioselectivities (Figure 3). When unprotected 3-phenyl oxindole was used as a nucleophile, the sulfenylation product **8d** was obtained in 57% yield and with only a 6% ee (Figure 3).

A plausible transition state model was proposed to account for the observed stereoselectivity (Scheme S1). In the favored TS model, the sulfenylation reagent attacks on the *Re* face of oxindole, giving the observed major

(23) CCDC 838460 contains the supplementary crystallographic data for **3k**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

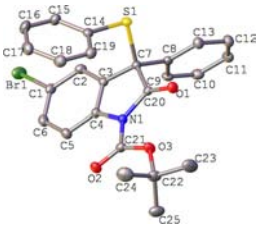


Figure 2. X-ray crystal structure of **3k**.

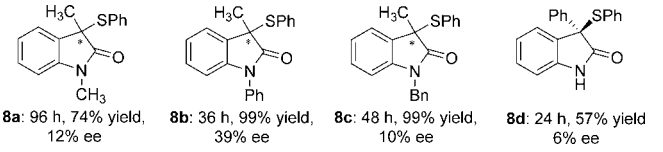


Figure 3. Effects of different *N*-substituted oxindoles.

R-product. The multi-H-bonding interaction between the catalyst and substrates, described in Scheme S1, would contribute to the stability of the proposed transition state.

To investigate the synthetic potential of the current sulfenylation strategy, the preparation of **3m**, **3o**, and **6b** at a 1 mmol scale were attempted under the optimal conditions. To our delight, corresponding products were obtained without any loss in yields and enantioselectivities (Scheme S2).

In summary, we have described the sulfenylation reaction of 3-substituted oxindoles with electrophilic sulfur reagents by Cinchona alkaloid type catalysts. Remarkably, in the presence of a very facile simple natural product, quinidine, a wide range of 3-aryl or 3-alkyl substituted oxindoles and substituted *N*-(arylthio)phthalimides underwent the reaction smoothly, providing chiral sulfur containing oxindole compounds with a quaternary stereocenter in excellent yields (up to 99%) and enantioselectivities (up to 99% *ee*).

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.