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A Facile Approach for the Asymmetric Synthesis of Oxindoles with a 3-Sulfenyl-Substituted Quaternary Stereocenter

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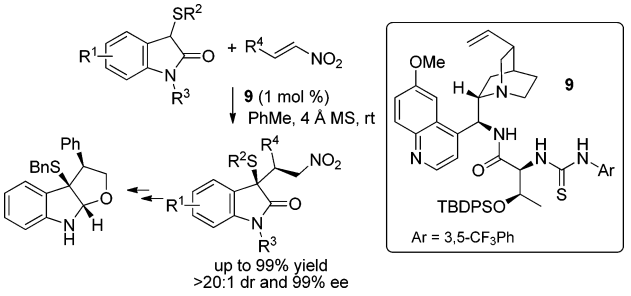
ABSTRACT



With the employment of a threonine-incorporating multifunctional catalyst 9, Michael addition of 3-sulfenyloxindoles to nitroolefins proceeded stereoselectively, leading to the formation of oxindoles with a 3-sulfenyl-substituted quaternary center in excellent yields, and with high diastereoselectivities and excellent enantioselectivities.

3,3-Disubstituted oxindoles are widely present in natural products and bioactive molecules.[1] In particular, oxindoles bearing a 3-heteroatom-substituted quaternary stereogenic center are extremely important in medicinal chemistry, and thus their asymmetric synthesis has been intensively investigated in recent years.[2] A wide range of synthetic methods have been developed for catalytic asymmetric synthesis of 3-substituted-3-heteroatom oxindoles, such as 3-aminooxindoles,[3] 3-hydroxyoxindoles,[4] 3-fluorooxindoles,[5] among others.[6] For sulfur-containing molecular frameworks, direct asymmetric sulfenylation[7] and C-alkylation of sulfenyl derivatives are commonly used. Surprisingly, 3-sulfenyloxindoles, an important class of biologically important molecules, were less explored.[8] Only a handful of examples appeared in the literature

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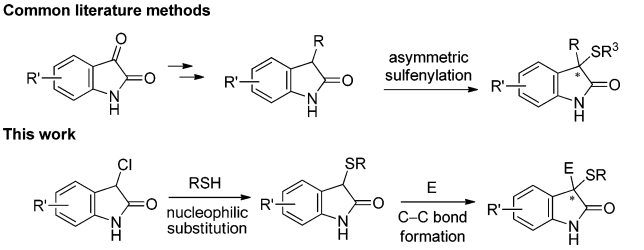
recently. Feng et al. employed the *N,N′*-dioxide-Sc(OTf)$_3$ complex to catalyze an enantioselective sulfenylation of 3-substituted oxindoles.[9] Asymmetric sulfenylations catalyzed by organic catalysts were independently reported by the groups of Enders,[10a] Cheng,[10b] and Jiang.[10c] Very recently, Zhou et al. disclosed an efficient synthesis of 3-sulfenyl-3-amino-oxindoles via asymmetric aminations of 3-thio/alkoxyoxindoles.[11] Our group has been actively investigating the synthesis of chiral oxindole derivatives bearing a quaternary stereogenic center.[12] Given the biological significance of oxindoles containing a 3-sulfenyl-substituted quaternary carbon, we intended to develop an efficient asymmetric synthetic method to access these molecules.

In the reported direct asymmetric sulfenylation methods, expensive isatins were commonly used as starting materials to prepare 3-substituted oxindoles. Moreover, the chiral 3-sulfenyloxindole products prepared contained only aryl or alkyl groups at the 3-position, which certainly posed restrictions to their synthetic manipulations. In our proposal, 3-chlorooxindoles are employed as starting materials, which can be readily prepared from inexpensive nitroolefins.[13] Subsequent reactions with thio nucleophiles are expected to install sulfenyl groups at the 3-position of oxindoles. In the presence of suitable catalysts, reactions between 3-sulfenyloxindoles[14] and electrophiles can yield the desired chiral 3-sulfenyl-3-substituted oxindole products (Scheme 1).

Scheme 1. Preparation of 3-Sulfenyl-3-substituted Oxindoles



We started our investigations by examining the catalytic effects of various organic catalysts on the asymmetric Michael addition of 3-sulfenyloxindole **1a** to nitroolefin **2a** (Table 1). Bifunctional tertiary amine catalysts[15] containing a Brønsted acid moiety are expected to effectively promote the projected reaction through cooperative interactions with both substrates. Cinchonidine-derived **4** showed high catalytic activity; however, the stereoselectivity of the reaction was poor (entry 1). L-Threonine-derived **5**[16] led to the formation of the desired product in relatively low yield, and with moderate diastereo- and enantioselectivity (entry 2). To further improve the results, we chose to employ our recently developed amino acid incorporating multifunctional catalysts.[17] To our delight, all the multifunctional catalysts were much more effective, affording the desired products in high yields and with high enantio- and diastereoselectivities. All the catalysts containing silylated L-threonine worked very well (entries 3−6), and quinine-derived **9** with a TBDPS-L-threonine moiety proved to be the best catalyst (entry 6). The silyl protection

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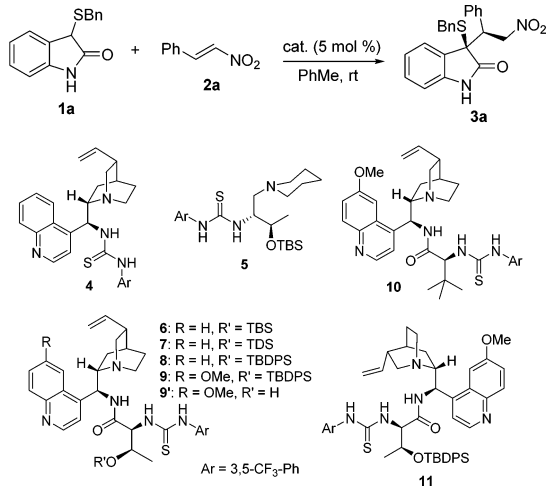
Table 1. Evaluation of Different Catalysts for the Michael Addition of 3-Sulfenyloxindole **1a** to Nitroolefin **2a**[a]



entry	catalyst	t (h)	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**4**	2	96	1.6:1	51, 53
2	**5**	24	83	4:1	78
3	**6**	3	95	16:1	96
4	**7**	6	98	12:1	92
5	**8**	2	96	16:1	97
6	**9**	1.5	98	19:1	97
7	**9′**	2	97	13:1	86
8	**10**	2	95	10:1	83
9	**11**	2	97	19:1	−86[e]

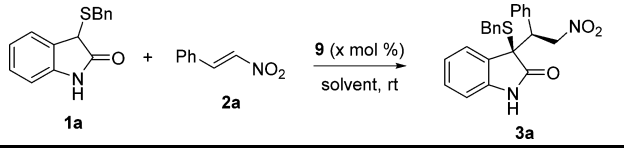
[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), and the catalyst (0.05 mmol) in toluene (1.0 mL) at rt. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase; *ee* value of the major isomer. [e] The opposite enantiomer was obtained.

was essential for the observed stereoselectivities; both diastereo- and enantioselectivities decreased when the non-silylated catalyst **9′** was used (entry 7). Moreover, *tert*-leucine-derived **10** was also shown to be less effective (entry 8). Interestingly, the opposite enantiomer could be obtained with the employment of a quinidine-derived **11** containing a TBDPS-D-threonine (entry 9).

Having identified **9** as the best catalyst, we then carried out further studies to optimize the reaction conditions (Table 2). Solvent screening confirmed that toluene is a solvent of choice for our reaction (entries 1−3). Additive studies proved that addition of 4 Å molecular sieves was beneficial (entries 4−6). The catalyst loading could be reduced to as low as 1 mol % without sacrificing the diastereo- and enantioselectivity of the reaction (entries 7−8). A further decrease of the catalyst loading to 0.5 mol % was feasible; both dr and ee values were practically maintained (entry 9).

With the optimal reaction conditions in hand, we continued to examine the substrate scope of the reaction (Table 3). Different aryl nitroolefins could be employed, including aromatic rings with different halogen substitutions, substituents of different electronic natures, and different

Table 2. Optimizing Reaction Conditions[a]



entry	cat. loading (x mol %)	solvent	additive	t (h)	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	5	CH_2Cl_2	none	4	93	>20:1	97
2	5	THF	none	12	<10	–	–
3	5	xylene	none	1.5	96	>20:1	96
4	5	PhMe	3 Å MS	1.5	98	19:1	97
5	5	PhMe	4 Å MS	1.5	98	>20:1	97
6	5	PhMe	5 Å MS	1.5	98	>20:1	96
7	2.5	PhMe	4 Å MS	3	98	>20:1	97
8	1.0	PhMe	4 Å MS	8	98	>20:1	97
9	0.5	PhMe	4 Å MS	15	96	19:1	95

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), and the **9** (x mol %) in the solvent (1.0 mL) specified at rt. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase; *ee* value of the major isomer.

substitution patterns (entries 1−6). Aryls other than phenyls could also be employed in the nitroolefin structures (entries 7 and 8). The reaction was also applicable to 3-sulfenyloxindoles containing different aromatic moieties (entries 9 and 10). Moreover, alkyl nitroolefins could also be employed, and the desired products were obtained with excellent diastereo- and enantioselectivities, although the yields were slightly lower (entries 11 and 12). In all the examples examined, very high diastereoselectivities (14:1 to >20:1 dr) and enantioselectivities (up to 99% *ee*) were attainable. Oxindoles containing different 3-thioether moieties were also examined. Various alkyl thioether substrates all worked well (entries 13−15). However, a phenyl thioether substrate displayed lower reactivity, and the stereoselectivities of the reaction also dropped (entry 16). If the oxindole NH was protected as a carbamate, the reaction became faster but less stereoselective (entry 17). To demonstrate the practicality of our method, a gram scale synthesis of **3a** was performed (entry 2).

3-Substituted-3-sulfenyloxindoles with a neighboring nitro group are highly versatile synthetic intermediates. The reduction of the nitro group in oxindole adducts and subsequent manipulations of the resulting amino group were well documented in the literature.[18] We opted to illustrate the synthetic value of our products via oxidation of the nitro group (Scheme 2). Adduct **3a** was smoothly oxidized to the corresponding acid **12a**.[19] Subsequent esterification, followed by reduction, then afforded hydroxy group containing oxindole **14**. To realize an intramolecular cyclization, a Boc group was first installed to **13**,

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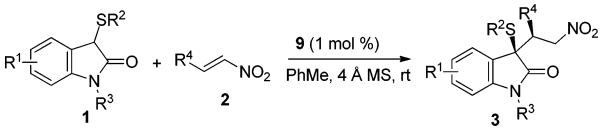
Table 3. Reaction Scope of Asymmetric Conjugate Addition of 3-Sulfenyloxindoles **1** to Nitroolefins **2**[a]



entry	**3**, $R^1/R^2/R^3/R^4$	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**, H/Bn/H/C_6H_5	8	98	>20:1	97
2[e]	**3a**, H/Bn/H/C_6H_5	12	97	>20:1	97
3	**3b**, H/Bn/H/2-Br-C_6H_4	10	95	14:1	99
4	**3c**, H/Bn/H/3-Br-C_6H_4	12	98	>20:1	97
5	**3d**, H/Bn/H/4-Cl-C_6H_4	12	98	>20:1	97
6	**3e**, H/Bn/H/4-Me-C_6H_4	16	97	>20:1	97
7	**3f**, H/Bn/H/2-naphthyl	10	99	>20:1	98
8	**3g**, H/Bn/H/2-furyl	12	96	19:1	96
9	**3h**, 5-Me/Bn/H/C_6H_5	12	97	>20:1	98
10	**3i**, 6-Cl/Bn/H/C_6H_5	10	95	19:1	96
11[f]	**3j**, H/Bn/H/*n*-butyl	12	81	19:1	98
12[f]	**3k**, H/Bn/H/phenethyl	12	84	16:1	98
13	**3l**, H/4-OMe-Bn/H/C_6H_5	6	99	19:1	95
14	**3m**, H/*n*-Bu/H/C_6H_5	12	95	>20:1	91
15	**3n**, H/Me/H/C_6H_5	20	97	>20:1	87
16	**3o**, H/Ph/H/C_6H_5	40	95	5:1	79
17	**3p**, H/Bn/CO_2Et/C_6H_5	0.5	99	13:1	83

[a] Reactions were performed with **1** (0.1 mmol), **2** (0.12 mmol), **9** (0.001 mmol), and 4 Å MS (10 mg) in toluene (1 mL) at rt. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase; *ee* value of the major isomer. [e] Reaction was performed on 2.5 mmol scale; 0.98 g of **3a** was obtained. [f] The catalyst loading was 5 mol %.

and reduction of the ester group in **15** then resulted in a smooth cyclization[20] to yield furoindoline **16**, which represents a core structure of antitumor agents.[7c] The absolute configurations of products were determined on the basis of the X-ray crystal structure of a **12b**−THF complex (see the Supporting Information). Furthermore, treatment of adduct **3l** with a catalytic amount of $Hg(OAc)_2$ in TFA[21]

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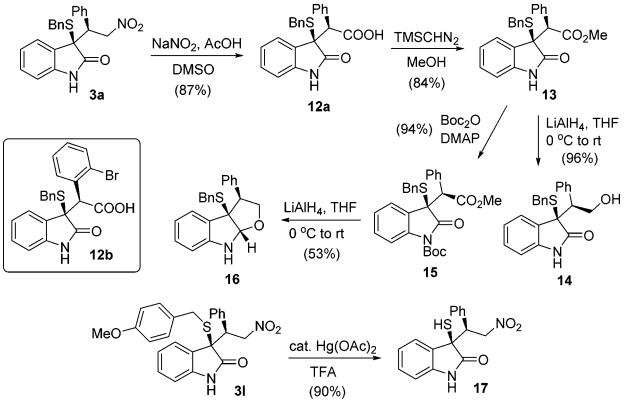
Scheme 2. Synthetic Manipulations of the 3-Sulfenyloxindole **3**



resulted in the formation of oxindole **17** containing a free thiol group at the 3-position in high yield.

In conclusion, we have prepared various 3-sulfenyloxindoles from 3-chlorooxindoles, which were readily derived from inexpensive nitroolefins. By utilizing our amino acid incorporating organic catalysts, we showed that Michael addition of 3-sulfenyloxindoles to nitroolefins proceeded in a highly stereoselective manner, affording oxindoles containing a 3-sulfenyl-substituted quaternary stereogenic center in excellent yields, high diastereoselectivities, and excellent enantioselectivities. The oxindole adducts are versatile synthetic intermediates and could be readily transformed into molecular structures of biological significance.

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Supporting Information Available. Representative experimental procedures, HPLC chromatogram, and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.