ORGANIC LETTERS

2012
Vol. 14, No. 17
4670–4673

Highly Enantioselective Organocatalytic Sulfenylation of 3-Aryloxindoles

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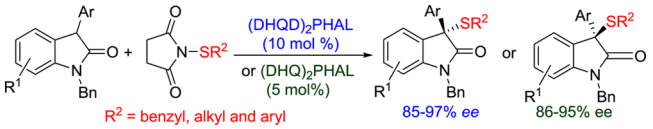
Received July 31, 2012

ABSTRACT



An organocatalytic asymmetric sulfenylation of 3-aryloxindoles with *N*-(sulfanyl)succinimides has been developed by using commercially available $(DHQD)_2PHAL$ as catalyst. Various chiral 3-benzylthio-, alkylthio-, and arylthio-substituted oxindoles, containing 3,3-disubstituted quarternary carbon stereocenters, could be obtained in high enantioselectivities (85−97% ee). Furthermore, the opposite enantiomers of the sulfenylated products were readily accessible with equal excellent enantioselectivities (86−95% ee) by replacing the catalyst with $(DHQ)_2PHAL$.

Enantioselective construction of quaternary stereogenic centers is of fundamental and practical significance but is often challenging.[1] In particular, the enantioselective construction of 3,3-disubstituted oxindoles has attracted special attention of organic chemists since the oxindole framework bearing a quaternary carbon stereocenter at the 3-position is a privileged heterocyclic motif, which is a core backbone of many natural products and pharmaceutical molecules.[2] The established methods include nucleophilic additions to isatins and miscellaneous reactions of 3-substituted oxindoles,[3] affording various 3,3-full carbons[4] and 3-heteroatoms, including 3-fluoro-,[5] 3-chloro-,[6] 3-amino-[7] and 3-hydroxy[8]-substituted oxindoles. Due to the important role of

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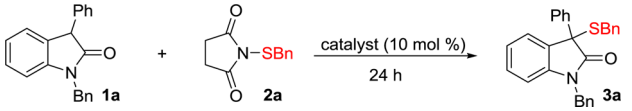
10.1021/ol3021176
Published on Web 08/24/2012

3-thio-substituted oxindoles in medicinal chemistry,[9] the specific incorporation of sulfur into the 3-position of oxindoles in a stereoselective manner has become a highly pivotal consideration. In 2012, Feng and co-workers presented the first asymmetric synthesis of 3-phenylthio-substituted oxindoles from an enantioselective sulfenylation of 3-substituted oxindoles with *N*-(phenylthio)phthalimide via cooperative catalysis of a chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ complex and an achiral Brønsted base.[10] Very recently, Enders and co-workers described the first organocatalytic enantioselective sulfenylation of *N*-Boc-protected oxindoles by using *N*-(sulfanyl)phthalimides as the sulfenylating agents catalyzed by *Cinchona* alkaloid-derived squaramide, affording a variety of 3-arylthio-substituted oxindoles with excellent enantioselectivities.[11] Notably, the highly stereoselective construction of 3-benzylthio- and alkylthio-substituted oxindoles has never been reported and remains highly in demand for their facile modification. As part of our ongoing investigation on the organocatalytic syntheses of chiral sulfur-substituted α-stereogenic amides[12] and 3,3-disubstituted oxindoles,[4g] we thus became interested in developing an efficient organocatalytic sulfenylation of 3-substituted oxindoles to allow easy access to alkylthio-, benzylthio-, and arylthio-substituted oxindoles.

In the past few decades, sulfenylations have been investigated intensively to construct valuable optically active sulfur-substituted α-stereogenic compounds, which are common key building blocks in many bioactive compounds,[13] and it is commonplace to employ chiral auxiliaries.[14] In 2005, Jørgensen and co-workers disclosed the first highly enantioselective organocatalytic sulfenlyation of aldehydes catalyzed by chiral pyrrolidine derivatives.[15] Meanwhile, they reported asymmetric sulfenylation of lactones, lactams, and *β*-dicarbonyl compounds with moderate to good enantioselectivities in the presence of *Cinchona* alkaloid derivatives as Brønsted base catalysts.[16] Afterward, Zhu and Cheng and co-workers successively demonstrated the highly enantioselective sulfenylation of *β*-ketoesters[17a] and *β*-keto phosphonates[17b] catalyzed by α,α-diaryl-L-prolinols. It is worth noting that the successful example on Brønsted-base-catalyzed sulfenylation is still rare.[11] Herein, we would like to report a highly enantioselective sulfenylation of 3-aryloxindoles with a variety of *N*-(sulfanyl)succinimides catalyzed by commercially avaliable (DHQD)$_2$PHAL, which leads to the efficient syntheses of various chiral 3-benzylthio-, alkylthio-, and arylthio-substituted oxindoles. Furthermore, this methodology is applicable to prepare the opposite enantiomers of the sulfenylated products with equal excellent enantioselectivities (86−95% ee) by replacing the catalyst with (DHQ)$_2$PHAL.

In organocatalytic asymmetric transformations, *Cinchona* alkaloid derivatives have been proven as a kind of highly effective catalyst and thus have attracted considerable interest.[18] Especially, the commercially available *Cinchona* alkaloids are the most favorable for the economical and practical standpoints. Therefore, we investigated several commercially available *Cinchona* alkaloids catalysts in the model sulfenylation of 3-phenyloxindole **1a** and *N*-(benzylthio)succinimide **2a** in methylene chloride at 25 °C in our initial studies. The results are summarized in

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	*t* (°C)	yield (%)[b]	ee (%)[c]
1	cinchonine	CH_2Cl_2	25	56	65
2	cinchonidine	CH_2Cl_2	25	53	−26
3	quinine	CH_2Cl_2	25	67	−14
4	quinidine	CH_2Cl_2	25	63	−10
5	$(DHQ)_2PYR$	CH_2Cl_2	25	60	−12
6	$(DHQD)_2AQN$	CH_2Cl_2	25	65	5
7	$(DHQD)_2PHAL$	CH_2Cl_2	25	77	70
8	$(DHQ)_2PHAL$	CH_2Cl_2	25	59	−50
9	$(DHQD)_2PHAL$	THF	25	63	20
10	$(DHQD)_2PHAL$	toluene	25	95	92
11	$(DHQD)_2PHAL$	Et_2O	25	72	91
12	$(DHQD)_2PHAL$	*p*-xylene	25	79	93
13	$(DHQD)_2PHAL$	*m*-xylene	25	87	93
14	$(DHQD)_2PHAL$	mesitylene	25	70	93
15	$(DHQD)_2PHAL$	*m*-xylene	10	65	82
16	$(DHQD)_2PHAL$	*m*-xylene	0	30	65
17	$(DHQD)_2PHAL$	*m*-xylene	30	97	93
18[d]	$(DHQD)_2PHAL$	*m*-xylene	30	63	93

[a] Unless otherwise noted, reactions were performed with 0.02 mmol of **1a**, 0.03 mmol of **2a**, and 0.002 mmol of catalyst in 0.2 mL of solvent. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] 5 mol % catalyst was used.

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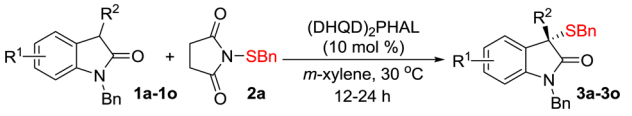
Table 1. We found that the reaction catalyzed by 10 mol % of cinchonine gave the desired adduct **3a** in 56% yield and 65% ee (entry 1). Better enantioselectivity (70% ee) was obtained when $(DHQD)_2PHAL$, as the C_2-symmetric (bis)cinchona alkaloid derivative containing a rigid enzyme-like pocket, was utilized (entry 7). Further optimization of the reaction conditions was carried out by examining different solvents using $(DHQD)_2PHAL$ as catalyst (entries 9–14); *m*-xylene was identified as the ideal solvent regarding the yield and enantioselectivity (entry 15). Excellent yield (98%) with the same ee (94%) was reached when the reaction temperature was increased to 30 °C (entry 17). When the catalyst loading was reduced to 5 mol %, the enantioselectivity of **3a** was kept but the yield was decreased to 63% (entry 18).

Table 2. Sulfenylation of 3-Aryloxindoles **1a**–**1o** to *N*-(Benzylthio)succinimide **2a** Catalyzed by $(DHQD)_2PHAL$[a]

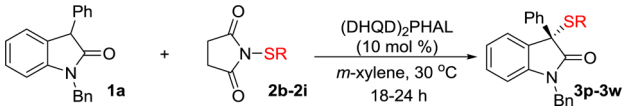


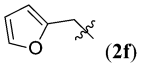
entry	R^1/R^2	3	yield (%)[b]	ee (%)[c]
1	H/Ph (**1a**)	**3a**	97	93
2	5-F/Ph (**1b**)	**3b**	95	92
3	5-Cl/Ph (**1c**)	**3c**	98	94
4	5-Br/Ph (**1d**)	**3d**	91	93
5	5-Me/Ph (**1e**)	**3e**	93	93
6	5-MeO/Ph (**1f**)	**3f**	95	93
7	6-Br/Ph (**1g**)	**3g**	85	92
8	7-F/Ph (**1h**)	**3h**	98	88
9	H/4-FC_6H_4 (**1i**)	**3i**	97	90
10	H/3-FC_6H_4 (**1j**)	**3j**	94	94
11	H/3-$CF_3C_6H_4$ (**1k**)	**3k**	98	96
12	H/4-MeC_6H_4 (**1l**)	**3l**	81	92
13	H/3-MeC_6H_4 (**1m**)	**3m**	97	96
14	H/4-$MeOC_6H_4$ (**1n**)	**3n**	72	91
15	H/2-naphthyl (**1o**)	**3o**	90	93

[a] All reactions were performed with 0.10 mmol of **1**, 0.15 mmol of **2a**, and 0.01 mmol of $(DHQD)_2PHAL$ in 1.0 mL of *m*-xylene. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

We then examined the scope of 3-aryloxindoles **1a**–**1o** reacting with *N*-(benzylthio)succinimide **2a** under the optimized reaction conditions (10 mol % of $(DHQD)_2PHAL$, *m*-xylene, 30 °C, Table 2). The reactions were complete within 12–24 h and gave products in good to excellent yields (72–99%) and with excellent enantioselectivities (88–96% ee). The introduction of various substituents on the 5-, 6-, and 7-position of the aromatic ring of 3-phenyloxindoles (**1a**–**1h**) appeared to have a very limited effect on enantioselectivity (entries 2–8). It was also found that the position and electronic properties of the substituents on the aromatic ring at the C3-position of 3-aryloxindoles (**1i**–**1o**) did not affect the ee (entries 9–15).

Table 3. Sulfenylation of 3-Phenyloxindole **1a** to *N*-(Sulfanyl)succinimides **2b**–**i** Catalyzed by $(DHQD)_2PHAL$[a]



entry	R (**2**)	3	yield (%)[b]	ee (%)[c]
1	2-$ClC_6H_5CH_2$ (**2b**)	**3p**	98	91
2	4-$ClC_6H_5CH_2$ (**2c**)	**3q**	92	92
3	2-$BrC_6H_5CH_2$ (**2d**)	**3r**	95	92
4	4-$BrC_6H_5CH_2$ (**2e**)	**3s**	97	90
5	 (**2f**)	**3t**	96	93
6	cyclohexyl (**2g**)	**3u**	73	97
7	Et (**2h**)	**3v**	98	91
8	Ph (**2i**)	**3w**	95	85

[a] All reactions were performed with 0.10 mmol of **1a**, 0.15 mmol of **2**, and 0.01 mmol of $(DHQD)_2PHAL$ in 1.0 mL of *m*-xylene. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

We subsequently evaluated the generality of the reaction with regard to the variation of *N*-(sulfanyl)succinimides (Table 3). Performing the reaction with the *N*-(*ortho*-chlorobenzylthio)succinimide **2b** gave **3p** in 98% yield and 91% ee (entry 1), while the *N*-(*para*-cholorobenzylthio)-succinimide **2c** gave **3q** in 92% yield and 92% ee (entry 2). The bromo substituent at the corresponding positions did not affect the yield and enantioselectivity (entries 3 and 4). The use of *N*-(benzylthio)succinimide with a heteroaromatic group, such as furyl (**2f**), also afforded the desired product **3t** with excellent yield and ee (entry 5). We were pleased to see that the reaction condition was also applicable to *N*-(alkylthio)succinimides (**2g**–**2h**), giving excellent enantioselectivities as well as good reactivity (entries 6 and 7). The use of *N*-(phenylthio)succinimide **2i** resulted in excellent yield and good enantioselectivity (entry 8).

It is highly desirable to prepare both of the enantiomeric products with equally high enantioselectivities in an asymmetric protocol. Using the pseudoenantiomeric pair of *Cinchona* alkaloids as catalysts is a unique approach to achieve this purpose,[19] which prompts us to explore the possibilities of our methodology.

It is interesting to note that *ent*-**3a**, as the enantiomer of **3a**, could be obtained with 50% ee when using $(DHQ)_2PHAL$ as catalyst in our screening experiments (Table 1, entry 8). Therefore, we investigated the sulfenylation of **1a** and **2a** catalyzed by 10 mol % of $(DHQ)_2PHAL$ under the established reaction conditions (*m*-xylene as solvent, 30 °C). We observed that the ee of *ent*-**3a** was enhanced to 81% (Table 4, entry 1). The ee could be improved to 88% when toluene was the solvent (entry 3). The best results were obtained in 96% yield and 90% ee when the catalyst loading was reduced to

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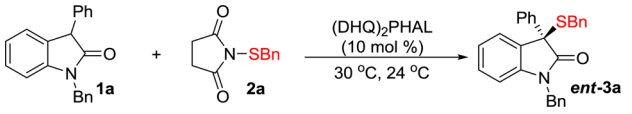
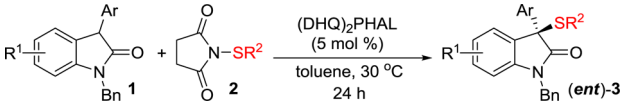
Table 4. Reaction Condition Screening on the Synthesis of *ent*-**3a** Catalyzed by $(DHQ)_2PHAL$[a]



entry	equiv of catalyst	solvent	yield (%)[b]	ee (%)[c]
1	0.1	*m*-xylene	80	81
2	0.1	*p*-xylene	76	87
3	0.1	toluene	98	88
4	0.05	toluene	96	90[d]
5	0.02	toluene	68	84

[a] Unless otherwise noted, reactions were performed with 0.02 mmol of **1a**, 0.03 mmol of **2a**, and 0.002 mmol of catalyst in 0.2 mL of solvent. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] 0.1 mmol scale in 1.0 mL of toluene, yield = 90%, ee = 90%.

Table 5. Sulfenylation of 3-Aryloxindoles **1** to *N*-(Sulfanyl)succinimides **2** Catalyzed by $(DHQ)_2PHAL$[a]

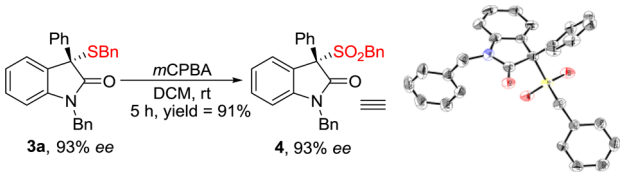


entry	R^1/Ar/R^2 (*ent*-**3**)	yield (%)[b]	ee (%)[c]
1	5-Cl/Ph/Bn (*ent*-**3c**)	98	91
2	5-Br/Ph/Bn (*ent*-**3d**)	97	90
3	5-MeO/Ph/Bn (*ent*-**3f**)	70	85
4	6-Br/Ph/Bn (*ent*-**3g**)	96	91
5	H/4-FC_6H_4/Bn (*ent*-**3i**)	95	90
6	H/3-FC_6H_4/Bn (*ent*-**3j**)	97	90
7	H/3-MeC_6H_4/Bn (*ent*-**3m**)	80	95
8	H/4-$MeOC_6H_4$/Bn (*ent*-**3n**)	72	90
9	H/H/2-$ClC_6H_5CH_2$ (*ent*-**3p**)	81	86
10	H/H/4-$ClC_6H_5CH_2$ (*ent*-**3q**)	90	88
11	H/H/cyclohexyl (*ent*-**3u**)	68	91

[a] All reactions were performed with 0.10 mmol of **1**, 0.15 mmol of **2a**, and 0.01 mmol of $(DHQD)_2PHAL$ in 1.0 mL of *m*-xylene. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

5 mol % (entry 4). However, the lower catalyst loading (2 mol %) compromised the enantioselectivity (entry 5). Subsequently, we carried out the sulfenylation of 3-aryloxindoles **1** with *N*-(sulfanyl)succinimides **2** using 5 mol % of $(DHQ)_2PHAL$ in toluene at 30 °C. Various sulfenylated products (*ent*-**3**) could be obtained in 68−99% yield and 86−95% ee (Table 5). On the basis of the experimental results, we have proposed two tentative transition states for the sulfenylations using $(DHQD)_2PHAL$ and $(DHQ)_2$-PHAL as catalyst (see Supporting Information).

Scheme 1. Synthetic Transformation of Adduct **3a** and the ORTEP Structure of the Product **4**



Next, by using *m*CPBA as the oxidant, the sulfenylation adduct **3a** was readily transformed into the corresponding sulfone[20] **4** in 5 h with 91% yield and without compromising the enantiomeric excess (Scheme 1). The absolute configurations of the sulfenylation products were assigned based on X-ray crystallographic analysis of a single crystal of **4**.[21]

In summary, we have developed a highly enantioselective sulfenylation of 3-aryloxindoles with *N*-(sulfanyl)-succinimides. $(DHQD)_2PHAL$, as the commercially available *Cinchona* alkaloid derivative, was demonstrated as an efficient catalyst to promote the reaction. Several chiral 3-benzylthio-, alkylthio-, and arylthio-substituted oxindoles, containing 3,3-disubstituted quarternary carbon stereocenters, could be readily obtained with excellent enantioselectivities (85−97% ee). By replacing the catalyst with $(DHQ)_2PHAL$, this methodology is applicable to prepare the opposite enantiomers of the sulfenylated products with equal excellent enantioselectivities (86−95% ee). This is the first report on the highly enantioselective construction of 3-benzylthio- and alkylthio-substituted oxindoles. Further investigations into the full reaction scope and mechanism of this catalytic system are still in progress.

Acknowledgment. This work was supported by NSFC (21072044) and the Program for New Century Excellent Talents in University of Ministry of Education (NCET-11-0938).

Supporting Information Available. General information, typical experimental procedures, characterization, HPLC and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Gutteridge, C. E.; de Laszlo, S. E.; Kamenecka, T. M.; McCauley, E.; van Riper, G.; Mumford, R. A.; Kidambi, U.; Egger, L. A.; Tong, S.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 885.

(21) CCDC-889149 (**4**) 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.

The authors declare no competing financial interest.