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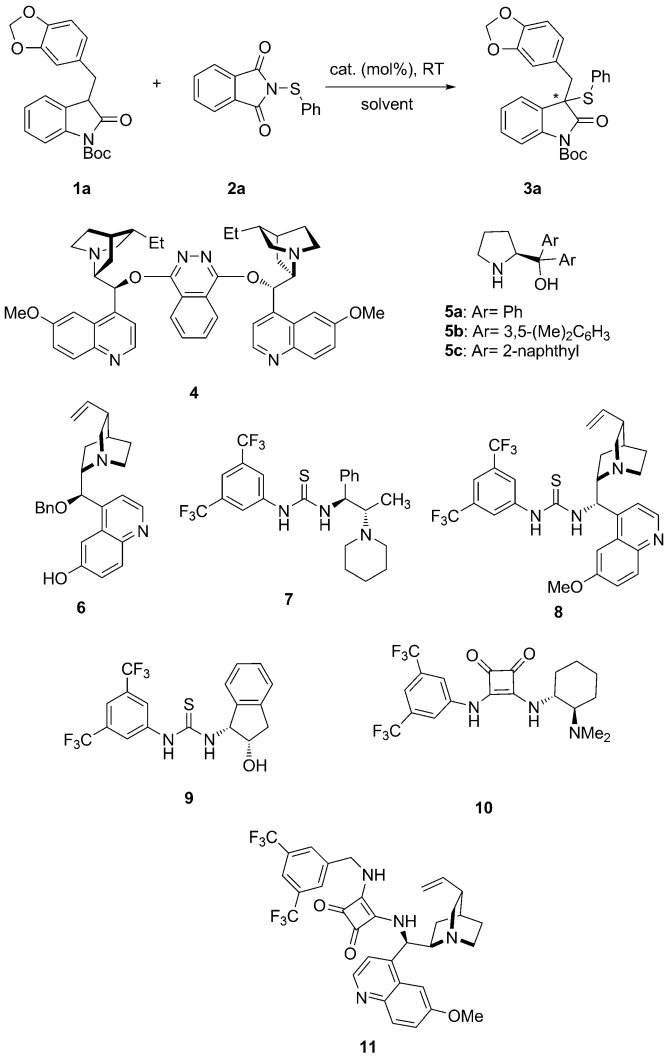
Organocatalytic, Asymmetric Synthesis of 3-Sulfenylated *N*-Boc-Protected Oxindoles

Chuan Wang, Xuena Yang, Charles C. J. Loh, Gerhard Raabe, and Dieter Enders*[a]

Dedicated to Professor Heribert Offermanns on the occasion of his 75th birthday

The oxindole core is present as a characteristic structural motif in numerous alkaloids that exhibit diverse biological and pharmaceutical activities.[1] In particular, 3,3-disubstitued oxindoles are important precursors for the synthesis of hexahydropyrrolo[2,3-*b*]indoles, which exist in a series of biologically active natural products.[2] Therefore, the asymmetric synthesis of 3,3-disubstituted oxindoles has been investigated intensively and many excellent results have been achieved by the use of both organo- and transition-metal catalysis.[3] Oxindoles with a heteroatom at the C-3 position have received considerable attention owing to their potential applications in medicinal chemistry.[1g–m] Recently, various methods for the asymmetric synthesis of 3-fluorooxindoles,[4] 3-chlorooxindoles,[5] 3-aminooxindoles,[6] and 3-hydroxyoxindoles[7] have been reported. Many oxindoles with a thio group at the carbon stereocenter have been found to have anticancer, antifungal, or antitubercular activities.[1k–m] Therefore, the synthesis of 3-sulfanyloxindoles has been widely explored and many approaches have been developed.[8] For example, Procter et al. successfully used the Pummer reaction for the efficient synthesis of 3-sulfanyloxindoles by employing various thiols and glyoxamides as precursors.[8d–g] Recently, Wang, Zhang et al. developed a Rh-$(OAc)_2$-catalyzed thia-Sommelet–Hauser rearrangement that led to the formation of 3-arylthiooxindoles in moderate to good yields.[8h] However, the direct, asymmetric construction of oxindoles that have a sulfur-containing tetrasubstituted stereocenter remains elusive.

The asymmetric, eletrophilic sulfenylation of oxindoles can be achieved through a variety of strategies. Sulfenylations employing either stoichiometric amounts of chiral agents or chiral auxiliaries have been used since 1979, and have proven to be a useful method for the preparation of sulfenylated compounds in an enantioselective manner.[9] Moreover, catalytic, asymmetric sulfenylation is a straightforward route for the construction of a sulfur-containing, stereogenic center from achiral precursors, but these enantioselective protocols are often restricted to aldehydes and ß-keto esters.[10] Herein, we report the first asymmetric sulfenylation of *N*-Boc-protected oxindoles by using *N*-(sulfanyl)phthalimides as the sulfenylating agent (Scheme 1).



Scheme 1. Asymmetric sulfenylation of **1a** by using different types of organocatalyst (**4**–**11**). Boc = *tert*-butoxycarbonyl.

[a] Dr. C. Wang, Dipl.-Chem. X. Yang, C. C. J. Loh, Prof. Dr. G. Raabe, Prof. Dr. D. Enders
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-809-2127
E-mail: enders@rwth-aachen.de

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Initially, we studied the cinchona alkaloid dimer $(DHQD)_2PHAL$ (**4**) and (*S*)-diarylprolinols **5** as catalysts for the sulfenylation reaction between the *N*-Boc-protected oxindole **1a** and *N*-(phenylsulfanyl)phthalimide (**2a**) in chloroform to give product **3a** (Table 1) because these catalysts showed good activity and a high level of asymmetric induction in the α-sulfenylation of ß-keto esters.[10e,j,k] Unfortunately, these catalysts turned out to be unsuitable for our thiolation reaction with regard to the enantioselectivity. When the catalyst $(DHQD)_2PHAL$ (**4**) was used, the reaction was complete within 48 h at −30 °C and gave the product in good yield (79 %), albeit with low enantiomeric excess (35 % *ee*; Table 1, entry 1). Three different (*S*)-diarylprolinols **5a–c** were also evaluated for the sulfenylation reaction at both room temperature and −30 °C; however, only a moderate level of asymmetric induction (50–73 % *ee*) was achieved (Table 1, entries 2–5). Next, we employed the quinine derivative **6** as a catalyst, which showed lower catalytic activity and almost no enantioselectivity (−3 % *ee*; Table 1, entry 6). Three enantiopure thioureas **7–9** were also tested for this reaction. In the case of thiourea **7**, the reaction proceeded smoothly at room temperature with excellent yield (98 %); however, the enantioselectivity obtained (75 % *ee*) was not satisfactory (Table 1, entry 7). When thiourea **8**, which has a quinine scaffold, was employed as a catalyst, the reaction took longer to complete (72 h), providing the product in moderate yield (73 %) and very low enantioselectivity (−11 % *ee*; Table 1, entry 8). In the case of thiourea **9**, which contains a secondary alcohol group, the reaction gave only a racemic mixture of products (Table 1, entry 9).

Table 1. Optimization of the reaction conditions for the sulfenylation.[a]

Entry	Cat.	Loading [mol %]	*T* [°C]	Solvent	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**4**	20	−30	$CHCl_3$	48	79	35
2	**5a**	20	RT	$CHCl_3$	36	89	50
3	**5b**	20	RT	$CHCl_3$	48	84	59
4	**5b**	20	−30	$CHCl_3$	48	86	73
5	**5c**	20	−30	$CHCl_3$	48	81	55
6	**6**	20	−30	$CHCl_3$	48	46	−3
7	**7**	20	RT	$CHCl_3$	24	98	75
8	**8**	20	RT	$CHCl_3$	48	73	−11
9	**9**	20	RT	$CHCl_3$	72	35	0
10	**10**	20	RT	$CHCl_3$	1	98	96
11	**11**	20	RT	$CHCl_3$	1	98	21
12	**10**	**5**	**RT**	**$CHCl_3$**	**12**	**98**	**96**
13	**10**	5	RT	MeOH	1	96	52
14	**10**	5	RT	MeCN	24	93	75
15	**10**	5	RT	THF	12	97	82
16	**10**	5	0	$CHCl_3$	48	91	78
17	**10**	5	50	$CHCl_3$	6	98	96

[a] The reactions were performed by using *N*-Boc-protected oxindole **1a** (0.5 mmol), *N*-(pheylsulfanyl)phthalimide (**2a**; 1.2 equiv), and a catalyst (**4**–**11**) in a solvent (10 mL). [b] Yields of isolated product. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Cat. = catalyst.

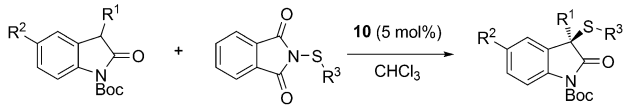
Recently, squaramides have been found to be more powerful hydrogen-bonding catalysts in many transformations, improving on their corresponding thiourea analogues in both catalytic activity and selectivity.[11–13] Therefore, we investigated two squaramides, **10** and **11**, for this sulfenylation reaction. To our delight, the squaramide **10**, which possesses an (*R*,*R*)-diaminocyclohexane subunit, was able to efficiently promote the sulfenylation to furnish the product in excellent yield (98 %) and enantioselectivity (96 % *ee*; Table 1, entry 10). In contrast, a reaction catalyzed by the squaramide **11**, which is derived from quinidine, gave the product only in very low enantioselectivity (21 % *ee*) (Table 1, entry 11).

Because a catalyst loading of 20 mol % resulted in a complete reaction within just 1 h, we repeated the reaction with a 5 mol % loading of catalyst **10** and a full conversion of the oxindole **1a** was achieved within 12 h. The product was obtained in excellent yield (98 %) without a decrease in enantioselectivity (96 % *ee*; Table 1, entry 12). Next, a number of solvents were screened at room temperature by using squaramide **10** (5 mol %) as the catalyst; however, no improvement in enantioselectivity was obtained (Table 1, entries 13–15). In an attempt to increase the enantioselectivity, we lowered the reaction temperature to 0 °C. Surprisingly, the reaction gave the product in a lower enantiomeric excess (78 % *ee*) (Table 1, entry 16). When the reaction was conducted at 50 °C, the reaction rate was increased, but no improvement in the enantioselectivity was obtained (Table 1, entry 17).

After optimizing the reaction conditions, we started to evaluate the substrate scope of this reaction by varying the structure of both *N*-Boc-protected oxindoles **1** and *N*-(sulfanyl)phthalimides **2**. First, we reacted different *N*-Boc-oxindoles **1a–i** with *N*-(phenysulfanyl)phthalimide (**2a**). In the cases of 3-benzyloxindoles **1a–d** and 3-methyloxindole **1i**, the reactions were complete within 12 h at room temperature under the catalysis of the squaramide **10**, furnishing the products **3a–d** and **3i** in high to excellent yields (86–98 %) and excellent enantiomeric excess (92–96 % *ee*; Table 2, entries 1–4 and 9). In contrast, 3-aryloxindoles **1e–h** were found to be more reactive precursors for the sulfenylation reaction. The corresponding reactions were completed within a shorter time (6 h) giving the products **3e–h** in excellent yields (91–98 %) and high enantioselectivities (85–87 % *ee*; Table 2, entries 5–8).

Subsequently, we treated various *N*-Boc-oxindoles, **1a–c**, **1e**, and **1i**, with several *N*-(sulfanyl)phthalimides **2b–g** which contained electron-withdrawing or -donating substituents at different positions. When the chloro-, methyl-, and methoxy-substituted *N*-(arylsulfanyl)phthalimides **2b**, **c**, and **e** were used as precursors, the reactions were conducted at room temperature providing the products **3j**, **k**, **m**, **o**, and **q** in high to excellent yields (88–98 %) and excellent enantiomeric excesses (90–95 % *ee*; Table 2, entries 10, 11, 13, 16, and 17 respectively). In the cases of nitro-substituted *N*-(arylsulfanyl)phthalimides **2d** and **f**, the reactions had to be carried out at 50 °C to give the products **3l** and **3n** in excellent yields (97–98 %) and enantioselectivities (90 % *ee*; Table 2, entries 12 and 14). When *N*-(benzylsulfanyl)phthal-

Table 2. Yields and enantioselectivities of the sulfenylation of *N*-Boc-oxindoles **1** with *N*-(sulfanyl)phthalimides **2** as the sulfenylating agent.[a]



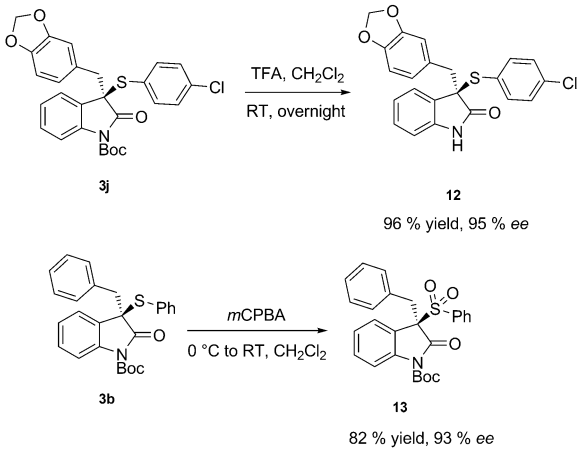
1 2 3

Entry		R^1	R^2		R^3	T [°C]	t [h]	Yield[b] [%]	ee[c] [%]
1	**3a**	(piperonyl)methyl	H	**2a**	Ph	RT	12	98	96
2	**3b**	Bn	H	**2a**	Ph	RT	12	96	96
3	**3c**	p-$CH_3C_6H_4CH_2$	H	**2a**	Ph	RT	12	95	95
4	**3d**	m-$FC_6H_4CH_2$	H	**2a**	Ph	RT	12	90	96
5	**3e**	Ph	H	**2a**	Ph	RT	6	96	85
6	**3f**	Ph	CH_3	**2a**	Ph	RT	6	95	86
7	**3g**	p-$MeOC_6H_4$	H	**2a**	Ph	RT	6	98	87
8	**3h**	p-FC_6H_4	H	**2a**	Ph	RT	6	91	86
9	**3i**	Me	H	**2a**	Ph	RT	12	86	92
10	**3j**	(piperonyl)methyl	H	**2b**	p-ClC_6H_4	RT	12	98	95
11	**3k**	(piperonyl)methyl	H	**2c**	p-$CH_3C_6H_4$	RT	12	94	93
12	**3l**	(piperonyl)methyl	H	**2d**	p-$NO_2C_6H_4$	50	6	98	90
13	**3m**	p-$CH_3C_6H_4CH_2$	H	**2e**	p-$MeOC_6H_4$	RT	12	98	95
14	**3n**	(piperonyl)methyl	H	**2f**	m-$NO_2C_6H_4$	50	6	97	90
15	**3o**	Bn	H	**2c**	p-$CH_3C_6H_4$	RT	12	88	95
16	**3p**	Ph	CH_3	**2g**	Bn	50	24	86	55
17	**3q**	Me	H	**2b**	p-ClC_6H_4	RT	6	92	94

[a] The reactions were performed by using *N*-Boc-protected oxindoles **1** (0.5 mmol), *N*-(sulfanyl)phthalimides **2** (1.2 equiv), and catalyst **10** (5 mol%) in chloroform (10 mL). [b] Yields of isolated product. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase.

imide (**2g**) was used as the electrophile in a reaction with the *N*-Boc-protected oxindole **1f**, the product **3p** was obtained after 24 h at 50 °C in high yield (86%), although the level of asymmetric induction was only moderate (55% *ee*; Table 2, entry 16).

Furthermore, the Boc group can be readily removed from the oxindole product, as demonstrated in Scheme 2. The *N*-Boc-protected oxindole **3j** was successfully deprotected by treatment with trifluoroacetic acid (TFA) at room temperature in dichloromethane to give the product **12** in excellent yield (96%). The thioether moiety in **3b** was also successfully converted into the corresponding sulfone **13** in good yield (82%) by using *meta*-chloroperbenzoic acid (*m*CPBA) as the oxidizing agent (Scheme 2). Notably, the enantiomeric excess remained at an excellent level for both of these reactions.



Scheme 2. Deprotection of the *N*-Boc-oxindole **3j**, and the oxidation of the *N*-Boc-oxindole **3b**.

The absolute configuration of **12** was unambiguously determined to be the *R*-configuration by X-ray crystal-structure analysis (Figure 1).[14] The *N*-Boc-protected products **3** were assumed to have the same configuration as **12**.

In summary, we have developed an organocatalytic, asymmetric sulfenylation of *N*-Boc-protected oxindoles by using *N*-(sulfanyl)phthalimides as the sulfenylating agents. This process was efficiently promoted by the use of a low catalyst loading of a squaramide, with a hydrogen-bonding activation mode furnishing the products, which contain a tetrasubstituted stereocenter, in high to excellent yields (86–98%) and, in most cases, excellent enantioselectivities (up to 96% *ee*).

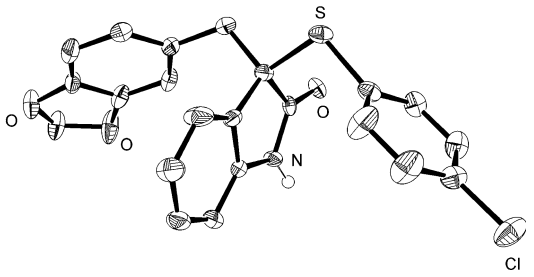


Figure 1. X-ray crystal structure of **12**. This compound crystallizes with two symmetrically independent species in the asymmetric unit, one of which is heavily disordered. Only the nondisordered molecule is shown. The Flack parameter for the refined structure is 0.027(17).

Experimental Section

General procedure: The (sulfanyl)phthalimide **2** (0.60 mmol) was added to a solution of 3-substituted *N*-Boc-protected oxindole **1** (0.50 mmol) and squaramide **10** (5 mol%) in chloroform (10 mL) at either room temperature or 50 °C. After stirring for the time shown in Table 2, the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel (pentane/ether) to give the corresponding 3-sulfanyl-*N*-Boc-oxindole **3**.

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Keywords: asymmetric synthesis · organocatalysis · oxindoles · squaramides · sulfenylation

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[14] CCDC-875714 (**12**) 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.

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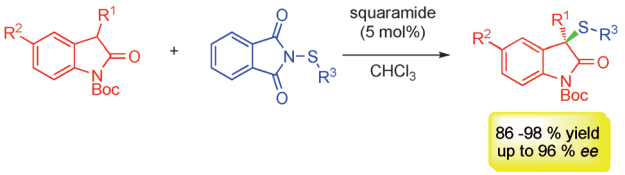

Sulfenylated oxindoles: The first asymmetric sulfenylation of *N*-Boc-protected oxindoles has been developed to provide products containing a tetrasubstituted stereogenic center in high to excellent yields (86–98 %) and, in most cases, excellent enantioselectivities (up to 96 % *ee*; see scheme).