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Direct Asymmetric Michael Addition of Cyclic *N*-Sulfonylimines to α,β-Unsaturated Aldehydes

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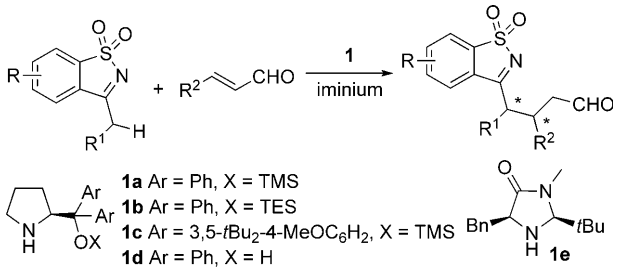
As traditional electrophiles, imines have been extensively applied in Mannich-type reactions for the synthesis of amine compounds.[1] On the other hand, owing to the electron-withdrawing character of the imine functionality, the α-protons of imines also show some acidity; thus, imines tend to act as nucleophiles for α-functionalization reactions, although stoichiometric amounts of strong base are usually required.[2] It is expected that the acidity of the α-protons of imines would be greatly increased in compounds that have highly electron-withdrawing substituents on the nitrogen atom; therefore, the direct-type reactions of imines might be realized under mild catalytic conditions. Indeed, in 2008, Kobayashi and co-workers proved this synthetic possibility in the direct Mannich reaction of the *N*-tosylimine of acetophenone with an activated imine by the catalysis of simple NEt_3; unfortunately, its applicability is limited due to tautomerization and elimination of the functional groups in the products.[3] As a consequence, the structurally more stable tautomers of imines, enecarbamates and enamides, are generally selected and utilized as the nucleophiles, and have been well explored by Kobayashi and other groups over the past few years, through the catalysis of either metal-based[4] or organic molecules.[5]

Cyclic *N*-sulfonylimines, which can be easily prepared from the abundant, commercially available industrial material saccharin, have long been employed in organic synthesis as electrophiles.[6] They are more stable than the acyclic *N*-sulfonylimines and are not likely to tautomerize to their corresponding enamides. Moreover, the α-protons are expected to have lower pK_a values owing to the strong electron-withdrawing effect of the *N*-sulfonyl group. As a result, we envisioned that the application of saccharin-derived cyclic imines as direct nucleophiles in asymmetric synthesis, such as the first Michael addition to α,β-unsaturated aldehydes, might be realized by iminium catalysis with chiral secondary amines **1**,[7] as outlined in Scheme 1.



Scheme 1. Reversal of the reactivity of cyclic *N*-sulfonylimines: direct Michael addition to α,β-unsaturated aldehydes; TMS = trimethylsilyl, TES = triethylsilyl, Bn = benzyl.

The study began with the reaction of cyclic *N*-sulfonylimine **2a** with crotonaldehyde **3a** by using the catalysis of α,α-diphenylprolinol *O*-TMS ether **1a** (10 mol%) and 4-nitrobenzoic acid (PNBA, 10 mol%) in THF at room temperature. Fortunately, the desired Michael addition proceeded smoothly, and adduct **4a** was isolated in high yield with moderate diastereoselectivity and a good *ee* value (Table 1, entry 1). Solvent screenings showed that inferior results were obtained in CH_3CN and DMF (Table 1, entries 2 and 3), and that almost no reaction occurred in toluene or CH_2Cl_2 (Table 1, entries 4 and 5). Acid additives were investigated next. Lower stereoselectivity was observed if *o*-fluorobenzoic acid (OFBA) was applied (Table 1, entry 6); fortunately, the enantioselectivity was greatly improved in the presence of benzoic acid (BA, Table 1, entry 7). However, slightly inferior stereocontrol was observed if AcOH was used (Table 1, entry 8).

Subsequently, additional secondary amine catalysts were tested. Better results could not be obtained by utilizing the catalysis of the more bulky **1b** and **c**[8] (Table 1, entries 9 and 10), and free α,α-diphenylprolinol **1d** and the MacMillan catalyst **1e** afforded no conversion (Table 1, entries 11 and 12). Gratifyingly, the Michael addition still completed at 0°C within 24 h and excellent enantioselectivity and a good d.r. were delivered (Table 1, entry 13), even at a higher concentration (Table 1, entry 14). Finally, we found that the diastereomeric mixture **4a** could be efficiently transformed into

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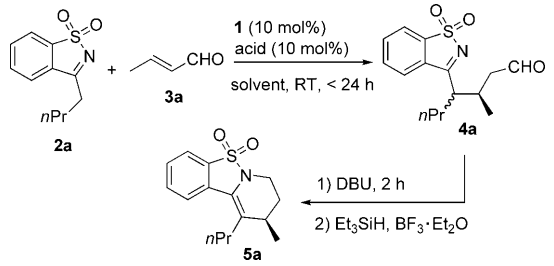
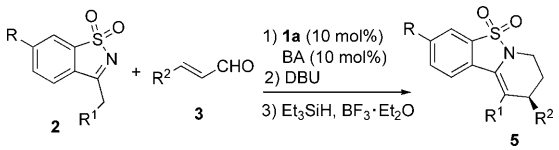
Table 1. Screening studies of the asymmetric reaction of cyclic *N*-sulfonylimine **2a** and crotonaldehyde **3a**.[a]



Entry	**1**	Acid	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	PNBA	THF	90	3.9:1	80
2	**1a**	PNBA	MeCN	85	3.6:1	71
3	**1a**	PNBA	DMF	87	3.8:1	77
4	**1a**	PNBA	toluene	–	–	–
5	**1a**	PNBA	CH_2Cl_2	–	–	–
6	**1a**	OFBA	THF	90	2.6:1	75
7	**1a**	BA	THF	88	4.0:1	92
8	**1a**	AcOH	THF	86	3.2:1	87
9	**1b**	BA	THF	90	3.0:1	92
10[e]	**1c**	BA	THF	85	5.1:1	85
11	**1d**	BA	THF	–	–	–
12	**1e**	TFA	THF	–	–	–
13[f]	**1a**	BA	THF	90	5.9:1	96
14[f,g]	**1a**	BA	THF	90	5.7:1	97
15[f,g]	**1a**	BA	THF	73[h]	–	97[h]

[a] Unless otherwise stated, the reactions were performed with **2a** (0.1 mmol), **3a** (0.15 mmol), **1** (10 mol%), and acid (10 mol%) in solvent (1.0 mL) in less than 24 h. [b] Isolated yield of diastereomeric **4a**. [c] By ^{1}H NMR analysis. [d] Based on chiral HPLC analysis after derivation (major isomer), see the Supporting Information. [e] For 40 h. [f] At 0 °C. [g] In solvent (0.6 mL). [h] Data refers to tricyclic product **5a**.

Table 2. Substrate scope and limitations.[a]



Entry	**2**	R	R^1	R^2	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	**2a**	H	*n*Pr	Me	20	**5a**, 73	97
2	**2b**	H	Bn	Me	20	**5b**, 73	96
3[e]	**2c**	H	Ph	Me	8	**5c**, 68	65
4	**2d**	H	H	Me	24	**5d**, 67	75
5[f]	**2e**	Cl	*n*Pr	Me	36	**5e**, 66	93
6	**2f**	*t*Bu	*n*Pr	Me	24	**5f**, 63	96
7	**2a**	H	*n*Pr	Et	30	**5g**, 70	96
8	**2a**	H	*n*Pr	*n*Pr	36	**5h**, 68	99
9	**2a**	H	*n*Pr	*n*Bu	36	**5i**, 65	97
10	**2d**	H	H	$PhS(CH_2)_2$	36	**5j**, 55	89
11	**2d**	H	H	Ph	20	**5k**, 55	90
12	**2d**	H	H	*m*-ClC_6H_4	18	**5l**, 51	90
13	**2d**	H	H	*p*-MeC_6H_4	28	**5m**, 48	93
14	**2d**	H	H	2-furyl	18	**5n**, 50	89
15	**2d**	H	H	2-thienyl	24	**5o**, 60	90

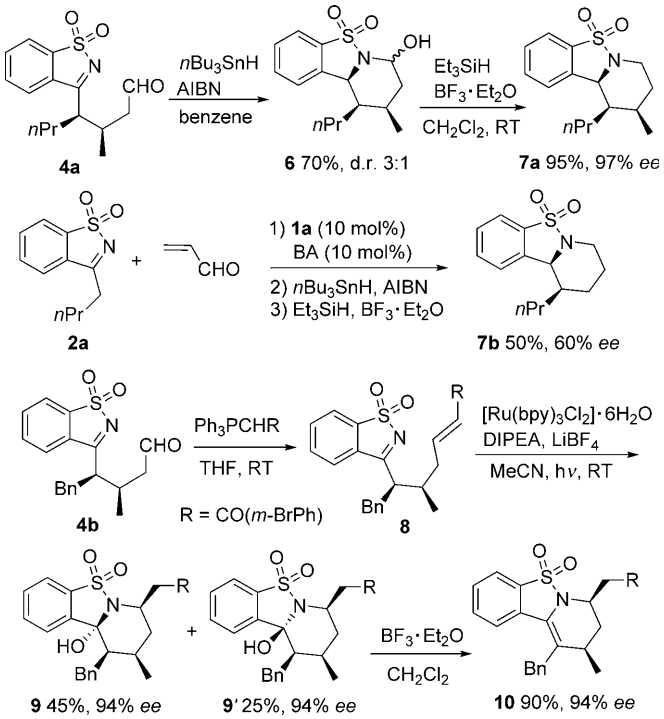
[a] Unless otherwise stated, the reactions were performed with **2** (0.1 mmol), **3** (0.15 mmol), **1a** (10 mol%), and benzoic acid (10 mol%) in THF (0. 6 mL) at 0 °C. Then a tandem process was conducted to give tricyclic compounds **5**. [b] For the first Michael addition step. [c] Isolated yield of **5** after the three steps. [d] Based on chiral HPLC analysis. [e] At −40 °C. [f] At −20 °C, **1b** (10 mol%) as the catalyst.

a single tetrahydropyridine **5a** by a tandem 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)-catalyzed tautomerization/hemiaminal formation/dehydroxylation process without affecting the high enantiopurity (Table 1, entry 15).

With the optimal reaction conditions in hand, we then examined the scope and limitations of the new organocatalytic asymmetric transformations. In general, the direct Michael addition of cyclic *N*-sulfonylimines **2** to α,β-unsaturated aldehydes **3** was conducted at 0 °C in THF by the catalysis of **1a** and benzoic acid. Then, the tandem sequence was performed to deliver tricyclic materials **5**, which are more easily analyzed. The results are summarized in Table 2. Initially, some cyclic imines **2** were tested in the reaction with crotonaldehyde **3a**. Excellent enantioselectivity was obtained for imine **2b**, containing an α-benzyl group (Table 2, entry 2). α-Phenyl-substituted imine **2c** exhibited high reactivity, even at −40 °C, but only a moderate *ee* could be obtained (Table 2, entry 3). Modest enantioselectivity was also attained for methyl imine **2d** (Table 2, entry 4). The substitution effect on the aryl ring of cyclic imines was explored, and good results were achieved for **2e** and **f** (Table 2, entries 5 and 6).[9] Subsequently, an array of α,β-unsaturated aldehydes were investigated. Outstanding *ee* values were obtained for other linear alkyl-substituted enals (Table 2, entries 7–9), as well as for a functionalized substrate (Table 2, entry 10). Unfortunately, poor reactivity was observed for enals containing a β-branched alkyl group. Finally, some enals with β-aryl or -heteroaryl substituents were studied in the reaction with simple methyl imine **2d**, and high enantioselectivity was generally achieved (Table 2, entries 11–15).

We conducted some further intriguing syntheses with the multifunctional Michael adducts **4**. Although the attempted intramolecular cross-coupling reaction between imine and aldehyde groups failed under nBu$_3$SnH/azobisisobutyronitrile-mediated radical conditions,[10] it was found that the imine group can be chemoselectively reduced to afford diastereomeric mixture **6**, after a domino cyclization, which was smoothly dehydroxylated to give enantiopure piperidine derivative **7a** (Scheme 2). Following this strategy, we utilized simple acrolein to prepare chiral product **7b**, which has no substitution at the 4-position of the piperidine ring, although the enantioselectivity was moderate. In addition, we applied Yoon's Ru-based photoredox catalytic method to Wittig-reaction derivative **8** that was formed from adduct **4b**.[11] The imine group still seems to be more electrophilic and reactive, and complicated piperidine derivative **9** (its absolute structure has been unambiguously determined by X-ray crystallographic analysis)[12] and its diastereomer **9′** were generated,[13] which were converted to a single product **10** after simple dehydration.

In conclusion, we have demonstrated that the electrophilic reactivity of the traditional cyclic *N*-sulfonylimines can be reversed, as exemplified in the first direct asymmetric Michael addition reaction of these compounds to α,β-unsaturated aldehydes, by employing the iminium catalysis of a chiral secondary amine. The subsequent base-mediated



Scheme 2. Synthetic transformations of the Michael adducts; AIBN = azobisisobutyronitrile, DIPEA = *N*,*N*-diisopropylethylamine, bpy = 2,2′-bipyridine.

imine group tautomerization/hemiaminal formation/dehydroxylation process efficiently delivered tricyclic piperidine derivatives in moderate to excellent enantioselectivity (up to 99% *ee*). We believe that these cyclic *N*-sulfonylimines could be applied in more direct asymmetric reactions with other electrophiles under mild conditions, and useful nitrogen-containing chiral products with molecular diversity would be accessible. The results of our investigations to that end will be reported in due course.

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Keywords: aldehydes · aminocatalysis · Michael addition · piperidines · sulfonylimines

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[12] CCDC-799810 (**9**) 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.

[13] For a plausible reaction mechanism, see the Supporting Information.

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