S-Chiral Sulfinamides as Highly Enantioselective Organocatalysts

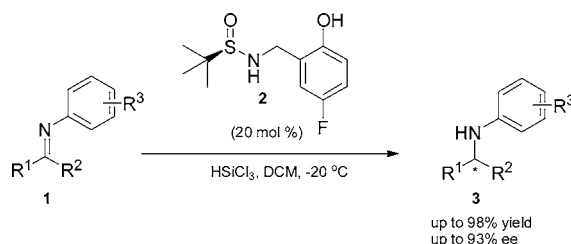**Dong Pei,[†] Zhouyu Wang,[†,‡] Siyu Wei,[†] Yu Zhang,[†] and Jian Sun*,[†]**

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ABSTRACT

Easily accessible chiral sulfinamide 2 has been developed as the first highly efficient and enantioselective organocatalyst relying solely on a chiral sulfur center for stereochemical induction. In the presence of 20 mol % of 2, a broad range of *N*-aryl ketimines 1 were reduced by trichlorosilane to produce amines 3 in high yield and enantioselectivity.

In recent years, there has been intense research interest in asymmetric organocatalysis, and significant progress has been made in the development of metal-free chiral organocatalysts.[1] The vast majority of the currently available enantioselective organocatalysts rely on chiral carbon centers for stereochemical induction. Although chiral sulfur centers have been well established as efficient and versatile stereocontrollers and have been extensively used as the chirality source of chiral auxiliaries and ligands,[2] organocatalysts incorporating chirality solely at sulfur have been rarely explored. Recently, several *S*-chiral sulfoxides were reported to activate allyltrichlorosilanes in asymmetric allylations,[3] and in one case, high enantioselectivities were obtained.[3a] However, these sulfoxides were not catalytic and were all used in at least a stoichiometric amount. Herein, we report the first example of *S*-chiral compounds as highly effective organocatalysts (Figure 1), which promoted the asymmetric reduction of ketimines with trichlorosilane (HSiCl$_3$) in high yield and enantioselectivity.

We recently initiated a program focusing on developing enantioselective Lewis base organocatalysts for the activation of HSiCl$_3$ for the asymmetric reduction of imines,[4,5] a useful yet challenging reaction for the production of chiral amines.[8] We were particularly interested in *S*-chiral sulfinamides due

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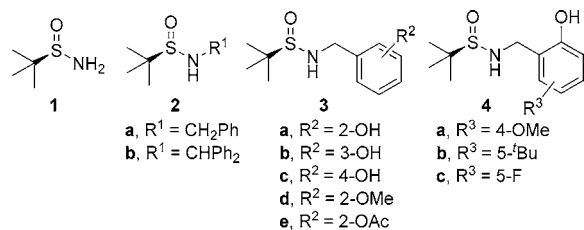
[‡] Xihua University.

(1) For general reviews on asymmetric organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.

(2) For recent reviews, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichim. Acata* **2005**, *38* (3), 93. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (d) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (e) Ellman, J. A.; Owens, T. D. *Pure Appl. Chem.* **2003**, *75*, 39. (f) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (g) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.

(3) (a) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610. (b) Massa, A.; Malkov, A. V.; Kocovsky, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179. (c) Rowlands, G.; Barnes, W. K. *Chem. Commun.* **2003**, 2712.

(4) (a) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999. (b) Wang, Z.; Cheng, M.; Wu, P.; Wei, S.; Sun, J. *Org. Lett.* **2006**, *8*, 3045.

(5) For work done by others on organocatalytic asymmetric reduction of imines, see ref 6 for Lewis base catalysis and ref 7 for Brønsted acid catalysis.

Figure 1. Structures of the catalysts.

to their ease of synthesis, chirality about sulfur, and the potential for silicon coordination through the Lewis basic oxygen atom.[9,10] In our initial practice, we examined the commercially available (R)-*tert*-butanesulfinamide (**1**), a well-known Ellman's chiral auxiliary,[2e,f,11] as the catalyst in the hydrosilylation of ketimine **5a** with HSiCl₃ at 0 °C in CH₂Cl₂. To our delight, in the presence of 20 mol % of **1**, the product was furnished in 60% isolated yield and 21% ee in 24 h (Table 1, entry 1). Encouraged by this preliminary result, we prepared a set of *tert*-butanesulfinamide derivatives **2−4** via simple reductive amination of **1** (see the Supporting Information for experimental details) and examined their catalytic efficiencies in the reduction of **5a**.

While no obvious improvement of efficacy was observed with either *N*-benzylated catalyst **2a** or *N*-benzhydrylated catalyst **2b** compared with **1** (entries 1−3), catalyst **3a** bearing an *N*-2-hydroxybenzyl group exhibited significantly improved reactivity and enantioselectivity, affording the product in 76% yield and 86% ee (entry 4). Apparently, the phenolic hydroxyl group in **3a** played a crucial role. Moving this group from the *ortho* to the *meta* position (**3b**) led to

Table 1. Asymmetric Reduction of Ketimine **5a**^{a}

entry	catalyst	T (°C)	yield^b (%)	ee^{c,d} (%)
1	**1**	0	60	21
2	**2a**	0	42	27
3	**2b**	0	54	6
4	**3a**	0	76	86
5	**3b**	0	72	77
6	**3c**	0	45	75
7	**3a**	−20	84	89
8	**3b**	−20	75	86
9	**3c**	−20	62	81
10	**3d**	0	38	26
11	**3e**	0	53	9
12	**4a**	0	75	58
13	**4b**	0	72	74
14	**4c**	0	81	89
15	**4c**	−20	92	92

^{a} Reactions were carried out with 2.0 equiv of HSiCl₃ on a 0.2 mmol scale in 1.0 mL of solvent for 24 h. ^{b} Isolated yield based on the imine. ^{c} The ee values were determined using chiral HPLC. ^{d} Product **6a** was *S* configured in all cases, as revealed by comparison of the optical rotation with the literature data.

slightly decreased reactivity and enantioselectivity (entry 5). Further moving this group to the *para* position (**3c**) caused a relatively large decrease in reactivity but had little effect on the enantioselectivity (entry 6). Notably, when the reaction temperature was lowered from 0 to −20 °C, **3b** and **3c** became closer to **3a** in terms of catalytic efficacy, particularly in terms of enantioselectivity (entries 7−9). These results seem to suggest that the *ortho* phenolic hydroxyl group in **3a** is much more likely to play a major role as a Brønsted acid than as a chelating Lewis base in the enantiodifferentiating process. This was further supported by the observation that methylation (**3d**) and acetylation (**3e**) of the hydroxyl group of **3a** resulted in a dramatic decrease in enantioselectivity (entries 10 and 11). Thus, it was not surprising to observe that the electron nature of the substituent on the phenol ring of **4a−c** had a strong effect on the enantioselectivity (entries 12−14),[16] and **4c** with an electron-

(6) (a) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. (b) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kocovsky, P. *Org. Lett.* **2004**, *6*, 2253. (c) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751. (d) Malkov, A. V.; Stoncius, S.; MacDougall, K. N.; Mariani, A.; McGeoch, G. D.; Kocovsky, P. *Tetrahedron* **2006**, *62*, 264. (e) Malkov, A. V.; Liddon, A.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432.

(7) (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.

(8) For recent reviews on asymmetric reduction of imines, see: (a) Taratov, V. I.; Börner, A. *Synlett.* **2005**, 203. (b) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (e) Carpentier, J. F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913. (f) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (g) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(9) For recent reviews on asymmetric Lewis base catalysis, see: (a) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (b) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (c) Koboyashi, S.; Sugiura, M.; Ogawa, C. *Adv. Synth. Catal.* **2004**, *346*, 1023. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167. (f) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.

(10) For leading references for other enantioselective oxo type Lewis base catalysts, see ref 12 for phosphoramides, ref 13 for phosphine oxides, ref 4, 6a−d, and 14 for carboxamide, and ref 15 for *N*-oxides.

(11) Liu, G.-C.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

(12) (a) Denmark, S. E.; Coe, D. M.; Patt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.
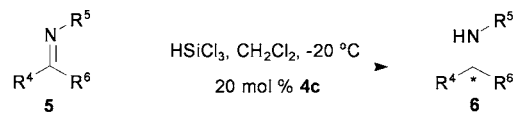
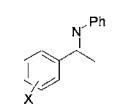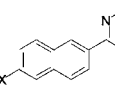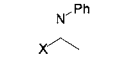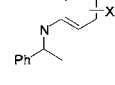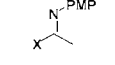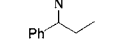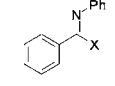(13) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491.

(14) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767.

(15) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (d) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1047. (e) Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674.

(16) It should be noted that the role of the internal Brønsted acidic phenol moiety of the catalysts could not be simply replaced by any external additives with similar or stronger Brønsted acidity (see the Supporting Information for data).

Table 2. Asymmetric Reduction of Ketimines **5** with Catalyst **4c**[a]

entry	imine		X =	time (h)	yield[b] (%)	ee[c] (%)
1		**5a**	H	24	92	92
2		**5b**	p-CF$_3$	24	93	92
3		**5c**	p-NO$_2$	24	94	90
4		**5d**	p-Br	24	92	92
5		**5e**	p-OMe	48	98	93
6		**5f**	H	48	96	90
7		**5g**	OMe	48	97	91
8		**5h**	c-C$_6$H$_{11}$	24	78	74
9		**5i**	^{i}Pr	24	78	79
10		**5j**	p-Cl	24	94	92
11		**5k**	p-Me	24	87	91
12		**5l**	p-OMe	48	97	91
13		**5m**	o-OMe	24	73	88
14		**5n**	p-CF$_3$Ph	24	80	90
15		**5o**	2-Np	24	86	88
16		**5p**		24	84	92
17		**5q**	Et	24	92	93
18		**5r**	^{n}Pr	24	87	91
19		**5s**	^{n}Bu	24	94	93
20		**5t**	^{i}Bu	24	82	86

[a] Reactions were carried out with 2.0 equiv of HSiCl$_3$ on a 0.2 mmol scale in 1.0 mL of solvent at −20 °C for 24−48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC.

withdrawing 4-F group and thus with a phenolic hydroxyl group having the strongest Brønsted acidity exhibited the highest enantioselectivity among those examined (entries 14 and 15).

We next selected catalyst **4c** for further studies. After the optimal reaction condition was established (see the Supporting Information for details), namely 20 mol % of catalyst loading, at −20 °C and with dichloromethane as solvent, the substrate generality was probed using a variety of N-aryl ketimines (**5a−t**). As illustrated in Table 2, the electron-deficient and electron-rich aromatic N-phenyl ketimines **5a−g** underwent facile reduction to yield the desired products **6a−g** in high yield and enantioselectivity (92−98% yield, 90−93% ee, entries 1−7). Moreover, ketimines **5p−t** bearing a relatively bulky R^6 group, such as ^{n}Et, ^{n}Pr, ^{n}Bu, and ^{i}Bu, were well tolerated by catalyst **4c** (82−94% yield, 86−93% ee, entries 16−20). Such tolerance was previously only observed with our piperazine-2-carboxylic acid based N-formamide catalyst system,[4b] which, however, is much less tolerant than **4c** toward ketimines **5j−p** with a substituent on the arene ring of R^5 (33−84% yield and 55−75% ee for the former[4b]). Notably, catalyst **4c** also proved to be applicable to aliphatic ketimines **5h** and **5j** (entries 8 and 9).

In summary, we have demonstrated the first example of S-chiral compounds being used as highly effective organocatalysts, which promoted the reduction of a broad range of N-aryl ketimines with trichlorosilane in high yield and enantioselectivity. The mechanistic aspects[17,18] and the further application of the present catalyst system and the development of other S-chiral organocatalysts are under active investigation.

Supporting Information Available: Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A clear, positive, nonlinear effect was observed in the **4c**-catalyzed hydrosilylation of **5a** (see the Supporting Information for the graphically depicted results), which seems to suggest that more than one molecule of catalyst is involved in the stereochemistry-determining step.

(18) A notable feature of this reaction system is that it becomes heterogeneous after initiation, which complicates the mechanism study.