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# Rationally-Designed *S*-Chiral Bissulfinamides as Highly Enantioselective Organocatalysts for Reduction of Ketimines

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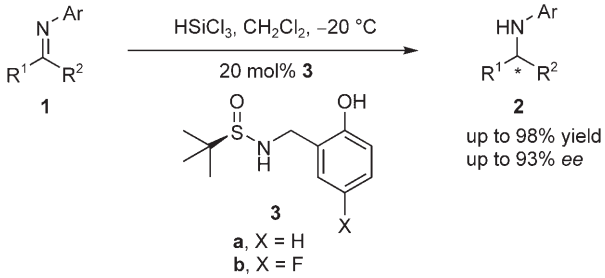
**Abstract:** We recently reported the first example of *S*-chiral organocatalysts, that are highly efficient and enantioselective in substoichometric amounts, and which use a chiral monosulfinamide group as Lewis base to activate trichlorosilane ($HSiCl_3$) to reduce *N*-arylketimines. A plausible mechanism involving two molecules of the monosulfinamde catalyst for the activation of $HSiCl_3$ prompted us to design *S*-chiral bissulfinamides as new catalysts. We herein describe our findings that an easily prepared *S*-chiral bissulfinamide bearing a five-methylene linkage not only inherited the excellent substrate generality from the monosulfinamide catalysts, but also exhibited further improved enantioselectivity.

**Keywords:** asymmetric reduction; *S*-chiral bissulfinamide; ketimines; organocatalysis

Chiral sulfur centers have been well established as efficient and versatile stereo-controllers in asymmetric synthesis and have been extensively used as the chirality source of chiral auxiliaries and ligands.[1] The development of *S*-chiral organocatalysts, however, had met with little success.[2] Recently, we reported the first example of *S*-chiral organocatalysts that are highly efficient and enantioselective in substoichometric amounts.[3] *S*-Chiral monosulfinamides **3** (20 mol%) catalyzed the asymmetric reduction of *N*-arylketimines with trichlorosilane ($HSiCl_3$) in high yield and enantioselectivity (Scheme 1).

Our previous observation of a clear positive nonlinear effect of the enantiomeric excess (*ee*) of catalyst **3b** on the product's enantioselectivity in the asymmetric reduction of ketimine **1a** ($R^1 = Ar = Ph$, $R^2 = Me$)[3] seemed to suggest that more than one molecule of such a monosulfinamide catalyst is involved in the stereochemistry-determining step. Since the phenolic hydroxyl group of **3** was found most likely not to play a chelating role,[3] we speculate that two molecules of catalyst are bound to the chlorosilane through their Lewis basic S=O groups. The main function of the indispensable phenolic hydroxy group might be to facilitate the assembly of two sulfinamides through hydrogen bonding (Figure 1). We envisioned that the incorporation of two sulfinamide units into one molecule through chemical bonds could lead to highly effective new catalysts.[4] Thus, we designed dimeric bissulfinamides **4**–**7** (Figure 2) as our second-generation catalysts. Herein, we report our discovery of a structurally simple new *S*-chiral bissulfinamide organocatalyst (**5d**) that promotes the asymmetric re-




**Scheme 1.**

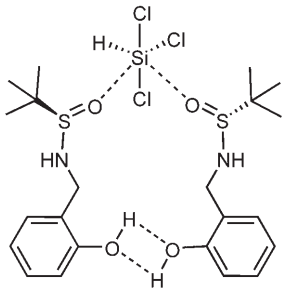



**Figure 1.** Proposed binding pattern.

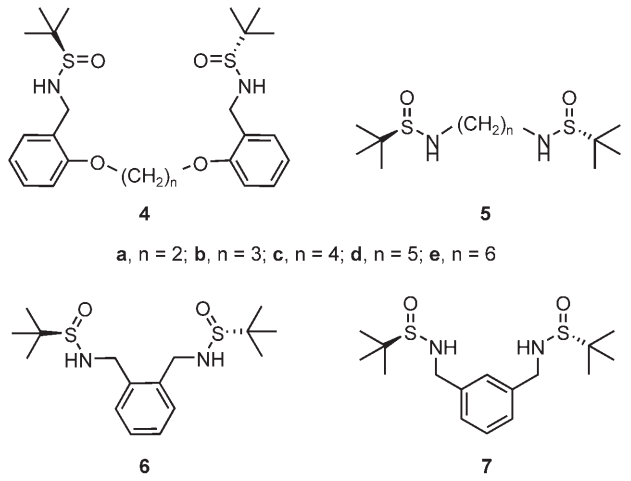



**Figure 2.** Structures of the newly designed bissulfinamide catalysts.

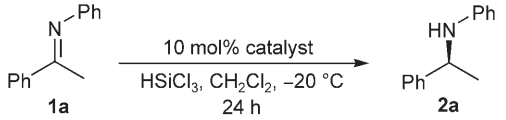
duction of *N*-arylketimines by $HSiCl_3$ with high efficiency and excellent enantioselectivity.[5,6]

Initially, we simply connected two molecules of sulfinamide **3a** with a polymethylene tether which was easily installed through the phenolic hydroxy groups. The resulting dimeric bissulfinamides **4a**–**e** of varying tether length were then examined as catalysts for the model reaction of **1a** with $HSiCl_3$ in dichloromethane at −20 °C. To our delight, all these bissulfinamides exhibited the same high level of enantioselectivity as the parent monosulfinamide **3a** regardless of the tether length (entries 1–6, Table 1). While 20 mol% of the catalyst loading of the monosulfinamide drove the reaction to completion in 24 h, half the amount of the bissulfinamides displayed similar reactivity.

In principle, if a cooperative binding of the bissulfinamide with silicon is essential to the stereocontrol, variation of the linkage that affects the spacing and thus the conformational alignment of the two sulfinamide functional groups should have a substantial influence on the catalytic outcome. Since the enantioselectivity of bissulfinamides **4** was only slightly affected by the polymethylene tether length, it seems to imply that there exists excessive spacing flexibility with the phenyl-containing linkage. Thus, we next simplified the linkage and prepared bissulfinamides **5a**–**e** with only a polymethylene tether connecting the two chiral sulfinamide functional groups.

As expected, the efficacy of bissulfinamides **5** is largely dependent on the tether length (entries 7–11, Table 1). Compound **5d** bearing a five-methylene tether proved to be the most effective catalyst, affording 93% yield and 91% *ee* (entry 10). Either decreasing or increasing the methylene unit number (catalysts **5a**–**c** and **5e**) had negative effects on both the reactivity and enantioselectivity. These results clearly imply a cooperativity of binding with bissulfinamides.

**Table 1.** Asymmetric reduction of ketimine **1a**.[a]




| Entry | Catalyst | Yield [%][b] | *ee* [%][c,d] |
|---|---|---|---|
| 1 | **3a** | 84 | 89 |
| 2 | **4a** | 85 | 90 |
| 3 | **4b** | 77 | 89 |
| 4 | **4c** | 80 | 90 |
| 5 | **4d** | 78 | 91 |
| 6 | **4e** | 80 | 86 |
| 7 | **5a** | 79 | 63 |
| 8 | **5b** | 42 | 75 |
| 9 | **5c** | 61 | 90 |
| **10** | **5d** | **93** | **91** |
| 11 | **5e** | 71 | 83 |
| 12 | **6** | 30 | 66 |
| 13 | **7** | 84 | 89 |

[a] Reactions were carried out with 2.0 equiv. of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of solvent.
[b] Isolated yield based on the imine.
[c] The *ee* values were determined using chiral HPLC.
[d] Product **2a** was *S* configured in all cases, as revealed by comparison of the optical rotation with the literature data.

It is likely that the five-methylene tether enables **5d** to chelate with silicon with a most favorable geometry.

Considering that the straight chain of the polymethylene tether is quite conformationally flexible, we also tried to constrain the sulfinamide groups into a less flexible arrangement by utilizing a phenyl-mounted tether (**6** and **7** in Figure 2), which, unfortunately, caused adverse effects on both the catalytic efficiency and the enantioselectivity (entries 12 and 13, Table 1). Notably, **7** with a phenyl-1,3-dimethylene tether displayed significantly higher reactivity and enantioselectivity than **6** with a phenyl-1,2-dimethylene tether, further supporting the cooperativity of binding with bissulfinamides, since if there were no chelation with silicon, the reactivity and enantioselectivity of these compounds would be independent of the relative positioning of the two sulfinamide functionalities.

As expected, for the **5d**-catalyzed reduction of **1a** with $HSiCl_3$, a linear effect of catalyst *ee* on product enantioselectivity was observed (Figure 3). Thus, it is clear that a single molecule of bidentate **5d** participates in the reaction.

To further improve the performance of catalyst **5d**, 2,6-lutidine was tested as an additive in the reduction of **1a** (entries 1–7, Table 2). We were delighted to find that the use of 0.3 equivalents of 2,6-lutidine was beneficial to the enantioselectivity (entry 4). When the amount of 2,6-lutidine was increased, the beneficial

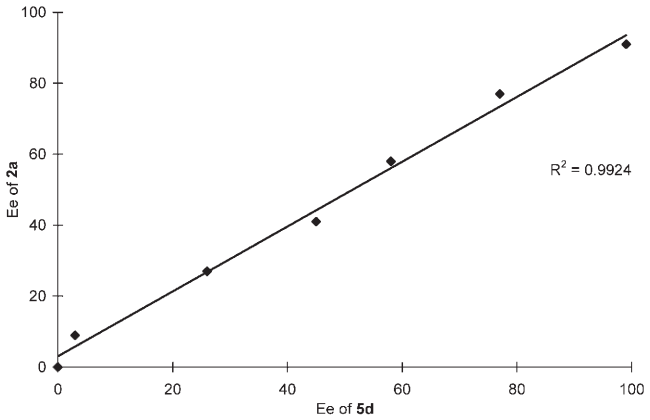



**Figure 3.** Linear effect in the **5d**-catalyzed reduction of ketimine **1a** with trichlorosilane.

**Table 2.** Asymmetric reduction of ketimine **1a** with catalyst **5d** and additives.[a]

| Entry | Additive | Amount (equiv.)[b] | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | none | | 93 | 91 |
| 2 | 2,6-lutidine | 0.1 | 90 | 90 |
| 3 | 2,6-lutidine | 0.2 | 90 | 91 |
| **4** | **2,6-lutidine** | **0.3** | **91** | **96** |
| 5 | 2,6-lutidine | 0.4 | 82 | 93 |
| 6 | 2,6-lutidine | 0.5 | 67 | 94 |
| 7 | 2,6-lutidine | 1.0 | $<5$ | nd |
| 8 | $NEt_3$ | 0.3 | 35 | 95 |
| 9 | *i*-$Pr_2NEt$ | 0.3 | 83 | 95 |
| 10 | DMAP | 0.3 | 66 | 95 |
| 11 | NMM | 0.3 | 72 | 92 |
| 12 | DBU | 0.3 | 68 | 94 |
| 13 | pyridine | 0.3 | 46 | 93 |
| 14 | HMTA | 0.3 | 54 | 93 |

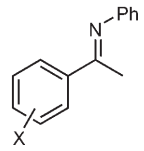
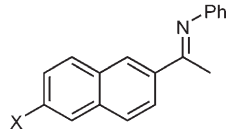
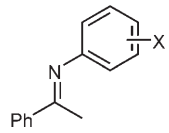
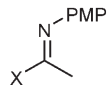
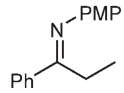
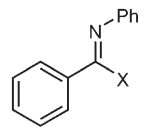
[a] Reactions were carried out with 10 mol% catalyst **5d** and 2.0 equiv. of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of solvent for 24 h.
[b] Based on the imine.

effect on the enantioselectivity persisted (entries 5 and 6); however, the reactivity was significantly lowered. When the amount of 2,6-lutidine reached one equivalent, the reaction became totally inactive (entry 7).

Several other bases were also examined as additives in the **5d**-catalyzed reduction of **1a** (entries 8–14, Table 2). In the presence of 0.3 equiv. of all these bases, similar beneficial effects on the enantioselectivity were observed. However, unlike 2,6-lutidine, these bases all had substantially negative effects on the reactivity.

Finally, the highly efficient new bissulfinamide catalyst **5d** was tested in the reduction of various ketimines under the optimal conditions to establish the generality. As shown in Table 3, **5d** inherited the extraordinarily broad substrate scope from the monosulfinamide catalyst **3b**. Moreover, **5d** exhibited higher enantioselectivity than **3b** in most cases (see *ee* values in parentheses for **3b**[3]). Thus, the bissulfinamide catalyst **5d** proved to be, in general, a better catalyst

**Table 3.** Asymmetric reduction of various ketimines **1** with catalyst **5d**.[a]

| Entry | Imine | No. | X= | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 |  | **1a** | H | 91 | 96 (92) |
| 2 | | **1b** | *p*-$CF_3$ | 95 | 95 (92) |
| 3 | | **1c** | *p*-$NO_2$ | 90 | 93 (90) |
| 4 | | **1d** | *p*-Br | 92 | 95 (92) |
| 5 | | **1e** | *p*-OMe | 83 | 95 (93) |
| 6 |  | **1f** | H | 77 | 94 (90) |
| 7 | | **1g** | OMe | 80 | 93 (91) |
| 8 |  | **1h** | *c*-$C_6H_{11}$ | 84 | 75 (74) |
| 9 | | **1i** | *i*-Pr | 87 | 82 (79) |
| 10 |  | **1j** | *p*-Cl | 93 | 95 (92) |
| 11 | | **1k** | *p*-Me | 88 | 92 (91) |
| 12 | | **1l** | *p*-OMe | 92 | 92 (91) |
| 13 | | **1m** | *o*-OMe | 75 | 72 (88) |
| 14 |  | **1n** | *p*-$CF_3Ph$ | 90 | 83 (90) |
| 15 | | **1o** | 2-Np | 86 | 91 (88) |
| 16 |  | **1p** | | 84 | 92 (92) |
| 17 | | **1q** | Et | 86 | 94 (93) |
| 18 |  | **1r** | *n*-Pr | 87 | 91 (91) |
| 19 | | **1s** | *c*-Pr | 70 | 93 |
| 20 | | **1t** | *n*-Bu | 89 | 91 (93) |
| 21 | | **1u** | *i*-Bu | 82 | 93 (86) |

[a] Reactions were carried out with 10 mol% catalyst **5d** and with 2.0 equiv. of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of solvent at $-20\,^{\circ}C$ for 24 h.
[b] Isolated yield based on the imine.
[c] The *ee* values were determined using chiral HPLC; the data in parentheses are for catalyst **3b**.

than the monosulfinamide catalyst **3b** for the reduction of ketimines with $HSiCl_3$.

In summary, we have developed *S*-chiral bissulfinamides as highly efficient and enantioselective organocatalysts for the reduction of *N*-arylketimines with trichlorosilane.[8] The structurally simple bissulfinamide **5d** with a five-methylene tether not only inherited the excellent substrate generality from the monosulfinamide catalyst we have previously developed, but also exhibited further improved enantioselectivity. The development of other *S*-chiral new organocatalysts is under active investigation in this laboratory.

## Experimental Section

All starting materials were of the highest commercially available grade and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. $^1$H - and $^{13}$C NMR (300 or 600 and 75 or 150 MHz, respectively) spectra were recorded on Brucker AVANCE 600 and 300 spectrometers. Chemical shifts of $^1$H and $^{13}$C NMR spectra are reported in ppm (**δ**). ESI-MS were recorded on a BioTOF Q. HPLC analyses were performed with a Perkin-Elmer Series 200 UV/VIS detector and Series 200 pump. Chiralpak OD-H, AD-H and OJ-H columns were purchased from Daicel Chemical Industries, Ltd. All enantiomer ratios have been controlled by co-injections of the pure sample with the racemic substrates.

### General Procedure for the Synthesis of 5[7]

To a solution of *tert*-butanesulfinamide (242 mg, 2.0 mmol) in $CH_2Cl_2$ was added anhydrous $CuSO_4$ (640 mg, 4.0 mmol) followed by $OHC(CH_2)_{n-2}CHO$ (0.8 mmol). The mixture was stirred at room temperature for 24 h and was then filtered through a pad of Celite. The filter cake was washed well with $CH_2Cl_2$ and the filtrate was concentrated under vacuum. The residue was dissolved in MeOH (10 mL), and $NaBH_4$ (68 mg, 1.8 mmol) was introduced at 0 °C. The mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with acetone (2 mL). After the volatiles had been evaporated, EtOAc (50 mL) and saturated aqueous ammonia chloride (10 mL) were introduced. The organic layer was separated, washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexane : EtOAc = 1:1) to give the pure product.

**Compound 5a:** White solid, yield: 87%; $[\alpha]_D^{25}$: −43.1 (*c* 0.14, MeOH); mp 120.0–122.0 °C; $^1$HNMR (600 MHz, $CDCl_3$): $\delta = 1.24$ (s, 18H), 3.29 (m, 2H), 3.41 (m, 2H), 4.52 (brs, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta = 22.7$, 47.2, 5.9; ESI-HR-MS: $m/z = 291.1162$, calcd. for $(C_{10}H_{24}N_2O_2S_2 + Na)^+$: 291.1171.

**Compound 5b:** Yellowish oil, total yield: 28%; $[\alpha]_D^{25}$: −58.4 (*c* 0. 40, MeOH); $^1$HNMR (300 MHz, $CDCl_3$): $\delta =$ 1.22 (s, 18H), 1.88 (m, 2H), 3.28 (m, 4H), 3.89 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta = 22.7$, 31.9, 43.9, 55.7; ESI-HR-MS: $m/z = 305.1321$, calcd. for $(C_{11}H_{26}N_2O_2S_2 + Na)^+$: 305.1328.

**Compound 5c:** Yellowish oil, yield: 84%; $[\alpha]_D^{25}$: −16.2 (*c* 0.15, MeOH); $^1$H NMR (600 MHz, $CDCl_3$): $\delta = 1.21$ (s, 18H), 1.64 (m, 4H), 3.11 (m, 2H), 3.23 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta = 22.6$, 28.3, 45.4, 55.6; ESI-HR-MS: $m/z$ 319.1493, calcd. for $(C_{12}H_{28}N_2O_2S_2 + Na)^+$: 319.1484.

**Compound 5d:** Yellowish oil, yield: 87%; $[\alpha]_D^{25}$: −33.0 (*c* 0.19, MeOH); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (s, 18H), 1.35 (m, 2H), 1.54 (m, 4H), 3.03 (m, 2H), 3.13 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta = 22.6$, 23.7, 30.6, 45.5, 55.6; ESI-HR-MS: $m/z = 333.1642$, calcd. for $(C_{13}H_{30}N_2O_2S_2 + Na)^+$: 333.1641.

**Compound 5e:** Yellowish oil, yield: 77%; $[\alpha]_D^{25}$: −41.0 (*c* 0.15, MeOH); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 1.15$ (s, 18H), 1.29 (m, 4H), 1.51 (m, 4H), 2.98 (m, 2H), 3.14 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 22.5$, 26.2, 30.8, 45.5, 55.4; ESI-HR-MS: $m/z = 347.1806$, calcd. for $(C_{14}H_{32}N_2O_2S_2 + Na)^+$: 347.1803.

### General Procedure for the Synthesis of Imines

A mixture of $NaHCO_3$ (50 mmol), amine (10 mmol), ketone (10 mmol), and activated 4 Å molecular sieves (8.0 g) in anhydrous toluene (10 mL) was stirred at 80 °C for 12 h under an argon atmosphere, and was then filtered through celite. The filtrate was concentrated under vacuum. The crude product was subjected to distillation or recrystallization to give pure imine **1**.

### General Procedure for the Catalytic Reduction of Imines

Under an argon atmosphere, trichlorosilane (40 μL, 0.4 mmol) was added dropwise to a stirred solution of imine **1** (0.20 mmol), catalyst **5d** (6.2 mg, 0.02 mmol) and 2,6-lutidine (7 μL, 0.06 mmol) in anhydrous $CH_2Cl_2$ at −20 °C. The mixture was allowed to stir at the same temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with EtOAc. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$ and the solvents were evaporated. Purification by column chromatography (silica gel, hexane/EtOAc) afforded pure amine **2**. The *ee* values were determined using established HPLC techniques with chiral stationary phases.

## Acknowledgements

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[6] For selected recent examples of highly enantioselective reduction of ketimines, see: a) Y. Wang, S. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729; b) Q. Yang, J. G. Deng, X. Zhang, *Angew. Chem.* **2006**, *118*, 3916; *Angew. Chem. Int. Ed.* **2006**, *45*, 3832; c) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360; d) S. Zhu, J. Xie, Y. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886; e) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; f) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; g) B.-M. Park, S. Mun, J. Yun, *Adv. Synth. Catal.* **2006**, *348*, 1029; h) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

[7] This general procedure was found to be ineffective for the synthesis of **5c**, for which a different multi-step synthetic procedure was developed (see the Supporting Information).

[8] It should be noted that the present catalyst system is not effective for the reduction of the following two different types of keimines under the optimal conditions:


(70% yield, 45% *ee*) (inactive).

  