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L-Valine derived chiral *N*-sulfinamides as effective organocatalysts for the asymmetric hydrosilylation of *N*-alkyl and *N*-aryl protected ketimines†

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L-Valine derived *N*-sulfinamides have been developed as efficient enantioselective Lewis basic organocatalysts for the asymmetric reduction of *N*-aryl and *N*-alkyl ketimines with trichlorosilane. Catalyst **3c** afforded up to 99% yield and 96% ee in the reduction of *N*-alkyl ketimines and up to 98% yield and 98% ee in the reduction of *N*-aryl ketimines.

Introduction

Chiral amines are fundamentally important structural components of biologically important compounds such as natural products and agrochemicals. Organocatalyst catalyzed enantioselective reduction of prochiral imines or enamines with trichlorosilane ($HSiCl_3$) represents one of the most important methods for preparing chiral amines.[1] Formamide,[2] picolinamide[3] and pyridyl-oxazoline[4] derivatives have been developed as efficient Lewis base organocatalysts for the asymmetric hydrosilylation of imines and enamines with trichlorosilane ($HSiCl_3$). In our earlier study, we found that L-pipecolinic acid[5] and L-piperazine-2-carboxylic acid[6] derived *N*-formamides have an unprecedented substrate scope and high enantioselectivities for the hydrosilylation of *N*-aryl ketimines. However, none of these *N*-formamide catalysts are tolerant to *N*-alkyl ketimines as a substrate for high enantioselectivity.

Chiral sulfoxides have been well established as efficient and versatile stereocontrollers and have been extensively used as the chirality source of chiral auxiliaries and ligands.[7] However, the development of chiral sulfoxides as Lewis base organocatalysts has been rarely explored. We reported the first example of chiral sulfoxides to activate trichlorosilane in the asymmetric reduction of *N*-aryl ketimines with high yield and enantioselectivity.[8] The *S*-chiral center in these catalysts not only plays a crucial role similar to the carboxamide groups of *N*-formamide catalysts as a Lewis base for the activation of $HSiCl_3$, but also serves as a source of chirality that the carboxamide group lacks for the asymmetric reduction. Encouraged by this result, we thus became interested in incorporating the dual functional chiral sulfinamide group(s) into an amino acid framework in the hope of obtaining new organocatalysts that have a broad substrate scope and high yield and enantioselectivity in the asymmetric hydrosilylation of ketimines.

We first prepared a set of catalysts **1a–f** *via* incorporating the *tert*-butanesulfinamide group into L-proline amide derivatives. For a wide range of *N*-alkyl ketimines, high yields and enantioselectivities could be obtained when these catalysts were used in the asymmetric hydrosilylation reaction under mild conditions.[9] Additionally, these catalysts could also be used in the enantioselective hydrosilylation of a broad range of *N*-alkyl β-enamino esters to prepare *N*-alkyl β-amino acid derivatives with high yields and enantioselectivities.[10] Recently, we found that L-phenyl alanine derived new chiral sulfinamides **2b** could also be used as an efficient and highly enantioselective catalyst for activating trichlorosilane in the asymmetric reduction of 3-aryl-1,4-benzooxazines to prepare the corresponding chiral 3-aryl-3,4-dihydro-2*H*-1,4-benzooxazine products (Fig. 1).[11]

Given the novel performance of L-proline and L-phenyl alanine derived *N*-sulfinamides in the asymmetric reduction of imines and enamines with trichlorosilane, it is desirable to search other types of amino acid derived *N*-sulfinamides for a new catalyst that could be used in the asymmetric hydrosilylation of more practical substrates. As part of our continuing efforts in this field, we have successfully developed catalysts

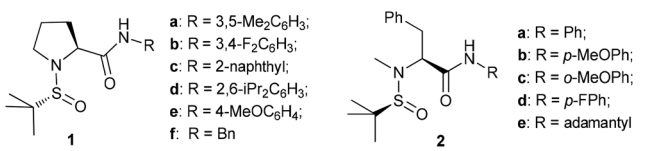

Fig. 1 Previously reported catalysts.

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†CCDC 1003514 and 1003515. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01257g

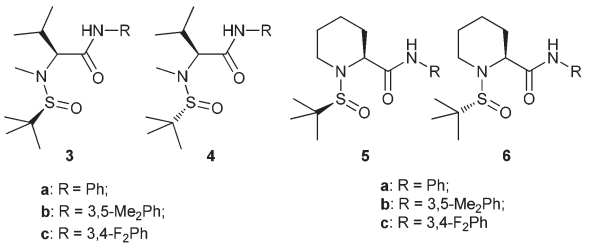


Fig. 2 Catalysts evaluated in this study.

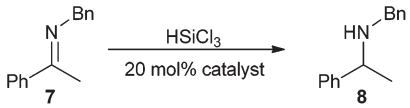
3–6 derived from L-valine and L-pipecolinic acid that could be used in the asymmetric hydrosilylation of both *N*-alkyl and *N*-aryl ketimines with high yields and enantioselectivities. Herein, we wish to report the results (Fig. 2).

Results and discussion

Kočovský and coworkers proved that the *N*-methyl L-valine derived *N*-formamide catalysts are superior to those prepared from proline in the catalytic reduction of imines with trichlorosilane. However, they reported that the *N*-methyl L-valine derived *tert*-butanesulfinamide catalyst is less efficient for activating $HSiCl_3$ in the asymmetric reduction of ketimines, and no more than 50% ee could be obtained.[12] We thought that this problem may be caused by the mismatch between the *S*-chiral center and the *C*-chiral center of the catalyst since catalysts **1** and **2** show dramatically different performance in enantioselectivity when the *R*/*S* chiral *tert*-butanesulfinamide group was incorporated into the amino acid backbones, respectively. In order to verify our hypotheses, catalysts **3a** and **4a** have been prepared according to a reported procedure. We observed that catalyst **3a** exhibited significantly higher reactivity and selectivity than **4a** in the reduction of *N*-benzyl ketimine **7a** with $HSiCl_3$. This observation prompted us to prepare compounds **3–6**. Starting from L-valine and L-pipecolinic acid, compounds **3b**, **3c**, **5a–c** and their diastereomers **4b**, **4c** and **6a–c** were easily synthesized as a mixture which could be separated by column chromatography. The stereochemistry of the chiral sulfur centers in **3c** and **4c** was determined by single-crystal X-ray diffraction analysis.[13] For the other catalysts, the stereochemistry on the sulphur atom was established from a clear analogy of their ^1H NMR profiles to those of **3c** and **4c**.

With the catalysts in hand, their ability to catalyse the asymmetric hydrosilylation of ketimines was evaluated. We found that L-pipecolinic acid derivatives **5** and **6** showed higher stereoselectivity and activity than L-valine derivatives **3** and **4** in the testing reaction. Up to 91% yield and 90% ee could be obtained when catalyst **5b** was used in the reduction of imine **7a** in the presence of 20 mol% catalyst in dichloromethane at −20 °C for 24 h (entry 9, Table 1). Interestingly, 88% ee could be reached for catalyst **3c** when the reaction solvent was changed from dichloromethane to toluene under the testing reaction conditions (entry 14, Table 1). The ee of the reaction could be further increased to 95% by decreasing the reaction temperature to −40 °C (entry 19, Table 1). In contrast, for catalyst **5a**, the ee fell to 23% from 89% when the solvent was changed from dichloromethane to toluene under the testing reaction conditions (entries 7 and 20, Table 1). The ee decreases to 71% as the reaction temperature goes down to −40 °C in dichloromethane (entry 22, Table 1). The obvious difference in enantioselectivity between catalysts **3c** and **5a** under identical reaction conditions indicates the pivotal role of the amino acid framework in the transition state to furnish the asymmetric reaction of imine **7a**.

Table 1 Asymmetric reduction of ketimine **7a**[a]

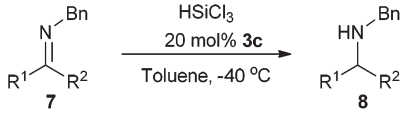


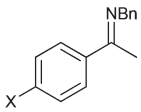
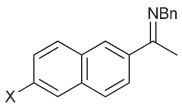
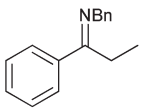
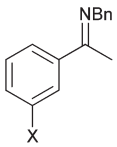
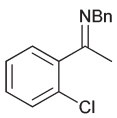
Entry	Catalyst	Solvent	T [°C]	Yield[b] [%]	ee[c] [%]
1	**3a**	CH_2Cl_2	−20	95	75
2	**4a**	CH_2Cl_2	−20	62	15
3	**3b**	CH_2Cl_2	−20	70	79
4	**4b**	CH_2Cl_2	−20	60	9
5	**3c**	CH_2Cl_2	−20	80	82
6	**4c**	CH_2Cl_2	−20	80	5
7	**5a**	CH_2Cl_2	−20	91	89
8	**6a**	CH_2Cl_2	−20	80	87
9	**5b**	CH_2Cl_2	−20	91	90
10	**6b**	CH_2Cl_2	−20	90	80
11	**5c**	CH_2Cl_2	−20	93	83
12	**6c**	CH_2Cl_2	−20	85	81
13	**3c**	THF	−20	50	52
14	**3c**	Toluene	−20	80	88
15	**3c**	$CHCl_3$	−20	45	85
16	**3c**	DCE	−20	50	83
17	**3c**	CCl_4	−20	80	90
18	**7c**	CH_3CN	−20	65	65
19	**3c**	Toluene	−40	80	93
20	**5a**	Toluene	−20	65	23
21	**5a**	CCl_4	−20	40	15
22	**5a**	CH_2Cl_2	−40	70	71
23[d]	**3c**	Toluene	−40	95	93
24[e]	**3c**	Toluene	−40	60	78

[a] Reactions were carried out with 2.0 equiv. of $HSiCl_3$ on a 0.1 mmol scale in 0.5 mL of solvent for 24 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] The reaction time is 48 h. [e] The catalyst loading is 10 mol%.

With the optimized reaction conditions in hand, the substrate scope of catalyst **3c** was explored. A wide range of aromatic *N*-benzyl ketimines (**7a–n**) were reduced with $HSiCl_3$ in the presence of 20 mol% catalyst **3c** in toluene at −40 °C for 48 h. As illustrated in Table 2, all the tested methyl ketimines **7** could be reduced to the corresponding products. Both the electron rich and electron deficient aromatic methyl ketimines **7a–h** reacted well to give the corresponding products **8** in moderate to good yields and high enantioselectivities (40–95% yield, 90–96% ee). However, for some substrates higher enantioselectivities and yields could be obtained on switching the solvent from toluene to dichloromethane. The steric hindrance of the aromatic groups of the ketimines played a pivotal role in the reaction activity; only 20–30% yields could be obtained when substrates **7i** and **7j** were reduced using the

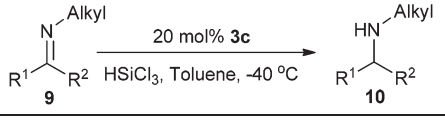
Table 2 Asymmetric reduction of *N*-Bn ketimines **7** with catalyst **3c**[a]

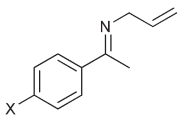
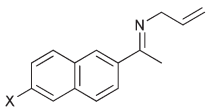
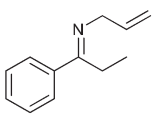
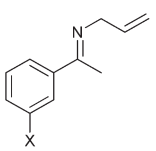
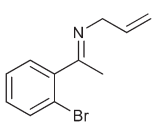
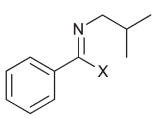


Entry	Ketimine		X =	Yield[b] [%]	ee[c] [%]
1		**7a**	H	95	93
2		**7b**	Me	60	95
3[d]		**7c**	Cl	85	93
4[d]		**7d**	Br	82	93
5		**7e**	OMe	40	92
6[d]		**7f**	CF_3	80	92
7		**7g**	F	80	94
8[d]		**7h**	NO_2	80	93
9		**7i**	H	20	91
10		**7j**	OMe	30	92
11		**7k**	—	89	77
12		**7l**	Br	85	90
13		**7m**	Cl	50	84
14		**7n**	—	20	57

[a] Reactions were carried out with 20 mol% catalyst **3c** and with 2.0 equiv. of $HSiCl_3$ on a 0.1 mmol scale in 0.5 mL of solvent at −40 °C for 48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] Reaction was carried out in dichloromethane.

Table 3 Asymmetric reduction of *N*-alkyl ketimines **9** with catalyst **3c**[a]



Entry	Ketimine		X =	Yield[b] [%]	ee[c] [%]
1		**9a**	H	99	94
2		**9b**	Me	90	95
3		**9c**	Cl	84	90
4[d]		**9d**	Br	84	95
5		**9e**	OMe	91	93
6		**9f**	CF_3	60	93
7		**9g**	F	83	93
8		**9h**	NO_2	92	92
9		**9i**	H	50	90
10		**9j**	OMe	85	89
11		**9k**	—	55	77
12		**9l**	Br	92	90
13		**9m**	Cl	90	89
14		**9n**	—	90	71
15		**9o**	Me	85	94
16		**9p**	Et	60	79

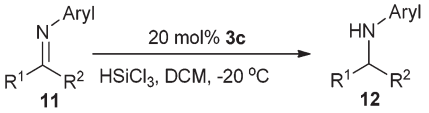
[a] Reactions were carried out with 20 mol% catalyst **3c** and with 2.0 equiv. of $HSiCl_3$ on a 0.1 mmol scale in 0.5 mL of solvent at −40 °C for 48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] Reaction was carried out in dichloromethane.

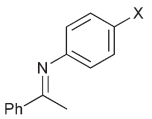
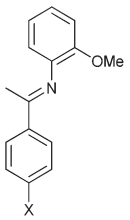
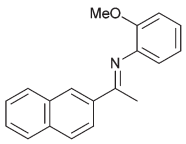
current system. The stereoselectivity of the reaction is sensitive to both the position of the substituents on the aromatic group and the steric hindrance of R^2 (entries 9–14, Table 2).

Additionally, we found that the aforementioned reduction system could also be used in the asymmetric hydrosilylation of other aromatic *N*-alkyl ketimines **9**. Good to high yields and enantioselectivities could be obtained when *N*-allyl ketimines were reduced and the reaction activity and the stereoselectivity were not sensitive to the electronic properties of the substitute group in the aromatic ring (entries 1–8, Table 3). Toluene was the appropriate solvent for most of the substrates. Only one substrate could afford higher ee on switching the solvent from toluene to dichloromethane (entry 4, Table 3). Again we found that the steric hindrance of the R^1 and R^2 groups was important both for the reactivity and the stereoselectivity of the reaction. Increasing the steric hindrance of R^1 or R^2 would cause a lower yield and ee.

Moreover, the catalyst **3c** could be used in the reduction of *N*-aryl ketimines with high enantioselectivities and moderate to good yields. In the testing reduction of **11a** in the presence of 20 mol% catalyst **3c** at −20 °C, 96% ee could be achieved when dichloromethane was used as the reaction solvent. However, the ee dropped to 93% when toluene was used (entries 1 and 2, Table 2). Thus a broad range of *N*-aryl ketimines were reduced with $HSiCl_3$ in dichloromethane. As shown in Table 4, ketimines with relatively bulky R, including Et, ^{n}Pr were all found to be good substrates for catalyst **3c**, affording excellent enantioselectivities (entries 2–4, Table 4). More significantly, ketimines **11d–f** with both electron rich and electron deficient anilines reacted well to give the desired products in moderate yields and high enantioselectivities (entries 5–7, Table 4). Furthermore, 95–98% ee could be achieved for those ketimines derived from *o*-methoxyaniline (entries 8–14, Table 4). To the best of our knowledge, such a

Table 4 Asymmetric reduction of *N*-aryl ketimines **11** with catalyst **3c**[a]



Entry	Ketimine		X =	Yield[b] [%]	ee[c] [%]
1[d]		**11a**	Me	92	93
2		**11a**	Me	90	96
3		**11b**	Et	40	96
4		**11c**	*n*-Pr	40	95
5		**11d**	*p*-NO_2	56	92
6		**11e**	*p*-OMe	95	96
7		**11f**	*p*-Cl	60	96
8		**11g**	H	98	97
9		**11h**	*p*-Cl	90	97
10		**11i**	*p*-NO_2	75	95
11		**11j**	*p*-OMe	45	98
12		**11k**	*p*-F	92	97
13		**11l**	*p*-Me	43	96
14		**11m**	—	62	97

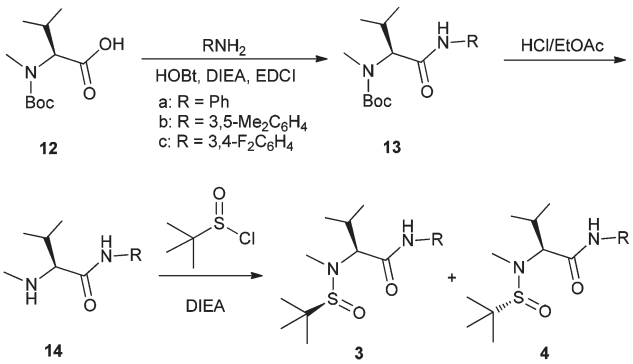
[a] Reactions were carried out with 20 mol% catalyst **3c** and with 2.0 equiv. of $HSiCl_3$ on a 0.1 mmol scale in 0.5 mL of solvent at −20 °C for 48 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] Reaction was carried out in toluene.

substrate profile has not been reported previously in the asymmetric hydrosilylation of N-protected ketimines.

Experimental section

To a stirred solution of *N*-Me-*N*-Boc-L-valine (2.31 g, 10.0 mmol) in DCM (50 mL) were added aniline (1.1 mL, 12.0 mmol), HOBt (1.62 g, 12.0 mmol), DIEA (4.0 mL, 24.0 mmol), and EDCI (2.35 g, 12.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, and then concentrated under vacuum. The residue was diluted with EtOAc (200 mL), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$ (15 mL) and brine, and then dried over anhydrous $MgSO_4$. Solvents were evaporated under vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 10 : 1) to give compound **13**.

Compound **13** (2.30 g, 7.2 mmol) was charged in a 50 mL round flask. A solution of HCl–EtOAc (4 mol L^{-1}, 10 mL) was then added. The mixture was stirred at room temperature until **13** disappeared completely. The volatiles were removed under vacuum. The residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give compound **14**.



Scheme 1 General procedure for the synthesis of **3** and **4**.

To a stirred solution of *tert*-butyl sulfinyl chloride[14] (3.16 g, 22.5 mmol) in THF (80 mL) were added triethylamine (3.1 mL, 22.5 mmol) and **14** (1.49 g, 6.8 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, and then concentrated under vacuum. The residue was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4. Solvents were evaporated under vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 5 : 1) to give pure **3** and **4** (Scheme 1).

(**3a**): White solid; yield: 25%; $[\alpha]_D^{20} = -50$ (c = 0.10, $CHCl_3$); mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.02 (s, 1H), 7.57 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 7.9 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 3.70 (d, J = 8.0 Hz, 1H), 2.68 (s, 3H), 2.5–2.45 (m, 1H), l.30 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.1, 138.0, 128.8, 124.2, 119.8, 75.5, 59.7, 28.8, 28.5, 24.3, 21.1, 19.8; ESI HRMS exact mass calcd for $(C_{16}H_{26}N_2O_2S_1 + Na)^+$ requires m/z 333.1607, found m/z 333.1611.

(**4a**): White solid; yield: 30%; $[\alpha]_D^{20} = -94$ (c = 0.10, $CHCl_3$); mp 205–208 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.41 (s, 1H), 7.61–7.57 (m, 2H), 7.33–7.26 (m, 2H), 7.11–7.06 (m, 1H), 3.64 (d, J = 10.4 Hz, 1H), 2.77 (s, 3H), 2.58–2.50 (m, 1H), l.26 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.0, 138.1, 128.9, 128.8, 124.0, 119.6, 119.5, 59.2, 26.5, 22.8, 19.9, 19.5; ESI HRMS exact mass calcd for $(C_{16}H_{26}N_2O_2S_1 + Na)^+$ requires m/z 333.1607, found m/z 333.1595.

(**3b**): White solid; yield: 32%; $[\alpha]_D^{20} = -65$ (c = 0.10, $CHCl_3$); mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.82 (s, 1H), 7.24 (s, 2H), 6.73 (s, 1H), 3.73 (d, J = 7.6 Hz, 1H), 2.67 (s, 3H), 2.53–2.46 (m, 1H), 2.28 (s, 6H), 1.26 (s, 9H), l.07 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.1, 138.5, 137.9, 125.9, 117.4, 75.4, 59.7, 28.9, 28.6, 24.3, 21.3, 21.1, 19.8; ESI HRMS exact mass calcd for $(C_{18}H_{30}N_2O_2S_1 + Na)^+$ requires m/z 361.1920, found m/z 361.1904.

(**4b**): White solid; yield: 35%; $[\alpha]_D^{20} = -103$ (c = 0.10, $CHCl_3$); mp 181–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.27 (s, 1H), 7.24 (s, 2H), 6.73 (s, 1H), 3.61 (d, J = 10.3 Hz, 1H), 2.76

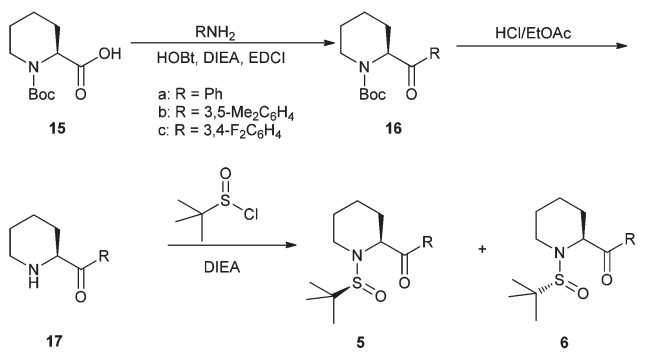
(s, 3H), 2.57–2.49 (m, 1H), 2.28 (s, 6H), 1.26 (s, 9H), l.07 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.9, 138.6, 138.0, 125.7, 117.2, 66.2, 59.2, 26.6, 22.8, 21.3, 20.5, 20.0; ESI HRMS exact mass calcd for $(C_{18}H_{30}N_2O_2S_1 + Na)^+$ requires m/z 361.1920, found m/z 361.1904.

(**3c**): White solid; yield: 30%; $[\alpha]_D^{20}$ = −71 (c = 0.10, $CHCl_3$); mp 154–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.45 (s, 1H), 7.65–7.63 (m, 1H), 7.18–7.13 (m, 1H), 7.00–6.97 (m, 1H), 3.71–3.67 (m, 1H), 2.69 (s, 3H), 2.48–2.41 (m, 1H), 1.34 (s, 9H), l.05–1.00 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.1, 149.7 (dd, J = 244, 13 Hz), 146.7 (dd, J = 243.1, 12.7 Hz), 134.8, 116.7 (d, J = 17.9 Hz), 115.1, 109.1 (d, J = 21.8 Hz), 75.8, 59.8, 28.5, 28.2, 24.5, 20.7, 19.8; ESI HRMS exact mass calcd for $(C_{16}H_{24}F_2N_2O_2S_1 + Na)^+$ requires m/z 369.1419, found m/z 369.1410.

(**4c**): White solid; yield: 33%; $[\alpha]_D^{20}$ = −108 (c = 0.10, $CHCl_3$); mp 176–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.76 (s, 1H), 7.72–7.65 (m, 1H), 7.14–7.03 (m, 2H), 3.64 (d, J = 10.4 Hz, 1H), 2.76 (s, 3H), 2.56–2.48 (m, 1H), 1.26 (s, 9H), l.07 (d, J = 7.0 Hz, 3H), l.02 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.0, 150.1 (dd, J = 244.5, 13.0 Hz), 146.7 (dd, J = 243.1, 12.7 Hz), 134.8, 117.0 (d, J = 17.9 Hz), 115.1, 109.1 (d, J = 21.5 Hz), 65.5, 59.3, 35.3, 26.5, 24.3, 22.7, 20.6, 19.8; ESI HRMS exact mass calcd for $(C_{16}H_{24}F_2N_2O_2S_1 + Na)^+$ requires m/z 369.1419, found m/z 369.1409.

(**5a**): White solid; yield: 25%; $[\alpha]_D^{20}$ = −223 (c = 0.10, $CHCl_3$); mp 134–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.1 (s, 1H), 7.63–7.60 (m, 2H), 7.31–7.26 (m, 2H), 7.07–7.03 (m, 1H), 4.36 (s, 1H), 3.27–3.16 (m, 2H), 2.42–2.38 (m, 1H), 1.88–1.56 (m, 5H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.5, 138.5, 128.7, 123.6, 119.1, 59.0, 56.1, 48.9, 25.6, 25.5, 23.4, 20.7; ESI HRMS exact mass calcd for $(C_{16}H_{24}N_2O_2S_1 + Na)^+$ requires m/z 331.1451, found m/z 331.1457 (Scheme 2).

(**6a**): White solid; yield: 40%; $[\alpha]_D^{20}$ = −66 (c = 0.10, $CHCl_3$); mp 120–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.12 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.56 Hz, 2H), 7.06 (t, J = 7.38 Hz, 1H), 4.38–4.37 (m, 1H), 3.29–3.21 (m, 2H), 2.39 (m, 1H), 1.78–1.54 (m, 7H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.6, 138.6, 128.8, 123.7, 119.2, 59.0, 56.1, 48.9, 25.7, 25.5, 23.4, 20.7; ESI HRMS exact mass calcd for $(C_{16}H_{24}N_2O_2S_1 + Na)^+$ requires m/z 331.1451, found m/z 331.1434.



Scheme 2 General procedure for the synthesis of **5** and **6**.

(**5b**): White solid; yield: 36%; $[\alpha]_D^{20}$ = −170 (c = 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.02 (s, 1H), 7.28 (s, 2H), 6.72 (s, 1H), 4.37–4.35 (m, 1H), 3.25–3.20 (m, 2H), 2.43–2.22 (m, 7H), 1.90–1.51 (m, 5H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.4, 138.5, 138.4, 125.5, 116.2, 59.0, 56.1, 48.9, 25.7, 25.5, 23.4, 21.3, 20.7; ESI HRMS exact mass calcd for $(C_{18}H_{28}N_2O_2S_1 + Na)^+$ requires m/z 359.1761, found m/z 359.1775.

(**6b**): White solid; yield: 32%; $[\alpha]_D^{20}$ = −72 (c = 0.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.94 (s, 1H), 7.28 (s, 2H), 6.76 (s, 1H), 4.19–4.17 (m, 1H), 3.46–3.43 (m, 1H), 3.06–2.97 (m, 1H), 2.56–2.52 (m, 1H), 2.30 (s, 6H), 1.76–1.56 (m, 2H), 1.39–1.19 (m, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.8, 138.6, 137.7, 126.0, 117.1, 60.2, 58.8, 44.5, 26.8, 24.6, 23.3, 21.3, 20.6; ESI HRMS exact mass calcd for $(C_{18}H_{28}N_2O_2S_1 + Na)^+$ requires m/z 359.1764, found m/z 359.1766.

(**5c**): White solid; yield: 35%; $[\alpha]_D^{20}$ = −102 (c = 0.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.55 (s, 1H), 7.77–7.70 (m, 1H), 7.18–7.04 (m, 2H), 4.38–4.36 (m, 1H), 3.32–3.14 (m, 2H), 2.41–2.36 (m, 1H), 1.88–1.52 (m, 5H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.7, 150.0 (dd, J = 244.6, 13.0 Hz), 146.4 (dd, J = 242.7, 12.8 Hz), 135.2, 116.9 (d, J = 17.9 Hz), 114.7, 108.7 (d, J = 21.7 Hz), 59.1, 55.8, 49.4, 25.7, 25.4, 23.4, 20.6; ESI HRMS exact mass calcd for $(C_{16}H_{22}F_2N_2O_2S_1 + Na)^+$ requires m/z 367.1262, found m/z 367.1262.

(**6c**): White solid; yield: 30%; $[\alpha]_D^{20}$ = −99 (c = 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.37 (s, 1H), 7.81–7.74 (m, 1H), 7.19–7.07 (m, 2H), 4.19–4.18 (m, 1H), 3.46–3.45 (m, 1H), 3.01–2.92 (m, 1H), 2.55–2.51 (m, 1H), 1.78–1.52 (m, 5H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.2, 149.9(dd, J = 245.9, 13.1 Hz), 146.9 (dd, J = 244.5, 11.8 Hz), 135.2, 117.0 (d, J = 17.9 Hz), 115.1, 109.2 (d, J = 21.8 Hz), 61.1, 58.9, 43.9, 27.1, 24.6, 23.5, 22.3, 20.6; ESI HRMS exact mass calcd for $(C_{16}H_{22}F_2N_2O_2S_1 + Na)^+$ requires m/z 367.1262, found m/z 367.1264.

General procedure for the catalytic reduction of imines

Under an argon atmosphere, trichlorosilane (20 μL, 0.24 mmol) was added dropwise to a stirred solution of imines **7**, **9** and **11** (0.10 mmol), catalyst **3c** (3.22 mg, 0.01 mmol) in anhydrous toluene or DCM at −40 or −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 was extracted with EtOAc. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$ and the solvents were evaporated under vacuum. Purification by column chromatography (silica gel, hexane–EtOAc or DCM–MeOH) afforded pure amines **8**, **10** and **12**. The ee values were determined using established HPLC techniques with chiral stationary phases.

General procedure for the acylation of 10

To a stirred solution of amine **10** in dichloromethane (2 mL) was added an acylating reagent (2.0 equiv.) at 0 °C. The mixture was stirred at room temperature for 10 h, and was then concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 20 : 1) to give the pure acylated amine, which was used for chiral HPLC analyses.

Conclusions

In summary, we have developed a highly efficient Lewis basic organocatalyst **3c** for the enantioselective reduction of both *N*-alkyl and *N*-aryl ketimines with trichlorosilane in high enantioselectivity and moderate to good yields. The broad substrate scope of this catalyst is unprecedented in asymmetric imine reduction. Further work is in progress to clarify the mechanism of the transformation and explore the full application scope of the present catalyst system.

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