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A Highly Enantioselective Organocatalytic Method for Reduction of Aromatic *N*-Alkyl Ketimines

Chao Wang,[a] Xinjun Wu,[a, b] Li Zhou,[a] and Jian Sun*[a]

Chiral amines are fundamentally important structural components of biologically important compounds such as natural products, drugs, and agrochemicals. Catalytic asymmetric reduction of imines is one of the most efficient methods for their preparation and has long been among the central topics in asymmetric synthesis.[1] However, thus far only limited success has been observed in the development of this transformation, in contrast to the extraordinary advances that have been made in catalytic asymmetric reduction of olefins and ketones. The currently available enantioselective catalytic methods for the reduction of imines mainly rely on chiral transition-metal catalysts, which often require elevated pressures and/or additives to afford high yields and *ee* values.[2,3] Recently, the development of organocatalytic methods for asymmetric reduction of imines has attracted a great deal of attention due to the environmental benignancy and the ease of operation compared with the transition-metal catalyzed reactions.[4–8] A number of effective chiral organocatalytic systems have emerged for the hydrogen transfer reduction of ketimines using either Hantzsch esters[4] or trichlorosilane ($HSiCl_3$) as the reducing agent.[5–8] Several such catalyst systems proved to be highly efficient and enantioselective for the reduction of *N*-aryl ketimines,[4,6,7] of which, however, none is tolerant to *N*-alkyl ketimines as substrate for high enantioselectivity. This substrate bias undoubtedly limits their applications since the aryl group (phenyl or substituted phenyl) on the nitrogen atom of the resulting amine in many cases needs to be removed or replaced with alkyl group(s), which is nontrivial. Herein, we present the first example of organocatalytic methods that allow for highly enantioselective reduction of a wide variety of *N*-alkyl ketimines.

Recently, Kocovsky and co-workers[6] and we[7a–d] have successfully developed several α-amino-acid-derived diamides as highly efficient and enantioselective Lewis base organocatalysts for the reduction of a broad range of *N*-aryl ketimines by $HSiCl_3$. Besides the *C*-chiral amino acid backbone, the key structural elements of these catalysts for their high efficacies are the *N*-formyl group and the aromatic or the well-elaborated non-aromatic carboxamide group (see the general structure in Figure 1), which function cooperatively as Lewis bases for the activation of $HSiCl_3$.

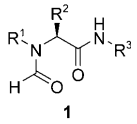

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Figure 1. General structure of alpha amino acid derived Lewis basic diamide organocatalysts reported previously.

We recently have also developed *S*-chiral monosulfinamide **2**[7e] and bissulfinamide **3**[7f] (Figure 2) as highly efficient novel Lewis base organocatalysts for the reduction of *N*-aryl ketimines by $HSiCl_3$. The *S*-chiral sulfinamide group(s) in these catalysts not only plays a crucial role similar to the carboxamide groups of **1** as Lewis base for the activation of $HSiCl_3$, but also serves as a source of chirality that the carboxamide group lacks for the asymmetric induction. We thus became interested in designing new Lewis base organocatalysts such as **4** and **5** (Figure 3) that incorporate the dual functional *S*-chiral sulfinamide group into a *C*-chiral α-amino acid framework bearing a Lewis basic carboxamide functionality in the hope of achieving new catalytic reactivity and selectivity.

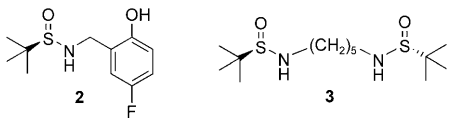

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Figure 2. *S*-chiral sulfinamide organocatalysts we previously developed.

[a] C. Wang, X. Wu, L. Zhou, Prof. Dr. J. Sun
Natural Products Research Center
Chengdu Institute of Biology
Chinese Academy of Sciences, Chengdu, 610041 (China)
Fax: (+86) 28-85222753
E-mail: sunjian@cib.ac.cn

[b] X. Wu
Chengdu Institute of Organic Chemistry
Chinese Academy of Sciences
Chengdu, 610041 (China)

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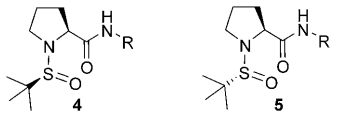


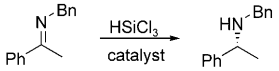
Figure 3. Catalysts evaluated in this study.

Starting from L-proline, compounds **4a** and **4b** and their diastereomers **5a** and **5b** were easily synthesized as a mixture at a diastereomeric ratio close to 1:1 and purified by column chromatography (see Supporting Information for the experimental details and analytic data). The stereochemistry of the chiral sulfur centers in **4a** and **5a** was determined by single-crystal x-ray diffraction analysis.[9] For **4b** and **5b**, the stereochemistry on the sulfur atom was established by a clear analogy of their ^{1}H NMR profiles to those of **4a** and **5a**.

Initial attempts to evaluate **4a** and **5a** as Lewis basic catalysts (20 mol%) for the reduction of *N*-benzyl ketimine **6a** by $HSiCl_3$ in toluene at −20 °C gave very good results: the desired amine **7a** was obtained in high yield in the presence of both diastereomeric catalysts in 24 h (entries 1 and 2, Table 1); catalyst **5a** with an *R*-configuration on the sulfur atom afforded a high *ee* up to 97%. Interestingly, a dramatically lower *ee* was obtained with catalyst **4a** bearing an *S*-configured sulfur atom, suggesting that a stereochemistry match between the chiral carbon and sulfur centers is critical for the stereocontrol in the course of asymmetric induction.

Replacement of the electron-rich 3,5-dimethylphenyl group in **4a** and **5a** with electron-deficient 3,4-difluorophenyl group in **4b** and **5b** had some negative effects on the reactivity (entries 3 and 4). Moreover, this also caused a slight decrease in the enantioselectivity of **5b** compared to **5a** (entry 4 vs 2).

Table 1. Asymmetric reduction of ketimine **6a** under various conditions.[a]



6a **7a**

Entry	Catalyst (mol%)[b]	Solvent	*T* [°C]	Yield [%][c]	*ee* [%][d,e]
1	**4a** (20)	toluene	−20	95	22
2	**5a** (20)	toluene	−20	96	97
3	**4b** (20)	toluene	−20	80	37
4	**5b** (20)	toluene	−20	86	94
5	**5a** (20)	CH_2Cl_2	−20	76	22
6	**5a** (20)	$CHCl_3$	−20	55	32
7	**5a** (20)	$ClCH_2CH_2Cl$	−20	90	47
8	**5a** (20)	THF	−20	91	55
9	**5a** (20)	CCl_4	−20	93	97
10	**5a** (10)	toluene	−20	95	96
11	**5a** (5)	toluene	−20	95	92
12	**5a** (10)	toluene	−40	90	88
13	**5a** (10)	toluene	0	98	96
14	**5a** (10)	CCl_4	0	90	97

[a] Reactions were carried out on a 0.1 mmol scale with 2.0 equiv of $HSiCl_3$ in 0.5 mL of solvent for 24 h. [b] The molar percentage is based on imine. [c] Isolated yield based on imine. [d] The *ee* values were determined using chiral HPLC. [e] Product **7a** was *R* configured in all cases, as revealed by comparison of the optical rotation with the literature data.

Astonishing solvent effects were observed with the present catalytic system. When toluene was replaced with either dichloromethane or chloroform, which are the best solvents for the previously reported Lewis base catalysts for similar transformations,[5–8] a dramatic decrease in both reactivity and enantioselectivity was observed in the **5a**-catalyzed reduction (entries 5 and 6). Interestingly, CCl_4 proved to be as an excellent solvent as toluene in terms of reactivity and enantioselectivity (entry 9).

When the catalyst loading of **5a** was reduced from 20 to 10 mol%, only a marginal effect on either the reactivity or enantioselectivity (entry 10 vs 2) was observed, whereas further lowering of the catalyst loading to 5 mol% led to a decrease of the enantioselectivity from 96 to 92% *ee* (entry 11 vs 10). A decrease of the enantioselectivity from 96 to 88% *ee* was observed when the reaction temperature was lowered from −20 to −40 °C (entry 12 vs 10). When the reaction was performed at 0 °C, a more practical and preferable reaction temperature, excellent reactivity and enantioselectivity in both toluene and CCl_4 remained (entries 13 and 14).

After the reaction conditions had been optimized, we set out to examine the substrate spectrum of the present catalyst system. A wide variety of aromatic *N*-alkyl ketimines (**6a**–**x**) was reduced in the presence of catalyst **5a** (Table 2). Generally, the desired amine were obtained in high yields and excellent enantioselectivities with toluene as the solvent (method A).[10] In particular, *ee* values up to 99.6% were achieved in the reduction of the *p*-nitrophenyl methyl ketone derived *N*-benzyl imine **6h** (entry 8). To the best of our knowledge, this is the highest enantioselectivity achieved for an organocatalytic reduction of imines.

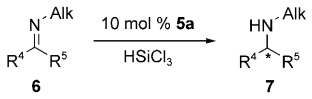
Although a few substrates gave only moderate results (entries 10, 12, and 20–22), change of the solvent to CCl_4 (method B) still gave high enantioselectivities. It should be noted that the *ee* values of the amine products do not correspond to the *E*/*Z* ratio of the starting ketimines,[11] for which we have no explanation at present.

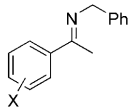
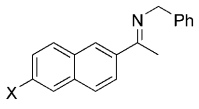
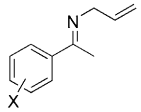
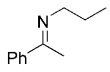
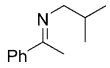
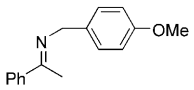
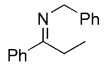
In summary, a highly enantioselective catalytic method has been developed for the reduction of aromatic *N*-alkyl ketimines by trichlorosilane under mild conditions using the newly designed Lewis base organocatalyst **5a** that incorporates *C*- and *S*-chirality. Excellent enantioselectivities of up to 99.6% *ee* and high yields were obtained for a wide range of substrates. Further work is in progress to clarify the mechanism of the transformation and explore the full application scope of the present catalyst system.

Experimental Section

General procedure for the asymmetric reduction: Under an argon atmosphere, trichlorosilane (20 μL, 0.20 mmol) was added dropwise to a stirred solution of imine **6** (0.10 mmol) and catalyst (0.01 mmol) in anhydrous toluene (method A) or CCl_4 (method B) at 0 °C. The mixture was al-

Table 2. Asymmetric reduction of various ketimines **6**.[a]



Entry	Ketimine		X=	*E*/*Z*[b]	Method A[c] Yield [%][e]	*ee* [%][f]	Yield [%][e]	Method B[d] *ee* [%][f]
1		**6a**	H	12:1	98	96	90	97
2		**6b**	4-F	21:1	80	96	82	97
3		**6c**	4-Cl	22:1	92	95		
4		**6d**	3-Cl	20:1	98	97		
5		**6e**	4-Br	22:1	80	96		
6		**6f**	3-Br	22:1	93	97		
7		**6g**	4-CF_3	22:1	94	98	93	96
8		**6h**	4-NO_2	40:1	80	99.6	98	94
9		**6i**	4-Me	12:1	95	91		
10		**6j**	4-MeO	18:1	54	78	90	92
11		**6k**	H	16:1	96	96	83	98
12		**6l**	OMe	20:1	70	82	89	95
13		**6m**	H	10:1	82	92	80	93
14		**6n**	4-F	16:1	88	90	83	96
15		**6o**	4-Cl	18:1	97	89		
16		**6p**	2-Cl	1:2	75	97		
17		**6q**	4-Br	18:1	83	93		
18		**6r**	4-CF_3	18:1	65	97		
19		**6s**	4-NO_2	33:1	97	96		
20		**6t**	4-Me	9:1	88	83	80	85
21		**6u**		12:1	67	66	60	90
22		**6v**		15:1	56	70	80	87
23		**6w**		12:1	85	93	83	95
24		**6x**		2:1	80	89		

[a] Reactions were carried out on a 0.1 mmol scale with 2.0 equiv of $HSiCl_3$ in 0.5 mL of solvent at 0 °C for 24 h. [b] Established by ^1H NMR spectroscopy. [c] Method A uses toluene as the solvent. [d] Method B uses CCl_4 as the solvent. [e] Isolated yield based on the imine. [f] The *ee* values were determined using chiral HPLC.

lowed 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 ethyl acetate. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$ and the solvents were evaporated under vacuum. Purification by column chromatography (hexane/EtOAc or CH_2Cl_2/MeOH) afforded pure amine **7**. The *ee* values were determined using established HPLC techniques with chiral stationary phases.

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Keywords: amines · asymmetric catalysis · Lewis bases · organocatalysis · reduction

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[9] CCDC 685373 for **5a** and 685374 for **4a** contain 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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