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A Highly Enantioselective Lewis Basic Organocatalyst for Reduction of *N*-Aryl Imines with Unprecedented Substrate Spectrum

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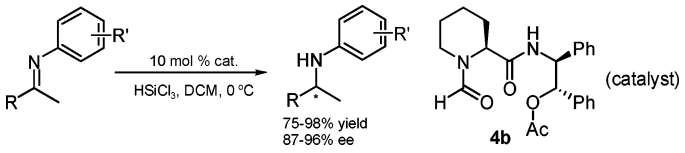
ABSTRACT



L-Pipecolinic acid derived formamides have been developed as highly efficient and enantioselective Lewis basic organocatalysts for the reduction of *N*-aryl imines with trichlorosilane. Catalyst 4b afforded high isolated yields (up to 98%) and enantioselectivities (up to 96%) under mild conditions with an unprecedented substrate spectrum.

Catalytic enantioselective reduction of imines represents one of the most important methods for preparing chiral amines,[1] a ubiquitous structural motif of natural products, drugs, and agrochemicals. Since the 1970s, considerable effort has been devoted to the development of this transformation, and remarkable progress has been made.[1,3] However, compared with the reduction of alkenes and ketones, relatively limited numbers of highly enantioselective procedures are currently available for the reduction of imines, and the development of efficient catalysts with high enantioselectivity has proven to be much more difficult. In particular, the highly enantioselective catalyst with a satisfactorily broad substrate scope remains elusive. Factors contributing to the difficulty of this transformation include the difference in reactivity among imines containing different nitrogen substituents, the existence of acyclic imines as inseparable mixtures of *E*/*Z*

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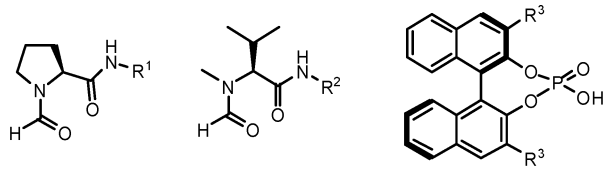


1
a, R^1 = Ph
b, R^1 = 1-Naphthyl

2
a, R^2 = Ph
b, R^2 = 3,5-$Me_2C_6H_3$

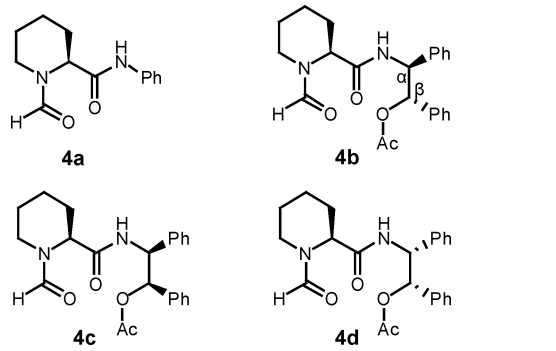
3
a, R^3 = 3,5-$(CF_3)_2C_6H_3$
b, R^3 = 2,4,6-$^i Pr_3C_6H_2$

Figure 1. Structures of the catalysts reported previously.

isomers, and the ease of interconversion between these two isomers in solution. Therefore, the search for efficient catalysts for highly enantioselective reduction of imines still remains a challenging task.

Currently available chemical catalysts for the enantioselective reduction of imines are mostly limited to chiral transition metal complexes, which often require elevated pressures and/or additives to afford high yields and ee values.[2,3] Recently, some attention has been turned to the development of chiral organocatalysts.[2−6] Effective catalysts reported thus far in the literature include the Lewis bases **1**[4a] and **2**[4b] (Figure 1) for the hydrosilation with trichlorosilane ($HSiCl_3$) and the Brønsted acids **3a**[5a] and **3b**[5b] for the transfer hydrogenation with Hantzch esters. High enantioselectivities have been obtained with **2** and **3b** in the reduction of a few *N*-aryl ketimines.[4b,5b] However, the generality of these catalysts is far less than satisfactory.[7] Herein, we report our discovery of the novel Lewis basic organocatalyst **4b** (Figure 2) that promotes the reduction of *N*-aryl ketimines with $HSiCl_3$ in high yield and excellent enantioselectivity with an unprecedented substrate spectrum.

Recently, great progress has been made in the development of highly enantioselective Lewis basic organocatalysts for the nucleophilic reactions of trichlorosilyl derivatives.[8] We are particularly interested to design novel formamide-based Lewis basic catalysts for the relatively less advanced asymmetric hydrosilation of imines with $HSiCl_3$ using the

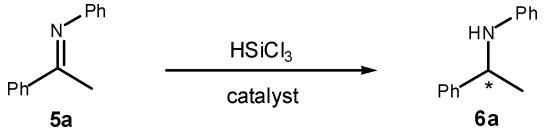


4a **4b** **4c** **4d**

Figure 2. Structures of the catalysts evaluated in this study.

commercially available L-pipecolinic acid as the template. In our initial practice, we observed that compound **4a** (Figure 2) exhibited significantly higher reactivity and selectivity than its congener **1a** in the reduction of imine **5a** with $HSiCl_3$ (entries 1 and 2, Table 1). This observation prompted us to prepare compounds **4b**−**d**, starting from L-pipecolinic acid and corresponding chiral 2-amino-1,2-diphenylethanols (see Supporting Information), and we examined their catalytic efficiencies (Table 1). In the testing reaction of imine **5a** in the presence of 10 mol % catalyst in CH_2Cl_2 at 0 °C for 16 h, **4b** afforded the highest yield and ee (97% yield and 94% ee, entry 3).[9] Its diastereomer **4c** gave the same yield and marginally lower ee (entries 3 and 4), indicating that the

Table 1. Asymmetric Reductions of Ketimine **5a**[a]



5a **6a**

entry	catalyst	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	**1a**	CH_2Cl_2	0	75[d]	59[d]
2	**4a**	CH_2Cl_2	0	94	73
3	**4b**	CH_2Cl_2	0	97	94
4	**4c**	CH_2Cl_2	0	97	93
5	**4d**	CH_2Cl_2	0	71	47
6	**4b**	$CHCl_3$	0	97	92
7	**4b**	$ClCH_2CH_2Cl_2$	0	91	94
8	**4b**	toluene	0	81	94
9	**4b**	CH_2Cl_2	rt	97	90
10	**4b**	CH_2Cl_2	−20	71	95
11[e]	**4b**	CH_2Cl_2	0	87	94
12[f]	**4b**	CH_2Cl_2	0	61	85

[a] Unless specified otherwise, reactions were carried out with 10 mol % catalyst and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of solvent for 16 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] The yield and ee at room temperature reported in ref 4a are 97 and 55%, respectively. [e] 5 mol % of catalyst was used. [f] 1 mol % catalyst was used.

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(7) At the time of the submission of this manuscript, an analogue of **3** (R = $SiPh_3$) was reported to catalyze the reduction of in situ prepared imines with Hantzch esters in high enantioselectivity with broad substrate spectrum: Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

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(9) The analogous L-proline derivative gave 71% yield and 75% ee under identical conditions.

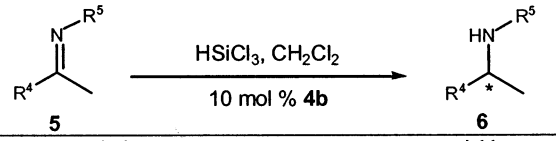
absolute configuration of C_β (see **4b** for labeling) has little impact on the reactivity and selectivity. In contrast, **4d** was found to be much less selective and reactive than **4b** and **4c**, affording only 71% yield and 47% ee under identical conditions (entry 5). Thus an (*S*)-configuration proved to be distinctly preferred for the C_α.

We also examined the influences of different reaction parameters on the performance of **4b** in the reduction of **5a** (entries 6−12, Table 1). Chloroform, dichloroethane, and toluene were all found to afford the same high level of enantioselectivities as dichloromethane (entries 6−8). Lowering the reaction temperature to −20 °C had little effect on the selectivity (entry 10), but the reactivity was significantly decreased. The lowest effective catalyst loading was found to be 10 mol %. The ee value remained at the same level with 5 mol % of **4b**, but the reaction slowed to some extent (entry 11). Further decrease of the catalyst loading to 1 mol % caused an unacceptable loss of reactivity and selectivity (entry 12).

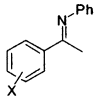
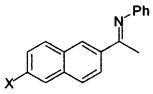
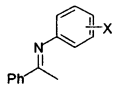
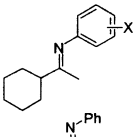
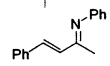
To probe the generality of catalyst **4b**, a broad range of *N*-aryl ketimines (**5a**−**s**) was reduced with $HSiCl_3$ under optimal conditions. As illustrated in Table 2, for the aromatic *N*-Ph and *N*-*p*-MeOPh ketimines **5a**−**i**, the desired products **6a**−**i** were obtained in very good yields (82−98%, entries 1−9) with excellent ee values (90−96%). The sterically hindered *N*-*o*-MeOPh imines **5k** and **5q** (entries 11 and 17) and imines **5l**−**o** with electron-withdrawing −Cl and −Br groups on the arene of R^5 (entries 12−15) all reacted well to give high ee values of 87−95% and yields of 75−98%. Furthermore, catalyst **4b** also exhibited high enantioselectivities for the challenging aliphatic ketimines **5o**−**r** despite that all the imines were used as *E*/*Z* isomeric mixtures, affording 87−95% ee values with 75−86% yields (entries 15−18). Additionally, in the presence of catalyst **4b**, α,*β*-unsaturated imine **5s** (*E*/*Z* = 2/1) was chemo- and enantioselectively reduced to afford allylic amine **6s** in 81% yield and 87% ee. Overall, the high enantioselectivity of **4b** proved to be remarkably general for *N*-aryl ketimines, which is unprecedented in catalytic asymmetric reduction of imines.

In summary, we have developed a highly efficient Lewis basic organocatalyst (**4b**) for the enantioselective reduction of *N*-aryl imines with trichlorosilane. This catalyst, easily prepared from the commercially available L-pipecolinic acid, promoted the reduction of a broad range of *N*-aryl imines in high yields and excellent ee values under mild conditions. The broad substrate spectrum of this catalyst is unprecedented in asymmetric imine reduction catalysis. The mechanistic aspects and the full application scope of this catalytic system are under exploration and will be reported in due course.

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



5 **6**

entry	imine		X =		yield (%)[b]	ee (%)[c]
1		**5a**	H		97	95
2		**5b**	*p*-CF_3		85	96
3		**5c**	*p*-NO_2		96	95
4		**5d**	*p*-Br		98	95
5		**5e**	*m*-Br		82	94
6		**5f**	*p*-OMe		95	93
7		**5g**	H		92	93
8		**5h**	OMe		91	90
9		**5i**	*p*-OMe		98	92
10		**5j**	*p*-Me		90	95
11		**5k**	*o*-OMe		92	89
12		**5l**	*o*-Cl		93[d]	90
13		**5m**	*p*-Cl		98	93
14		**5n**	*p*-Br		91	93
				E/*Z*		
15		**5o**	*p*-Br	10/1	80	95
16		**5p**	H	10/1	81	95
17		**5q**	*o*-OMe	8/1	75	87
18		**5r**		6/1	86	91
19		**5s**		2/1	81	87

[a] Unless specified otherwise, reactions were carried out with 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of solvent at 0 °C for 16 h. [b] Isolated yield based on the imine. [c] The ee values were determined using chiral HPLC. [d] The reaction time is 48 h.

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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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